Reviewer's report

**Title:** Everolimus and long acting octreotide as a volume reducing treatment of polycystic livers (ELATE): study protocol of a randomised clinical trial

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**Reviewer:** John Norrie

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Everolimus and long acting octreotide as a volume reducing treatment of polycystic livers (ELATE) - study protocol of a randomised clinical trial

Statistical review

Discretionary revisions

1. The authors indicate that there are two major genetic distinct disorders - PCLD and ADPKD - is it possible that there will be a differential response to the combination over the monotherapy according to underlying genetic cause?

2. The authors mention surgery as the invasive alternative with no convincing evidence of benefit - will those randomised all not have had this surgical option? And what about post randomisation? Will surgery be banned? Likewise, what about other mTOR drugs and/or additional somatosatin analogues as rescue interventions? Will these be allowed?

3. The trial is open - the authors should discuss more fully why it was not feasible to create a dummy for the everolimus? They just say in the discussion that the monitoring of everolimus effectivly unblindscthe trial - more detail is needed. And also why the specific choice of everolimus at that dose and frequency?

4. The study is single centre - the authors should discuss here in the protocol what limitations that is likely to place on the generaliability of whatever the findings are? Likewise the list of inclusion and exclusion criteria in table 2 looks extensive - so roughly what proprtion of those that might be considered for this treatment if successful are excluded from this evaluation?

5. Primary outcome - will the change in total liver volume at 12 months be assesses by a technician / CT operator unaware of what treatment was randomly assigned? The authors say 'CT scans will be anonymized to allow blinded assessment of the liver volume' - so this is reassuring - but more explicit detail is needed on this important methodological issue.

6. And likewise the authors give useful data on intra and inter observer variability, but do not seem to say who will be taking the 12 month scan and whether this will be the same operator that took the baseline scan?

7. The authors are looking for a huge effect size: a difference of 166 ml with an
assumed standard deviation of 130 (or an ES of ~1.3). The obvious concern is that a smaller but nonetheless worthwhile improvement e.g. a doubling with an extra 60 mls, will be missed.

Also, is this the standard deviation of the change over baseline? That should be smaller than either the baseline or the 12 month SD.

8. What percentage of the baseline liver volume does a reduction of 166 ml represent? Is it possible that those with smaller livers will struggle to achieve that absolute level of change? Did the authors consider a percentage change, or is it an absolute change above a threshold that will deliver the anticipated benefit?

9. How are the authors going with deaths and loss to follow up - they have added a couple of subjects assuming a 10% loss, but under intention to treat they should have a plan to deal with these missing data?

10. The definition of Per Protocol looks pretty strict - with only about 20 per group maximum, will this be a viable analysis?