Author's response to reviews

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

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Version: 4 Date: 27 November 2012

Author's response to reviews: see over
Cover letter to Trials journal regarding revisions for manuscript:

MS: 7436935207294253

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

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Copenhagen, Date 26/11/2012

Dear Editors-In-Chief at Trials

Thank you very much for the very relevant comments by Dr. John Norrie. Please find the responses to these comments and additions below. The revisions in the manuscript (version 2) have been marked with red and underlined.

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 summarizing 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.

Answer: Typically, high risk patients considered for TAVI in current clinical practice have a logistic EuroSCORE above 20% and STS score above 10% predicted 30-day operative mortality. Low risk patients could have a logistic EuroSCORE of 3% and a STS score of 1%.

This paragraph has been added.

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?

Answer: The statistics on the treatment pattern for aortic valve stenosis patients are from the time the trial was designed. This has been clarified in the manuscript. Nonetheless, these data from large population studies are still widely quoted. From the screening process for the current trial we have learned (unpublished data), that 30% of patients referred in 2011 for valve intervention were actually considered to have a prohibitive high surgical risk. 20% of these patients received optimal medical therapy and the remaining 10% received TAVI outside the trial.

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 randomized effectiveness trials would ideally use all available devices, so that at least (probably non-randomized) analyses could be undertaken to compare devices? Answer: We mention the fact that the PARTNER trial was supported and designed by the valve prosthesis manufacturer, which also managed the sites, collected, monitored, and stored the data as opposed to our trial, where Medtronic the manufacturer of the prosthesis used did not have any influence on any aspects of the trial. 

One of the primary investigators of our trial serves as a proctor for Medtronic. This role implies supervising other centers in implementing the device and implantation system. He has received consulting and lecture fees, grant support, and reimbursement for travel expenses from Medtronic. This has been added to the manuscript.

Since there is a step learning curve and the TAVI procedure requires a substantial amount of experience, it is common not to use more than one device at a center. Also the design of the devices and delivery systems, technique of implantation, and the types of patients (ex. the extend of atherosclerotic disease) in which they are used differ somewhat and could potentially make the interpretation of the TAVI results more difficult and unclear. In our trial we wanted to compare surgery with this specific device.

However, as experience with more devices grow a more complete picture of TAVI, and its effectiveness should be evaluated in trials comparing surgery to TAVI using all available devices. In the manuscript we have added: Only one TAVI system is used in the trial. Most centers only use one system as the technology is still new and requires a substantial amount of experience to be performed safely. However, as experience with more devices grow a more complete picture of TAVI and its effectiveness should be evaluated in randomized trials comparing surgery to TAVI using all available delivery systems and prostheses.

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? Answer: a) We have not planned to adjust for these temporal effects, because the TAVI interventionists (whom are not cardiac surgeons) performing TAVI in the current trial had already at the time of trial commencement done enough TAVI procedures (more than 75) to be above the steep part of the learning curve. The cardiac surgeons performing the conventional surgical treatment are all senior consultants with extensive valve replacement experience. No investigator will perform both procedures. We have commented on this issue in the discussion section. The sentence referred to above is a general statement about the development of TAVI from its infancy with large caliber delivery catheters, a small number of available prosthesis sizes, and very few interventionists actually performing the procedure. b) This is indeed an interesting part of introducing the TAVI procedure in broader clinical practice, especially considering the proven excellent outcomes for low risk surgical patients also recruited in our trial. Performing the TAVI procedure in the setting of a RCT with only a handful of experienced TAVI interventionists is very different from general practice, and this should be strongly emphasized when reporting the results of the trial. The important effect of being on the beginning of the learning curve and outcomes in TAVI has been reported. The multicenter design of the trial should improve the external validity.
5. The DMSC does not seem to have any specific statistical or trials methodological expertise?
Answer: A statistician has been added to the DMSC.

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?
Answer: This is a misprint, the interim analysis will be done after 20 events as stated in our approved protocol. We have not yet reached the first 20 (71% of expected outcomes) primary outcomes. This is based on an aggregate event rate of around 14%.

7. Why exclude subjects <70 years old (if on all other criteria they are eligible, say)?
Answer: Since the durability of the new TAVI prostheses are unknown and redo procedures carries a higher risk and thus should be avoided, we have excluded younger patients to avoid potential prosthesis re-interventions. Biological valve prostheses used for conventional surgery are known to last at least 10-15 years, and TAVI valve prostheses are expected to have the same durability. According to valve treatment guidelines younger patients also have the choice of mechanical valve prostheses, and these carries a very different thromboembolic risk profile, and would make the interpretation of the results even more difficult. We have added: To avoid redo valve procedures due to expected prosthesis degeneration and mechanical valve prostheses, we choose the 70 years age minimum criterion.

8. Page 9 ‘Potential demasking of the committee will be checked after completion of each outcome assessment’ – how do you do this?
Answer: This has now been omitted from the manuscript according to the CONSORT guidelines.

9. The authors say that the outcomes will be compared between the randomized 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?
Answer: The statistic section has been thoroughly revised together with a trialist and statistician. We will adjust the primary analysis for stratification.

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?)
Answer: See revised Statistical analysis plan section. All outcomes apart from the primary outcome measure are exploratory, hypothesis generating.

Further changes:
The trial has been named The Nordic Aortic Valve Trial abbreviated The NOTION Trial which has been added to the title.
Since statistical and methodological assistance has been consulted the author list has been updated.
Only three trial sites will participate, and these are now mentioned in the methods section. The randomization process has been clarified and specified. The name of the ethical body that granted approval for the study at the Copenhagen University Hospital is the Research Ethics Committee in the Capital Region of Denmark and has been added. The regional ethics committee at the two other sites has approved the protocol locally.

3.5% attrition have been omitted and sample-size changed to 280. Patients withdrawing their consent will be replaced.

The number of recruited patients has been updated.

The list of acknowledgments has been updated.

The reference list has been updated.

A few minor clarifying changes have been added to the manuscript. These are all underlined.

We hope these changes and modifications are satisfying.

Sincerely on behalf of all authors,

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