Reviewer's report

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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Reviewer: John Norrie

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Statistical / methodological review

Discretionary revisions

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. 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?

   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 1 error rate of #=0.025 is specified with a boundary for the one-sided P-value for accepting the null hypothesis within the interim analysis of #0=0.40, a one-sided significant level for early rejection of the null hypothesis of #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# =0.0038’ – it isn’t really that clear to a statistician what the plan is here?

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?

3. Page 5 ‘und’ misspelt (presumably 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?

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.

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.

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?

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)?

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?

10. Page 9 ‘Missing data with respect to the primary outcome variable will be replaced by the ICA-r method described by Higgins etc 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?

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?