Author's response to reviews

Title: Design and current status of CONTINT: Continuous versus interrupted abdominal wall closure after emergency midline laparotomy - A randomised controlled multicenter trial [NCT00544583]

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Author's response to reviews: see over
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Design and current status of CONTINT: Continuous versus interrupted abdominal wall closure after emergency midline laparotomy – A randomised controlled multicenter trial [NCT00544583] - MS: 1176847981607571

Dear Editors,

Thank you very much for the opportunity to revise our manuscript entitled “Design and current status of CONTINT: Continuous versus interrupted abdominal wall closure after emergency midline laparotomy – A randomised controlled multicenter trial [NCT00544583]”.

The comments made by the reviewers were very helpful to improve the manuscript in form and content. We followed these comments and the advice they offered strictly and hereby submit a revised version of the manuscript. Revised passages were highlighted red in the manuscript.

Below, please find our point-by-point response to the referee comments.

Thank you very much for your consideration.

Best personal regards,

Nuh Rahbari
Point-by point response:
The authors provide a very clear protocol on an interesting topic. The design seems rigorous and the statistical methods seem appropriate for the design.
There are several minor issues to consider, as follows:
1. The authors indicate that due to the almost complete lack of data to inform the design of the study, they are adopting an adaptive design with an interim look at 80 patients. They are very close to this target after expanding the study from a single centre (which recruited about 1 subject per month) to a multi centre platform.

The former description was in fact misleading. For clarification, we added the following phrases:
Consequently, the trial protocol was amended and an investigators’ meeting was held at Frankfurt, Germany on 31.08.2009. ‘Up to this date 26 patients were recruited.’
A total of eleven trial centres have approved participation in the CONTINT trial. A total of 73 patients have been randomized ‘at the date of submission of this paper.’

However, the reader could benefit from a bit more detail on the adaptive design – as follows:
a. Despite the lack of data to inform the assumptions, the authors seem to leave it wide open at the adaptive interim analysis – either close the study down, or continue. It would be usual to provide some indication of what the target sample size would be, even if this was just on the assumption that the original assumptions were met?

When the study was planned, there existed no pilot data and there was no evidence with respect to the scientific question of the study [19]. Therefore, the values of the parameters required for sample size calculation (overall rate and treatment effect to be expected) were completely unknown. For this reason, it was not possible to make any reliable assumptions for sample size calculation. In fact, it was not even possible to define a target sample size. We therefore decided to plan the study as an adaptive trial to calculate the sample size on the basis of the data of the first stage which served as an internal pilot study.
In the revised version of the manuscript, we now describe the background of the sample size calculation more precisely (see response to comment 5. below).
b. The authors reference Bauer and Kohne (17) – but it would be useful to walk the reader through the design in lay terms – for example, ‘A global one sided type I error rate of $\alpha=0.025$ is specified with a boundary for the one-sided $P$-value for accepting the null hypothesis within the interim analysis of $\alpha_0=0.40$, a one-sided significant level for early rejection of the null hypothesis of $\alpha_1=0.0115$ and a boundary for the product of one-sided $p$-values for the rejection of the null hypothesis in the final analysis of $c\alpha =0.0038$’ – it isn’t really that clear to a statistician what the plan is here?

We clarified the description of the adaptive design and replaced the former passage by the following:

‘The global one sided type I error rate of the trial is controlled by 0.025. This is achieved by implementing the following decision rules. The study is stopped after the interim analysis with acceptance of the null hypothesis, if the one-sided $p$-value lies above 0.40, and with rejection of the null hypothesis, if the one-sided $p$-value falls below 0.0115. Otherwise, the study is continued with a second stage, and the null-hypothesis is rejected in the final analysis if the product of the stage-wise one-sided $p$-values falls below 0.0038.’

2. The authors could be a bit clearer about who qualifies for this trial – yes, they have listed the inclusion/exclusion criteria, but it isn’t that easy to get a picture of who will be eligible and who won’t – in more detail:

a. The authors describe this as an ‘emergency procedure’ and say that any patient unable to consent will be excluded – useful to give some insight into the context here e.g. all patients would be expected to be conscious?

b. But what of the distress of needing emergency surgery and the pain etc? Would this limit the number wanting to go through the consent process?

c. And how many of those otherwise eligible have failed to consent or otherwise not participated in the trial? This would influence the generalisability.

d. Page 4 ‘Furthermore, a septic abdominal focus (e.g. perforated stomach ulcer, perforated diverticulis) must be present’ – is this for all patients to be eligible?

It is correct that the inclusion criterion of a septic abdominal focus applies to all patients. This patient population is of particular risk for wound healing complications including the abdominal wall. Due to the
lack of controlled clinical trials, high level evidence is urgently required to determine the optimal abdominal wall closure strategy in these patients.

To assess the number of patients not included in the trial who would otherwise be eligible for participation in the study, there is a screening log for documentation. As described in the section ‘Subjects and patient recruitment’ screened patients who have not been enrolled into the trial will be documented in the screening log, including the reason for non-inclusion.

We are aware implementation of a randomized trial in the setting of emergency surgery is challenging. This is probably one of the reasons for the lack of such trials. However, these obstacles may not prevent scientists and clinicians to perform such trials, as data from these trials are urgently required to improve patient care. Furthermore, previous trials have in principle demonstrated the feasibility of trials in emergency setting.

3. Page 5 ‘und’ misspelt (presumably and).
We removed this word and replaced it be ‘and’.

4. The authors do not indicate how many surgeons will be taking part, what the distribution of how many of each type of closure they will undertake, and what the distribution of experience and skill is. And how will the authors address centre & surgeon effects in the analysis?

We agree with the reviewer that the experience of the surgeon is an important issue. As already stated in the manuscript the expertise of the surgeon who is present at the closure is documented including the number of abdominal wall closures performed by the surgeon.

5. Page 7/8 ‘... the assumptions to be made for sample size calculation are highly uncertain and with it, it is doubtful whether the desired power is actually achieved in a fixed sample size’ – not really sure what the authors are saying here – is this just justifying the need for an adaptive design? Could be clearer.
We clarified the description by replacing the former passage by the following:
‘When the study was planned, there existed no pilot data and there was no evidence with respect to the scientific question of the study [19]. Therefore, the values of the parameters required for sample size calculation (overall rate and treatment effect to be expected) were completely unknown. Within a fixed sample size design, it was hence rather uncertain whether the desired power is achieved or not. For that reason …’

6. The authors state that various aspects of the procedures will be left to ‘local practice’, including prophylactic antibiotic use – did the authors consider stratifying by this, and are they going to adjust for this in the analysis? Age and BMI were mentioned as adjusting factors.

We deliberately decided to leave substantial parts of the procedures to ‘local practice’ in order to improve the generalisability of the study. However, a logistic regression analysis is planned including the covariates ‘wall closure procedure’, ‘BMI’ and ‘age’.

7. The authors inflated the sample size by 10% to allow for loss to follow up – will this be reassessed as part of the input to the revised sample size at the adaptive interim look?

The reviewer is right: The information on the rate of loss to follow up will in fact be used when revising the sample size. We added the following sentence:

‘The rate of loss to follow up observed so far is also taken into account when calculating the sample size for the second stage.’

8. Are the authors going to look at the primary outcome in terms of all the technical measures of success of the operation (listed as several secondary outcomes e.g. suture length etc)?

The primary outcome is within the trial is incisional hernia within 12 months or burst abdomen within 30 days after surgery. All other outcomes are secondary outcomes and will be subject to exploratory analyses.

9. The authors are using sealed envelopes – generally there is concern about this method as being open to manipulation – but the authors say they have had
previous good experience with this method. Might be useful to expand on this, to provide additional reassurance?

We added the following sentence to explain our procedure:

‘To avoid manipulations, a thick black bar was placed on the opposite side of the sheet, exactly at the position where the randomization information is located.’

Sealed envelopes have been used successfully in a large number of trials. We hope that the information provided in the manuscript is now sufficient to describe the production and handling of the envelopes.

10. Page 9 ‘Missing data with respect to the primary outcome variable will be replaced by the ICA-r method described by Higgins et al (18)’ – this could benefit from a bit more detail. The Higgins paper is about missing data in meta-analyses, not necessarily the most appropriate for an individual trial, where there would be substantial individual level covariate information available to explore multiple imputation and/or pattern mixture models for data missing at random and informatively, respectively?

We agree that alternative imputation methods using individual covariate information could also have been used in this trial. However, it is an advantage of the method of Higgins et al. that (i) it takes into account the reasons for missingness when imputing missing values, and (ii) that it applies rules that are simple and much easier to communicate as compared to other methods as, for example, multiple imputation or pattern mixture models. For these reasons, we decided to apply this methodology for the primary analysis. Of course, alternative methods for dealing with missing values, e.g., multiple imputation, are applied as sensitivity analyses.

11. Page 9 ‘A trend indicated by a one-sided P-value of P<0.20 can be achieved ... ’ – I wasn’t really sure I understood what the authors meant here?

We agree that this sentence is not sufficiently clear and we therefore removed it from the manuscript. (What we meant is that we additionally provided the power for achieving a p-value with P<0.20, a result we would consider as a “trend” for the treatment effect towards a difference between the groups).
Literature