Reviewer’s report

Title: Study Design and Rationale for a Randomized Trial Comparing Transcatheter and Surgical Valve Implantation in Aortic Valve Stenosis

Version: 1  Date: 18 September 2012

Reviewer: John Norrie

Reviewer’s report:

Discretionary Revisions:

The authors present a very clear protocol for what is clearly a challenging clinical area to conduct a multicentre randomised controlled trial in. Recruitment is almost complete and the following queries are primarily intended to help the authors optimise the write up of the findings.

1. The authors describe the target cohort as ‘low risk’, which is clearly a relative term. Although there is good discussion of the inclusion and exclusion criteria, it would be useful to have a summarising paragraph to quantify how much lower this risk is from, say, the type of underlying risk level of those patients routinely considered for the TAVI operation in the present day.

2. Page 3 – the authors state that ‘almost one third of patients referred for valve intervention will not receive valve replacement’ – an issue running through the paper is whether the quoted statistics are up to date to a 2012 perspective, or whether this is as written when the study was designed 4 or 5 years ago? And in this specific instance, what treatment or intervention does this one third get when they are considered unsuitable – useful to clarify this?

3. The protocol is clear on the available devices, and the authors mention that the PARTNER trial used just the Edwards SAPIEN device, and was ‘sponsored by the systems manufacturer’ – yet the current trial likewise seems only to use one device – the Medtronic CoreValve – and in the declarations of interest section the lead author is described as a ‘physician proctor’ for Medtronic. Useful to clarify that this role involves, and comment on the presumed desirability that future pragmatic randomised effectiveness trials would ideally use all available devices, so that at least (probably non-randomised) analyses could be undertaken to compare devices?

4. The authors state that ‘operator experience has grown and implantation systems have improved …’ – given that the trial has recruited over several years are the authors (a) intending to adjust for these temporal effects to hopefully increase the precision of the estimated treatment effects and (b) consider the surgeon learning curves in their own right as an interesting part of rolling these interventions out to a wide population of surgeons?

5. The DMSC does not seem to have any specific statistical or trials methodological expertise?
6. And did the interim analysis ‘after 14 primary outcome events’ take place? And what were the statistical considerations that arrived at undertaking this at 14 events – it seems a small number? Or is this based on an aggregate event rate of around 10% so this would be around half time?

7. Why exclude subjects <70 years old (if on all other criteria they are eligible, say)?

8. Page 9 ‘Potential demasking of the committee will be checked after completion of each outcome assessment’ – how do you do this?

9. The authors say that the outcomes will be compared between the randomised groups using simple chi-squared tests or t-tests. Although it probably won’t make much difference, it is usual to adjust the primary analyses for any variables you have stratified for e.g. via a logistic regression model, or a linear model?

10. Page 10 – useful if the authors could justify their approach of ITT for confirmatory analyses (this seems fine) and per-protocol for ‘hypothesis generating’ analyses (which seems a bit more unusual?)