Reviewer's report

Title: Protocol for a randomized controlled trial on risk adapted damage control orthopedic surgery of femur shaft fractures in multiple trauma patients

Version: 2 Date: 11 June 2009
Reviewer: Gordon Doig

Reviewer's report:

Thank you very much for considering and addressing my initial comments. The protocol now contains considerable additional details. Because the appropriate exploration and adjustment for baseline balance may be considered an internal validity issue, I would like you to re-consider your response to Issue 3:

Reviewer Comments on original version:
3.) Baseline balance
You describe the process to be used to inspect balance with regards to ISS. Since these patients will be admitted to the ICU, and since there are many other baseline factors that are accepted to determine outcome, such as mechanism of injury, other trauma type, chronic health state, APACHE score, SOFA at time of randomization, Gender, Age and today even BMI. Please describe how you intend to assess balance in these factors.
If you do not intend to assess balance in these commonly accepted predictors of outcome, I have concerns with the internal validity of your trial.

Authors Response:
The reviewer is right in stating that outcome of severely injured patients depends on more than ISS alone. However, among the parameters mentioned above, only age has a similar importance as ISS. The type of injury has a rather limited impact, as well as BMI and gender, and chronic health states are highly correlated with age (results from data from more than 35,000 multiple trauma patients in the Trauma Registry of the German Trauma Society and the development of RISC score).

Additional Reviewer Comment on Revision 1.
3a) Type of Injury, BMI, gender and CHS are related to outcome and, although they may be correlated with age, unless they are fully correlated with age, may add additional information beyond age alone.
They are easy to collect and are accepted to be related to outcome in all ICU-based trials. It would be ‘irregular’ to fail to collect and report these variables in your baseline balance table.

The APACHE score is usually determined AFTER the intervention when the patient is admitted to ICU, and could thus be effected by the operative procedure
performed. This is also true for the initial SOFA score assessment. Both scores are based on a 24 hour time period after ICU admission.

Additional Reviewer Comment on Revision 1.
3b) In ICU based clinical trials, it is accepted practice to calculate APACHE using variables collected over the 24 h period immediately PRIOR TO randomisation. This avoids the bias you refer to above. Same with SOFA, or other MODS scores. It would be a major limiting defect in your trial if you failed to collect APACHE, SAPS or other ICU-based severity of illness score using the techniques currently appropriate for ICU-based trials.

Authors Response:
Thus we decided to use age and ISS for baseline comparison before evaluating the primary outcome variable. In case of significant imbalances, adjustments will be performed. All other factors will of course be presented in a comparability table. Please note that excessive statistical testing for baseline imbalances can find spurious significance for one of the many variables. Therefore, many journals discourage authors from testing baseline imbalances (see: Bhandari M, Devereaux PJ, Li P, Mah D, Lim K, Schünemann HJ, Tornetta P 3rd: Misuse of baseline comparison tests and subgroup analyses in surgical trials. Clin Orthop Relat Res 2006; 447: 247-51).

Additional Reviewer Comment on Revision 1.
3c) This Editor agrees that excessive testing should be avoided. To this end, no more than 10 to 12 variables typically appear in the assessment of baseline balance. ALL variables reported in your baseline balance table should be assessed for baseline balance AND should be controlled in the final analysis if found to be potential confounders. Please explicitly list ALL variables to be reported in the baseline balance table. If in imbalance, ALL should be available to a multivariate model.

Authors Response:
Additionally, the effect of the operative strategy will be analysed in a multivariate model (regression analysis) using more factors than ISS and age alone. The Trauma Registry of the German Trauma Society also uses a prognostic scoring system which combines 10 different data elements, including age, ISS, physiology and initial laboratory parameter. However, the ability to show statistically sound relationships is limited by the number of cases in the trial, and also by the number of factors included in the multivariate analysis.

Therefore, this analysis is performed on an explorative basis only.

Additional Reviewer Comment on Revision 1.
3d) I am uncertain of the purpose of this proposed explorative analysis.
Please specify and explicitly report which variables will be assessed and why.

Thank you for addressing these issues.

Dr Gordon Doig,
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Australia and
Associate Editor, Trials.