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

Authors:

EMILIANO RODRIGUEZ-CAULO (erodriguezcaulo@hotmail.com)
Ana Guijarro-Contreras (anaguij@gmail.com)
Juan Otero-Forero (juanjoseoteroforero@yahoo.es)
María Mataró (mjmataro@hotmail.com)
Gemma Sánchez-Espín (gemmase@hotmail.com)
Arantza Guzón (arantza605@gmail.com)
Carlos Porras (capoma@yahoo.es)
Miguel Such (drsuch@hotmail.com)
Antonio Ordóñez (ranonet@hotmail.com)
José Melero-Tejedor (makjom@hotmail.es)
Manuel Jiménez-Navarro (mjmeneznavarro@gmail.com)

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Author’s response to reviews:

Dear Reviewers:

Thank you for the review of our manuscript and for the suggestions that will for sure improve its quality. After the changes, and with over 90% of your suggestions included, 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) Reviewer #1 point-by-point responses:

1.1-Traditionally aortic valve surgery is done through a full sternotomy that is easy to perform. This incision is characterized by the aesthetic problem, leading to the search for technical alternatives such as the one proposed by the present investigation. The QUALITY-AVR Trial is a single-blind, single-center, independent, pragmatic randomised clinical trial comparing ministernotomy ("J" shaped upper hemisternotomy toward right 4th intercostal space) versus full sternotomy in patients with isolated severe aortic stenosis scheduled for elective aortic valve replacement. This is a simple but relevant proposal, as well as having the profile of TRIAL. It may be necessary to improve the quality of the figures.

Response: Recommendation accepted. Figures are now with 300 dpi.

2) Reviewer #2 point-by-point responses:

Major Compulsory Revisions:

2.1. The study design was a single-blind, single center, randomised clinical trial. I am wondering if it is a real single-blind clinical trial as surgeon and patient would realize the FS vs. MS after surgery and masking of the surgeon and patients would be difficult.

Response: In our study it is the patient who is blinded until Hospital discharge. Our Institutional Review Board recommended this denomination instead of unblinded.

2.2. Sample size was determined for primary end point with an alpha error of 0.05 and with a power of 90% in detecting differences between intervention groups ≥0.10 points in change from baseline quality of life Questionnaire EuroQOL-index (EQ-5D-5L®), measured at 1, 6 or 12 months. The first concern is which time point would be considered as for the measurement of comparison? Two groups of 48 patients are necessary for a minimum of n=96 patients. In view of possible losses to follow-up, 100 patients will be randomised. The potential loss of follow-up or drop is less 10%, of which is relatively low than the average loss in clinical trials. In addition, several secondary points were clearer than the primary end point as the determination of sample size and might be better when compared to the primary end point as its clinical importance.

Response: A previous study of our team showed only 1% follow up loss after AVR surgery during the last 5 years of this study, so that we decided to expect an increase of the follow up loss rate of 4%, if not, an increase of patient recruitment is planned in order to sum up 96 patients in total.

The variable Quality of Life (QOL) has never been measured comparing Ministernotomy (MS) vs Fulls Sternotomy (FS). Transcatheter Aortic Valve Implantation (TAVI) treatment shows
better QOL at 1 month but not at 6 or 12 months. This is why we decided to perform the QOL measurements at these time intervals, to allow a more realistic comparison with TAVI. If MS provides similar QOL outcomes, MS would be the Control Group for future Low to Intermediate Risk trials. If we obtain positive results, this trial could be an incentive to perform a large multicentric trial with mortality as the primary endpoint (the number of patients needed is around 2,500).

2.3. Both groups of patients will receive clinical follow-up and complete the EQ-5D-5L® quality of life questionnaire at 1, 6 and 12 months, and SATISCORE® at 1 and 6 months. Why did not add an additional 12-month of SATISCORE® questionnaire assessment?

Response: Satisfaction with the surgery is not expected to improve after six months, and it is the recommendation of the SATISCORE creator questionnaire (1-6 months, reference number 26). Additional 12-month of SATISCORE® would not add any relevant information.

2.4. The primary endpoint measure is to detect differences between the two intervention groups greater than or equal to 0.10 points change from the baseline questionnaire EQ-5D-5L® Index, at 1, 6 or 12 months after the surgery. The 0.10 point change is really less different and significant? In addition, authors used the quality of life as the major determination as it would be hard to actually reflect the superiority of MS to FS in clinical practice.

Response: Yes, QOL is a very important outcome for patients. If safety and outcomes were quite similar in previous trials, QOL may be the “difference to consider” when choosing the type of surgical approach as the Gold Standard.

The Minimal Important Difference (MID) in previous research was 0.08 points on the EQ-5D index for cancer, and 0.10 points for patients who suffered a stroke [28]. This difference was also 0.06 points (CI 95% 0.02-0.10) on the EQ index during the first month in the PARTNER 1 (transfemoral TAVI versus FS)[ Ref 17], and 0.12 (CI 95% 0.08-0.16) in the CoreValve PIVOTAL trial study[ Ref18]. As there was no existing specific calculation of MID for cardiology patients with severe aortic stenosis, we arbitrarily established the interval of 0.10 points on the EQ-5D index (the mean value of previous studies). We believe 0.10 points is a really significant difference in QOL improvement.

5. Authors anticipate this trial could modify the surgical "Gold-Standard" for aortic stenosis surgery, and subsequently the need to change the control group in transcatheter aortic valve implantation trials. Please describe in more details how this trial would change the control
Response: Patient quality of life reported outcomes were selected to be the primary endpoint because at present, cardiologists argue that TAVI are better, due to the fact that with the same results in complications in the short term, the recovery time is shorter and with better and improved quality of life. All data came from secondary analysis, not primary endpoints.

We added in the manuscript: “QOL matters a lot to patients nowadays, and is usually better and statistically significant in the first month in favour of TAVI”.

6. In abstract section: to date, few clinical trials have been conducted that compare AVR surgery using MS versus FS, and no significant differences have been found, due to inadequate design, a lack of statistical power or a sample size too small for the primary endpoint of mortality, although significant differences did exist in morbidity on the side of MS (lower rates of pain, transfusions, bleeding, mechanical ventilation time, stay in intensive care and hospital...etc.). However, the current study design still not yet provide the most important information or elements to readers or even probably lead to misunderstanding regarding the role between FS and MS under the current study design.

Response: We think that it is well explained in the text. The most important information in our study design is that it establishes a difference in QOL measurements, because the study is sufficiently powered to do so. No differences in hard endpoints were obtained in previous trials.

In every previous trial, it seems to be a benefit in the MS, but excepting less bleeding, each study indicated a different one.

The role of MS is: if a QOL similar to TAVI is shown against FS, MS provides the capacity for the implantation of better and more durable valves, therefore: Why not try it in low and intermediate risk patients given the non-proven long term durability of TAVI valves?

3) Reviewer #3 point-by-point responses

An interesting trial about the quality of life, satisfaction and outcomes after ministernotomy versus full sternotomy access in isolated aortic valve replacement procedures.

The Trial is well designed. However, some English language editing is needed for improvement of the presentation.
3.1* Background

This section could be rewritten to provide more details regarding the primary outcome and less details regarding secondary outcomes such as Mortality.

Response: We add these details in the manuscript: “Nowadays QOL matters a lot to patients, and it is usually better and statistically significant in the first month in favour of TAVI [17,18]. If similar QOL as TAVI’s is demonstrated, MS provides the capacity of implantation of more durable valves, so, it would be used in low and intermediate risk patients given the unknown long term durability of TAVI valves beyond 5 years”.

We talk about mortality due to the great difficulty to perform a trial powered to detect differences in it.

3.2* Design

This study is single-blind. However, no details regarding the blinding process is given. A separate section for blinding could be added, delineating the different details of blinding.

Response: Only the patient is blinded regarding treatment, but only until hospital discharge. It is explained in the text. We believe that adding a section would not be very useful and we would exceed the manuscript word limit.

3.3 * Secondary Outcome measures

It is mentioned that the AKIN criteria was used here to define acute renal failure. However, the KDIGO criteria is the most recent update of this definition. Please provide in-text a brief statement explaining the rationale for using the AKIN criteria.

Response: 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.

3.4* Sample Size

It is mentioned that a sample size of 100 patients will be used to account for any loss to follow-up. Please provide detail regarding the plan for any loss or withdrawals from the trial.

Response: Added, including missing data management. Previous studies of our surgical team showed only 1% follow up loss after AVR surgery for the last 5 years of the study. We consider an augmentation of this rate of up to 4%, to increase the probability of success at the end of the
study. If the rate would be higher, an increase of patient recruitment is planned in order to sum up 96 patients in total.

3.5* Ministernotomy  "Use of CO2 via drain at surgeon's criterion" This statement could be rewritten to clarify the meaning.

Response: We accept the recommendation. CO2 has been used in all MS.

3.6 * Finally, please provide a SPIRIT checklist and Figure to accompany the manuscript.

Response: We added a SPIRIT figure and checklist.

4) Reviewer #4 point-by-point responses:

The current trial protocol investigates a clinically relevant problem in patients undergoing major cardiovascular surgery. The minimally invasive MS strategy is compared to the FS standard approach which even in light of the TAVI procedure is a relevant question. However, the manuscript in the current form lack important information and structure that needs to be provided. The authors could benefit from following the SPIRIT guidelines to the letter.

4.1-Title

The current title is too long and repeats itself unnecessarily. The acronym (QUALITY-AVR) should be moved before the :, and it should be mentioned the study is a protocol. A possible title could read:

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

Response: We accept to change the Title: “QUALITY of life, satisfaction and outcomes after ministernotomy versus full sternotomy in isolated Aortic Valve Replacement (QUALITY-AVR): Study protocol for a randomised controlled trial”

Abstract

4.2- The abstract is overly detailed regarding the sample size calculation which should be addressed in the method section.
The sentence line 15-17: ("J" shaped upper hemisternotomy toward right 4th intercostal space) should be deleted.

Response: We disagree with this point, we believe that this definition is very important in understanding the abstract (due to the multiple existing ways to perform a MS), as well as the sample size calculation with a 90% power (and not the usual 80% power).

4.3- Drop the notation Major secondary endpoints. The sentence describing secondary endpoints is cryptic and should be rewritten.

The first sentence in the abstract discussion describes several aims, which should be broken into separate sentences. The wording a "positive" result is unfortunate and should be rephrased.

Major issues

Response: We accept your recommendations. The sentence has been rewritten in the manuscript.

BACKGROUND

4.4* In all a well written background. It is clearly argued that MS is superior to FS in many aspects; however, the reason to choose a patient reported outcome as the primary outcome is not clear. It could be argued that the proper trial to preform would be the trial with mortality as an outcome. As the background reads now, it seems the patient reported approach was chosen in light of the lower sample size and feasibility to perform a trial in a single centre setup.

A patient centred approach is highly relevant, however, this choice needs to be argued in the background.

Response: Patient quality of life reported outcomes, were selected to be the primary endpoint because currently cardiologists argue that TAVI is better because with the same results in complications in the short term, the recovery time is shorter and better with improved quality of life. All data came from secondary analysis, not primary endpoints.

We add in the manuscript: “QOL matters a lot to patients nowadays, and is usually better and statistically significant in the first month in favour of TAVI. 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”.
4.5* Page 4 line 9-16 is one long sentence and needs to be broken into two. Furthermore, it is unclear from the sentence if MS was apart of the PARTNER or PIVOTAL trials. This needs to be clear.

Response: It is explained that MS was never compared in a trial with TAVI. We divided the sentence.

4.6* Again "quality of life, satisfaction and outcomes” are all mixed into one. These needs to be described as separate specific aims.

Response: We accept the suggestion and rewrote the sentence.

METHODS

4.7* The structure of the method section should be rearranged so it follows the SPIRIT statement.

Response: All items were checked in the SPIRIT checklist (added as additional file 1).

4.8* No SPIRIT figure is provided which is essential to follow the SPIRIT statement which is required by the Trials Journal.

Response: We added a SPIRIT figure and checklist.

4.9* The method section mentions a pragmatic and independent design. How is this and why is it relevant for the current trial? Does the authors mean researcher initiated or?

Response: A pragmatic trial is described in the presented reference nº 19 (Ford I, Norrie J. Pragmatic Trials. N Engl J Med 2016; 375:454-463.) Pragmatic trial means a trial designed to show the real-world effectiveness of the intervention in an “all comer” population. Independent means we do not have any industry funding.

4.10* The authors have a tendency to write to long sentences, which makes the manuscript tedious to read. Throughout the manuscript this needs to be addressed.

Response: We modified the sentences as much as possible, to avoid exceeding the word limit.
4.11* The "EuroQoL 5" was chosen as it was tested in a Spanish population. Is this the same as a validated translation. Please give references in this regard. The current reference is internet reference to a Spanish website, which is irrelevant to the reader.

Response: We believe it is very relevant because it refers to the Ministry of Health of the Government of Spain webpage, which is the institution that holds such results, and where they can be consulted.

4.12* No reference is given to the SATISCORE®. Furthermore it is unclear, how the total score is 100 when the text mentions 20 statements with 6 possible outcomes (120 total). More specific information needs to be provided.

Response: Ref nº 26 was SATISCORE reference. It consists of 20 statements (Table 1) with 6 possible responses on a Likert scale: 0: no Response (no points), 1: very unsatisfied, 2: unsatisfied, 3: don’t know, 4: satisfied, 5: very satisfied. Scores range from 0-100 and it is valid specifically to evaluate the satisfaction of patients who have undergone heart surgery.

4.13* Multiple assessment are performed on multiple outcomes, however, the timing is unclear from the current manuscripts. Produce a spirit figure and reference it actively to help the reader instead of confusing the reader.

Response: We added a SPIRIT figure (Fig 2).

4.14* In the "selection of patients" section: "current clinical practice and meet the inclusion and exclusion criteria" drop "the inclusion and" as they are mentioned in the text just before.

Response: We modified this sentence.

4.15* Block randomisation is mentioned. Why was this chosen in a single centre study? Do the authors mean stratification on a given variable instead?

Response: It is one of the types of randomisation independently of unicentric or multicentric studies. There was no stratification in the randomisation; it was only a simple in block randomisation.
4.16* AleatorMetod is mentioned as a computer randomisation program. Give a reference or delete if not relevant.

Response: We accept the suggestion and rewrote the sentence.

4.17* Allocation concealment is briefly described as performed by an administrative officer. Who are the medical personnel? Is the patient intended to be blinded? If so describe in detail how this is achieved. The study is described as single-blind, however, no follow-up description is given. Is the outcome assessor blinded and who assess the different outcomes? Provide sufficient detail so the study could be replicated.

Response: The patient is blinded until discharge from hospital where his report is delivered. The outcome assessors are two staff doctors who are unaware of the type of surgery performed on the patients at the time of the questionnaire (usually by telephone interview as stated in the protocol). The data are subsequently reviewed by the Clinical Trials Unit, independently, every three months.

We modified the manuscript.

4.18* The study endpoint is written in bold text. Why is this? The description is of two interventions, however, the current trial test MS (active treatment) against FS (control/standard of care) write this instead.

Response: We accept the suggestion and rewrote the sentence.

4.19* Several combined endpoints regarding complications are mentioned. Furthermore, the MAC are nested within the other. This constitutes a reporting issue and should be discouraged. Composite outcomes are problematic as the direction of interventions effect could balance each other out. So separate incidences should be reported.

Response: We accept the suggestion and rewrote the sentence. All separate incidences would be reported.

4.20* Nosocomial infections are mentioned, however, the time period is one month postoperatively. Does the authors expect the patients to be hospitalized for an entire month. Are infections at home not a relevant complication?
Response: Nosocomial infections are infections acquired during the index hospitalization, or even up to 12 months after surgery in case of early endocarditis according to VARC criteria in the case of cardiac infections. All infections or complications would be considered relevant and therefore will be registered.

4.21* Postoperative stay in total and in the intensive care unit are mentioned as outcomes. The correct terminology is length of stay (LOS) and should be changes accordingly. When reporting hospital stay it is vital to report if the unit had ERAS protocols in the department and what were the discharge criteria. This could be provided as supplementary material.

Response: We accept your suggestion and used more accurate terminology. Hospital discharge depends on Surgeon’s criteria and patient status, without ERAS protocols. We believe that this is not relevant for the protocol.

STATISTICAL ANALYSIS and sample size

4.22* As the authors also correctly address the SD of 0.15 and MID of 0.10 are arbitrarily chosen on the best available information resulting in a 2 x 48 setup and planned inclusion of 100 patient. I.e. expected drop-out of 4 patients over 12 month period.

Such a low drop-out rate is overly optimistic and will only likely result in an underpowered trial. Will additional patients be recruited.

Response: In former aortic valve surgery studies previously published by our group, follow up loss was 1%. If drop-outs or exclusions occur during the protocol, additional patients will be recruited until a minimum of 96 patients is achieved.

4.23* The authors have chosen a repeated measure design (1, 6, and 12 months), however, not specified a repeated measure analysis for the primary outcome. T-test will be used (depending on distribution) to test group differences, however, a mixed model analysis would be a more appropriate analysis model.

Response: It is explained and already planned in line 42 on page 10 (ANOVA model for analysis of variance for repeated measures).
4.24* Distribution of data will be tested using the Kolmogorov-Smirnov test. Why not use the histograms or QQ plots to asses distribution. If relevant do the authors intend to use transformation of data?

Response: Kolmogorov-Smirnov test, histograms or Q-Q plot are three ways to detect normality or not. The preferred is irrelevant for the study, if normality is well tested. Our biostatisticians check all three in all of the cases. Data transformation will not be attempted, we will use non parametric tests if needed. We added this information to the manuscript.

4.25* No information regarding how "missing data" will be handled is provided. This needs to be described in detail.

Response: Intention to treat analyses can improve management of missing data. Nevertheless, we add to the paper according to our protocol:

“Differences between MS and control FS group scores at each follow-up time point will be estimated with longitudinal random-effect growth curve models that will be fit to the repeated measurements for each health status outcome. These longitudinal analyses will use all available quality-of-life data, including data from patients who subsequently will die, withdrew, or will be lost to follow-up, and accommodate missing data under the missing at random assumption. Variables included in the models were treatment assignment, prespecified patient characteristics (age, sex, EuroScore), follow-up time and interactions between treatment and time.

These models were used to calculate mean between-group differences for the EQ-5D index score and the individual subscales at each follow-up time point, as well as the associated 95% confidence intervals (CIs) and P values.

To examine the potential impact of missing data, which, given the illness severity of the trial population, would most likely not be missing at random, we will repeat growth curve analyses after imputing missing scores among surviving patients as the lowest reported score among respondents within each treatment group for each respective time point. We also examined the magnitude of potential survivor bias by comparing the mean baseline scores between treatment groups for the subgroups of patients with available quality-of-life data at each successive follow-up time point.”

4.26* "Effectiveness of treatment" is described in the end of the statistics section, however, no measure is given.
Response: Effectiveness means surgery success regarding morbimortality (in the “as treated” population) as described in the manuscript.

4.27* Description of the intention to treat and per protocol is insufficiently described. This needs to be detailed and related to the planned analysis.

Response: We added: The intention to treat population is defined to include all randomised subjects. This population will be used for endpoint analyses. The as treated population (“per protocol”) is defined to include all subjects actually undergoing the index procedure. This population will be used for the analysis of adverse event analyses.

4.28* The statistical section could greatly benefit from a consultation from a statistician and be described in a detailed analysis plan.

Response: Statistical Plan was practically copied from PARTNER 2A Trial (TAVI vs FS-AVR) for posterior comparison and yet explained and revised by a statistician. All data are in the full protocol.

SUMMARY AND TRIAL STATUS

4.29* No details regarding data-sharing policy is described in the current protocol. This needs to be described in detail.

Response: We added in the manuscript: Data-Sharing Policy will be under request to the sponsor and publicly shown in clinicaltrials.gov.

Thank you again for your attention.