Reviewer's report

Title: OPAL: Randomized, controlled clinical trial to investigate oxygen persufflation as adjunct in liver preservation

Version: 2 Date: 22 September 2011

Reviewer: John Norrie

Reviewer's report:

The authors present a well written protocol on a fascinating study. The design seems rigorous and the statistical methods seem appropriate to that design. There are a number of issues arising for consideration:

1. The randomisation of the participants to either the oxygen persufflation or the standard preparation of the liver to be transplanted is well described, and seems standard – however, what about the allocation of the livers?
   a. What reassurance is there that the process by which a liver becomes allocated to either the novel or standard preparation is effectively random? If there is any imbalance in the ‘quality’ or ‘viability’ of the livers that end up being used in the two randomised groups, this could bias the findings.
   b. Could the randomisation be extended to include randomly allocating the livers to the treatment groups, or would that be logistically unfeasible (coupled with the patient sided randomisation, leading to missed transplants?).
   c. For example, it seems that livers after cardiac death may be different; likewise, steatotic livers may have different performance, and so on – how might it be arranged to make sure equal numbers of these end up in the two randomised groups?
   d. At the least the authors should consider adjusting for liver characteristics in the analysis?

2. The protocol would benefit from a fuller discussion of the blinding issue – the authors just say ‘However, due to the fact that the surgeon inevitably gets aware of the pinpricks during the implantation procedure, it is not possible to do the trial in a double blinded fashion’ – couple of points:
   a. Is it impossible / unethical to include sham pinpricks in the standard procedure to effect a blind?
   b. If so, what are the likely implications of the lack of blinding on the measurement of the primary (and secondary) outcomes?

3. The description of the Safety Reporting is a bit light at present. The authors just say that ‘any unexpected clinical adverse event ... must be reported to the study co-ordinator within one working day of occurrence’, and ‘an independent safety board monitors closely the proper conduct of the trial and all SAE reports’ – but how does the study co-ordinator interact with this independent safety board (e.g. within what time, and with what clinical authority etc)?
4. It would be useful to get more detail and background on the transplant process – for example:
   a. ‘Enhancement of donor criteria’ and ‘viability of marginally preserved livers’ – more detail on explaining and quantifying the magnitude of the problem of using less than ideal livers would be helpful.
   b. The authors specifically mention ‘steatotic livers’ – again, useful to explain this in less technical terms?
   c. And the actual process if ‘venous systemic oxygen perfusion’ and ‘at the time of warm reperfusion’ – and why ‘two hours of ‘a posterioriy’ (?) is likely to be optimal – just a bit more detail explaining the process to a non-expert.
5. The Inclusion Criteria – not quite clear why the authors specify ‘or donor age > 65’? Explain this in more detail.
6. In terms of the generalisability of the findings, what impact does excluding those with ‘present alcohol or drug abuse’ have? And this is just current, not previous, correct?
7. The authors could usefully discuss in more detail the choice of serum peak of liver transaminases as the surrogate for ‘the extent of reperfusion injury’? And by taking the peak AST in 3 days, might this overcome some of the skewness in the underlying AST measure?
8. Sample size calculation – not really sure what the ‘#’ parameter as in ‘which translates into a relative effect #=0.5′ actually is – this could do with a clearer explanation, and why moving this to 0.66 represents a worthwhile change to detect?
9. Randomisation and Treatment – ‘... and strata 30 Meld-Score’ – not really clear what is meant here.
10. Couple of issues with the statistics:
   a. ‘Missing data on the primary endpoint will be replaced by the maximum global (across both groups) AST values mimicking a ‘worst-case scenario’” – this assumes that the missingness is equal across the groups – it will not be conservative if there are more missing data in the control arm?
   b. ‘To address the non-parametric Behrens-Fisher problem’ – explain this in simple English.
11. There are a number of typos:
   a. Abstract – ‘ijury’; ‘will be assesses’
   b. Background – ‘maintaines’, ‘to some extend’
   c. Exclusion criteria ‘any oft he’
   d. Table 1 ‘dismissions’?

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being
published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests