Author’s response to reviews

Title: QUALITY of life, satisfaction and outcomes after ministernotomy versus full sternotomy isolated Aortic Valve Replacement (QUALITY-AVR): study protocol for a randomised controlled trial

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Author’s response to reviews:

Dear Reviewers:

Thank you again for the review of our manuscript and for the suggestions that will definitely improve its quality. After the changes, we hope that it can be now accepted for publication in the TRIALS JOURNAL.

All point-by-point responses have been answered below.

Sincerely yours.
1. Associate Editor point-by-point responses

1.1. The authors should provide figures with acceptable Quality. The current ones are not sufficient despite being improved.

Response: We increased the figure’s quality up to 500 dpi.

1.2. Please provide highlighted changes in the manuscript in comparison to first Version. This is usually required for Publishing manuscripts and I think the authors should be familiar with the process.

Response: We apologize for the inconvenience. We have provided the highlighted changes in the updated version.

1.3. Explain in Detail how the blinding is performed and maintained and discuss if this is valid. I am concerned this will not work as real blinding, especially since the main outcomes are evaluated after discharge of patients and the blinding is only until discharge, if I understand correctly. Please compare to internationally accepted definitions of blinding and reference accordingly.

Response: As you say, blinding is controversial in surgical patients (reference 26). In our case, the patient is blinded with respect to the treatment received up until hospital discharge. All wounds will be covered up to this moment with standardised wound dressings. There is a great difficulty in blinding surgical procedures for a long time, due to the need to provide a hospitalization report letter, and because incisions and scars may differ between groups. That is why the size of the wounds in both arms will be intended to be as small as possible; about 10 cm in the ministernotomy and 13-15 in conventional surgery. With these measures we will try to reduce the risk of bias, which will always be present in this type study involving surgical procedures. The outcome assessor is the Hospital Clinical Trials Data Monitoring Unit, independent from Sponsor, which reviews and confirms all the outcomes and endpoints values every 3 three months.

This is why we consulted with our IRB on the convenience of defining as a single blind vs. as an open label trial, since the international definitions in these cases are not very clear. Following our IRB recommendations, we defined our study as a single blind trial.

2. Reviewer #3 point-by-point responses: Thank you for making the changes and providing SPIRIT checklist and Figure.
2.1 Regarding blinding of patients:

"Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how _____6_____  
17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial _____N/A_____

Per SPIRIT checklist and guidelines;

Point 17a: In page "6": details regarding how patients are going to be blinded are not provided. For e.g. Will wounds be covered until discharge? Such details are essential to provide for presentation of the trial methodology and reproduction of similar methodology in future trials.

Response: Details regarding how patients are blinded are now provided on page 7. As you mentioned, we have included more details regarding how the patients will be blinded, for example, all wounds will be covered until discharge with standardised wound dressings.

We answered this question in point 1.3, and we added this explanation on page 7: “the patient is blinded with respect to the treatment received up until hospital discharge. All wounds will be covered up to this moment with standardised wound dressings. There is a great difficulty in blinding surgical procedures for a long time, due to the need to provide a hospitalization report letter, and because incisions and scars may differ between groups. That is why the size of the wounds in both arms will be intended to be as small as possible, about 10 cm in the ministernotomy and 13-15 in conventional surgery. With these measures we will try to reduce the risk of bias, which will always be present in this type of study involving surgical procedures. The outcome assessor is the Hospital Clinical Trials Data Monitoring Unit, independent from Sponsor, which reviews and confirms all the outcomes and endpoints values every three months.

2.2. Regarding the rationale for using AKIN criteria. Please provide this statement in the manuscript

"AKIN was used in VARC 2 criteria according to ESC/EACTS societies, and it is the only way to compare our results with previous reports/trials of TAVI"

Response: We accept the recommendation and have provided this statement in the text on page 10.

Otherwise, I find the manuscript acceptable.
3. Reviewer #4 point-by-point responses:: Overall a good revision especially the statistical section, however, minor issues still remain.

For future reference, provide a version with marked changes throughout the manuscript. As the current version is, it is not clear what has been added. However, there exists disagreement between point-by-point response and the manuscript.

Response: We accept the recommendation. We have included the changes highlighted in this review.

3.1 The authors argument that TAVI is advocated on the basis equal complications but shorter recovery and improved QOL (1 month) although only shown as secondary outcomes. This is the valid and relevant argument. Therefore, write this in the text instead of the current poorly formulated text with conflicting versions R1, R2 and R3.

QOL have always been relevant to the patient, however, clinicians have not given it relevant focus.

Response: We accept the suggestion and rewrote the sentence:

“QOL have always been relevant to the patient, however, clinicians have not given it relevant focus, and it is usually better and statistically significant in the first month in favour of TAVI [17,18], with all data coming from secondary analysis, not primary endpoints. Patient quality of life reported outcomes, were selected to be the primary endpoint because if similar recovery time and QOL as TAVIs is demonstrated, MS provides the capacity of implantation of more durable valves, therefore, it would be used in low and intermediate risk patients given the unknown long term durability of TAVI valves after 5 years. To date, however, there has been no specifically QOL designed study. For all of these reasons, we designed this clinical trial to compare the QOL of MS versus FS. Surgery satisfaction and morbimortality outcomes will be already measured”

3.2 Please provide concrete corrections instead of mentioning something has been performed to the manuscript. Again a version with marked changes is relevant so the review process can be transparent.

Response: We have now highlighted the modified text.

3.3 This issue has not been addressed. If the authors cannot provide a proper reference then simply write it, so it is transparent.
Response: We cannot provide a proper reference. The only reference was the one already provided. We have decided to delete this reference.

3.4 Fair if reference 26 is the SATISCORE. However, if you have a reference then use it in the body of the manuscript. Reference 26 is only mentioned in the sample size calculation on a topic of EQ-5D-5L.

Response: We apologize for the mistake. The Satiscore reference is now reference number 25.

3.5 How was the manuscripts modified?

Response: We answered this question in point 1.3, and we added this explanation on page 7: “The patient is blinded with respect to the treatment received up until hospital discharge. All wounds will be covered up to this moment with standardised wound dressings. There is a great difficulty in blinding surgical procedures for a long time, due to the need to provide a hospitalization report letter, and because incisions and scars may differ between groups. That is why the size of the wounds in both arms will be intended to be as small as possible, about 10 cm in the ministernotomy and 13-15 in conventional surgery. With these measures we will try to reduce the risk of bias, which will always be present in this type of study involving surgical procedures. The outcome assessor is the Hospital Clinical Trials Data Monitoring Unit, independent from Sponsor, which reviews and confirms all the outcomes and endpoints values every three months.

3.6 Good additional patients are included if drop-out or exclusion should occur.

Where specifically is this mentioned in the manuscript?

And essentially what time-point will be considered for additional inclusion. 1 month, 6 months or the relevant 12 months assessment?

Response: We have responded to this in the in the manuscript on page 9:” If drop-outs or exclusions occur during the protocol, additional patients will be recruited until a minimum of 96 patients is achieved, additional inclusion will be considered again for each patient not achieving a one year follow-up assessment”.

Thank you again for your attention.