Author's response to reviews

Title: The percutAneous Coronary inTervention prlor to transcatheter aortic VALve implantation (ACTIVATION) trial

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Author's response to reviews: see over
Re: MS: 1169951794118641 - The percutAneous Coronary inTervention prior to transcatheter aortic VAlve implantation (ACTIVATION) trial

Dear Professors Altman, Furberg and Grimshaw,

We would be pleased if you would consider our revised manuscript on the rationale and design of the ACTIVATION trial. We have carefully considered the comments of the editorial board and reviewers. Please find herein our responses to the comments of the Editorial Committee and the reviewers. We would like to thank all parties for taking the time to review our work.

Reviewer's report:

The protocol submitted by Khawaja consist of a open label randomized controlled trial of 310 patients to test the non-inferiority of combined PCI+TAVI vs TAVI alone on a composite primary outcome of 12 month mortality and rehospitalisation. There are also several secondary end-points assessing efficacy and safety. Overall, this is an interesting protocol that addresses an important clinical question that pertains to TAVI.

Major Compulsory Revisions:

1. My major concern with manuscript is the readability and clarity of the Background section. The authors should review this section.
Thank you for the careful review given to our manuscript. We gratefully acknowledge the reviewers comments and agree that the readability of this section could be improved. We have therefore re-written large portions of the background as marked in the revised manuscript. Dealing with the specific reviewer comments:

**p.7, line 11:** "Other variables such as approach were not identified". Please clarify this statement.

This has been changed on page 5, para 2, line 7:

“The access approach used was not included in their risk model, an important omission given the known differences in risk profiles between, for example, TF-TAVI and TA-TAVI cohorts”

**p.8, line 5:** "The one year overall mortality is..." Please clarify this statement.

This has been made clearer by changing the text on page 6, para 1, line 5 to:

“The mortality in the overall group one-year after TAVI was reported as 77.9% and was found to be 80% in those with pre-emptive PCI - though no comparison between the two cohorts was performed”

**p.8, line 6:** "A swiss group reported..." Can the authors provide the actual data rather than simply stating "showed no difference".

We have provided more detail in discussing this reference.

“Abdel Wahab et al reported that 55 patients who underwent PCI prior to TAVI during showed no difference in adverse events at either 30 days (2% v. 6%; p=0.27) or 6 months (9% v. 14%; p=0.42) when compared to a group undergoing isolated TAVI”

**p.8, line 8:** "More recently Goel et al..." This sentence is unclear. Please rephrase.
Again we agree that that this was not clear as written. It has therefore been changed to:

“The feasibility of PCI for CAD in patients with severe AS has been demonstrated by Goel et al in a cohort of 258 patients over a 10-year period with a favorable comparison with propensity matched patients without the aortic disease”

2. In the methods (p.9) can the authors further clarify why a non-inferiority (as opposed to a superiority) design was chosen.

We have added a paragraph on page 7 to further explain the decision:

“The trial has an open label, randomised non-inferiority study. The safety of TAVI with revascularization performed as deemed necessary by the Heart Team has been demonstrated in previous trials and registries [29, 30, 32]. From the available data detailed in the statistical design section our hypothesis is that the no PCI strategy will have comparable effectiveness to the PCI (the active control) strategy, hopefully helping the cardiology community decide whether the extra procedure of pre-TAVI PCI can be safely avoided. From an ethical standpoint a sham procedure in the no PCI arm could not be countenanced. Given the complexities of the TAVI procedure and the recommended Heart Team approach, we could not blind operators as to whether patients had undergone revascularization or not. To minimize bias towards the null we have robust inclusion/exclusion criteria and clearly defined clinical endpoints and boundaries. The trial will be conducted strictly following Good Clinical Practice and Standard Operation Procedures to minimize potential bias.”
3. **In the statistical considerations p.15, 2nd paragraph, can the authors further clarify and provide more context for the sentence “From a rehospitalisation and PCI perspective...”**

We have provided a more detailed explanation as to what rehospitalisation or further treatment may entail on page 13, para 2, line 4:

“PCI may lead to restenosis of the stent, requiring rehospitalisation in 5% of patients over 12 months. The rate of rehospitalisation with stable angina, acute coronary syndrome or ischaemia-related heart failure requiring treatment, including possible PCI, is thought to be in the region of 15% in all patients with CAD.”

4. **Conclusions, p16, final sentence: Given the rate of concomitant CAD...”. Please complete this sentence.**

As per the request of the Editorial board we have moved the points in the conclusions section into the main part of the manuscript, page 6 para 2. The sentence has been edited and expanded into:

“There has been a rapid, global expansion in the use of TAVI to treat aortic stenosis in patients who are not candidates for sAVR. The efficacy of this technique has been successfully demonstrated in randomized, controlled trials[28, 29] and in large registries[30, 31] and there is now a need to improve patient safety and outcome, including how to manage patients with concomitant CAD. Given the paucity of data on the issue and variation in practice and recommendations we feel a randomized controlled trial (RCT) is essential for safe evidence-based practice. ACTIVATION is the first randomised controlled trial of elective PCI prior to TAVI. Its findings will help define the optimum revascularisation strategy in this procedure and help create evidence-based guidelines on this controversial issue.”
Minor Essential Revisions

1. There were several typographical errors. Please revise accordingly.

We apologise for this oversight.

Here are a few that I noted:

p.7, line 13: "...OR a stenosis of >50% and noted..." Add "was" before noted.

This has been corrected as requested.

p.7, line 17: "...and higher logistic Euroscores." Add "in patients with CAD" at the end of the sentence.

This has also been corrected as above.

Editorial requests:

1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format __________: study protocol for a randomized controlled trial.?

   This has been changed to fit the style requirements.

2. Please include the date your study was registered with your trial registration number at the end of your Abstract.

   This has been added as below:

   “Clinical Trial Registration: ISRCTN75836930, http://www.controlled-trials.com/ISRCTN75836930 (registered 19-11-2011)”

3. Please remove your Conclusion. This information can be incorporated into your Discussion.
We have incorporated this into the main discussion on page 6 para 2 as detailed above.

4. Please move your funding statement to an Acknowledgements section before the reference list.
This has been done as below:

“Acknowledgements

The trial is sponsored by Guy’s & St Thomas’ NHS Foundation Trust via educational grants from Edwards LifeSciences (Irvine, CA, USA) and Boston Scientific (Nantick, MA, USA). The conception, design, conduct and dissemination of the trial and its results is independent of the funding organizations.”

5. Please include a figure title and legend section after the reference list. The figures should not be included in the main body of the manuscript.
We have added the titles and legends in the manuscript and removed the figures.

We hope that our answers to these comments are understandable and satisfactory to you and your editorial team. Please do not hesitate to contact me if there is any problem or if further corrections are required.

Yours sincerely,

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