PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Lenient rate control versus strict rate control for atrial fibrillation. A protocol for the Danish Atrial Fibrillation (DanAF) randomised clinical trial
AUTHORS	Feinberg, Joshua; Olsen, Michael; Brandes, Axel; Raymond, Ilan; Bjorn, Walter; Nielsen, Emil; Stensgaard-Hansen, Frank; Dixen, Ulrik; Pedersen, Ole; Gang, Uffe; Gluud, Christian; Jakobsen, Janus

VERSION 1 – REVIEW

REVIEWER	Jo Jo Hai The University of Hong Kong, Hong Kong SAR
REVIEW RETURNED	28-Sep-2020

GENERAL COMMENTS	This proposed study seeks to compare the effect of lenient rate control versus strict rate control of AF on QOL. The authors aim at mimicking the real-life situation in the entire study. As such, they use a standard 12-lead ECG instead of Holter monitoring to guide treatment, and measure activities by accelerometer and ET by 6MWT instead of performing a cardiopulmonary exercise test. The follow-up duration is 3-year, which is considered appropriate for this type of study. While the research questions and methods are clear, there are several major flaws in this protocol from the clinical point of view. Here are my comments: 1) The authors compare the effect of lenient rate control and strict rate control in unselected patients with persistent or permanent AF. However, previous studies have suggested that patients who have heart failure may require faster basal heart rate than their non-heart failure counterparts to maintain adequate cardiac output. Although the authors stated that heart failure patients who are 'dependent on fast ventricular rate' to maintain cardiac output will be excluded, the word 'dependent' is vaguely defined, and not formally assessed. Including both patients with and without heart failure may yield erroneous results. If the authors cannot provide a reliable definition and formal assessment of the 'dependency on ventricular rate' in heart failure patients, they should consider limiting the study to those who have normal or near normal LVEF, or at least stratifying the patients according to LVEF. 2) Similarly, it may be better for the authors to clearly state the type and degree of valvuar dysfunction that will be excluded in this study.

	3) The authors stated that 'pacing therapies, alone or with atrioventricular node ablation, are utilised as indicated in the view of the treatment provider.' However, the authors did not specify the treatment of this group of patients. In particular, I do not understand how patients who undergo AVN ablation can continue this study. Obviously it is not acceptable to prescribe these patients different pacing rate, since pacing itself can affect patients' symptoms and cardiac function (particularly with RV apical pacing). Do the authors have a pre-specified plan on how to manage / evaluate this group of patients? 4) Similarly, treatment of patients who undergo cardioversion (particularly those who remains in sinus rhythm afterwards) should be specified. 5) I can understand why the authors used ECG to guide treatment and accelerometers / 6MWT to evaluate activities / exercise tolerance. However, in a research setting, holter / cardiopulmonary exercise test should be considered to provide additional information for us to interpret and understand the results. Other minor comments: 1) Please state the date of study commencement and end. 2) Please correct all typos in the manuscript.

REVIEWER	D. George Wyse University of Calgary Department of Cardiac Sciences/Libin Cardiovascular Institute Canada
REVIEW RETURNED	01-Oct-2020

GENERAL COMMENTS	Synopsis The authors describe an RCT to compare the impact of strict vs. lenient rate control on quality of life in patients with a mixture of persistent and permanent AF. Critique Major The authors have identified an important and under-researched aspect of the management of atrial fibrillation. In view of the large proportion of AF patients treated with rate control, it is indeed astonishing that so little research has been done to explore important unresolved issues. It is also true that the major consideration when choosing method for rhythm control in AF is symptom relief and quality of life. I would encourage them to continue with this effort to fill some gaps in knowledge but to take into consideration a number of the issues I have outlined below in planning their trial. My general sense is that these investigators would benefit from some advice by an experienced trialist or at least use of a template model from a previously successful trial. I am not familiar with the intent of this review and the aims of this journal. It seems impossible to separate a critique of and judgement of the acceptability of the manuscript without pointing out what I perceive as difficulties with the protocol design. My comments are a mixture of both a critique of the manuscript and a critique of the protocol.

	In general, the manuscript if fairly clear but seems lacking in brevity at times and lacks focus on detail at other times. The presentation seems scrambled and does not seem to follow a logical pattern. For example, the introduction seems too long but the description of the Data and Safety Monitoring Committee is relegated to the Supplementary material and not mentioned at all in the main manuscript. The description of obtaining informed consent makes the process seem inadequate from my experience in doing RCTs. It seems to me that research candidates should be provided with printed material, rather than a simple oral discussion as it is currently described. The consent form itself is terse and very brief. I am pretty sure it would not be approved by a REB or regulatory body with which I have ever worked. There is repeated mention of the Zealand Regional Ethics Committee throughout the manuscript but exactly what its role has been and will be is not clear. It is also not clear how it will interact with the DSMC (reporting of SUSAR?). An actual diagram of the committee structure and organizational aspects of the trial would be helpful in Supplementary File 8. The mixing of persistent and permanent AF may not be a good idea and is a potential pitfall. If there is an unequal split in the two types of AF after randomization, the results may be confounded. In addition to site and age, they probably also need to stratify their randomization by persistent vs. permanent AF. In fact, this may be an even more important stratum than age or site (and is probably related to age) and would then allow a prespecified subgroup analysis of the two types of AF. I would recommend confining subgroup analysis to the randomized strata. The multiple subgroups proposed later seem excessive for the proposed sample size of 350 subjects. In general, the efforts to reduce bias in a study with incomplete blinding, including the analysis plan are a valiant effort. Unblinding, even partial is a greater problem when the primary outcome is quality of life, which is a largely subjective outcome. However, the study is probably not as free from bias as the investigators suggest – as treating physicians are unblinded, they will be tempted to lower the heart rate further if the subject continues to complain of symptoms (in spite of the protocol discouraging doing so). It will be important to compare actual heart rate achieved in the two groups, especially at the point in time that the primary outcome (quality of life) is assessed. If the heart rates actually achieved are not substantially different between the two groups (see comment below about heart rates in RACE II), the superiority hypothesis may be doomed. Given that “lenient” in this protocol is not <110 but 80-110, that seems a likely outcome. I think the authors need to specify a little more precisely exactly how the resting heart rate will be pursued in the strict group. A heart rate that is too low can also cause symptoms. Even better, to parallel the lenient group, why not a range to 60 to 80 rather just <80? Given recent evidence of the advantage of rhythm control rather than rate control (EAST), the authors need to consider specifying these patients have recurrent AF and also specify the entry level age as something more like ≥50 years.

	In the case of digoxin use, a therapeutic target range of serum trough digoxin level should be recommended. I cannot comment in a meaningful way about statistics. I think a statistical review would be helpful. However, there a number of things planned that make me generally uneasy. The sample size calculation seems overly optimistic. The selection of a clinical meaningful difference of 3 points in the SF-36 physical functioning score is rather meagre. A poll of QoL experts' opinions to buttress the choice of this number would be helpful. The estimates of dropouts and crossovers may be too optimistic as well. There are other troublesome aspects with the protocol described. These include: too many "secondary/exploratory outcomes" (you cannot answer every question with a single protocol); too many subgroup analyses planned; a per protocol analysis; is the primary outcome to be analyzed as a continuous or discrete variable? Minor Page 6 Last Para Line 45: With respect to guidelines, the Canadian Cardiovascular Society recommendation is not <110 but <100. That recommendation is based on the fact that although the RACE II protocol recommended <110, the heart rate achieved in RACE II was actually much lower than 110 and over time decreased further and averaged 86 (75 for strict) at 1 year, 84 (75) at 2 years and 85 (76) at end of study (see RACE II Supplemental Material). Very few patients had a heart rate >100. I applaud the fact that resting heart rate will be measured at several time intervals (see Table 1). It will provide an estimate of protocol deviation. Page 13 Line 45: What is the correct spelling? In English I think it is amiodarone.

REVIEWER	Dan Wright UNLV, USA
REVIEW RETURNED	12-Oct-2020

GENERAL COMMENTS	I am a quantitative methodologist, not a medical expert, so focused on the methods and statistical plans. Regarding the methods, the plan seems appropriate. The authors state the SF-36 is of primary interest, but presumably this is a proxy for things like mortality. There are many secondary variables. The authors need to describe how they will avoid p-fishing on these (i.e., dealing with dozens of hypothesis tests ... standard adjusting procedures would lower the power to such a degree for these to not be of value). On the statistical procedures, the authors say that they will publish the plans later. Normally with registered reports this is where I focus my review. Without this I can't say whether the authors' plans are appropriate. The author list is fairly long, so I assume there are a couple of biostatisticians on this list.

REVIEWER	Antonio Nenna Università Campus Bio-Medico di Roma, Rome, Italy
REVIEW RETURNED	21-Oct-2020

GENERAL COMMENTS	Sample size calculation is performed on the primary endpoint (SF-36/PC score). Your sample size calculation should be performed to compare 2 scores, rather than 2 continuous outcomes (as you performed, see below). In case of ordinal data (such as those for quality of life scores), different approaches are required. Also, an "a priori" power of 80% is generally poor. Also, some patients are lost to follow up or exit the study, and should be taken into account (generally 5-10% in clinical trials). Sample size calculation should be revised. Estimated sample sizes for a two-sample means test t test assuming sd1 = sd2 = sd Ho: m2 = m1 versus Ha: m2 != m1 Study parameters: alpha = 0.0500 power = 0.8000 delta = -3.0000 m1 = 3.0000 m2 = 0.0000 sd = 10.0000 Estimated sample sizes: N = 352 N per group = 176

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jo Jo Hai
Institution and Country: The University of Hong Kong, Hong Kong SAR
Please state any competing interests or state ‘None declared’: None declared

This proposed study seeks to compare the effect of lenient rate control versus strict rate control of AF on QOL. The authors aim at mimicking the real-life situation in the entire study. As such, they use a standard 12-lead ECG instead of Holter monitoring to guide treatment, and measure activities by accelerometer and ET by 6MWT instead of performing a cardiopulmonary exercise test. The follow-up duration is 3-year, which is considered appropriate for this type of study.

Our response: We thank the peer reviewer for these thoughtful comments.

While the research questions and methods are clear, there are several major flaws in this protocol from the clinical point of view. Here are my comments:

1) The authors compare the effect of lenient rate control and strict rate control in unselected patients with persistent or permanent AF. However, previous studies have suggested that patients who have heart failure may require faster basal heart rate than their non-heart failure counterparts to maintain adequate cardiac output. Although the authors stated that heart failure patients who are 'dependent on fast ventricular rate' to maintain cardiac output will be excluded, the word 'dependent' is vaguely defined, and not formally assessed. Including both patients with and without heart failure may yield erroneous results. If the authors cannot provide a reliable definition and formal assessment of the 'dependency on ventricular rate' in heart failure patients, they should consider limiting the study to those who have normal or near normal LVEF, or at least stratifying the patients according to LVEF.

Our response: We agree that it is unknown whether patients with and without heart failure respond differently to different rate targets and this is part of the motivation behind this trial. We therefore plan to assess the validity of this hypothesis in a subgroup analysis.
Furthermore, we also agree that there is a theoretical concern that some heart failure patients (and also patients with other comorbidities) require a faster basal heart rate and cannot be randomised to a strict rate control target. However, we believe that comorbidity status and severity alone is not enough to determine whether a participant should be excluded. Instead, we have designed this exclusion criteria to
focus on an individual assessment if a possible participant requires a higher basal heart rate and hence cannot be randomised to the strict rate control group.
We believe this approach is the right approach as it mimics clinical practice. In clinical practice (and in our trial) the treating physician will consider whether the patient in question depends on a faster heart rate based on a comprehensive, individual assessment. The assessments will weigh factors such as type of comorbidity, severity of disease, echocardiographic outcomes, and previous number of hospitalisations.
We recognize that this may lead to some degree of clinical heterogeneity in the sense that e.g. some patients in NYHA IV will be excluded and some included and some might consider this as losing 'scientific rigidity'.
We also recognize that this individual assessment was not clear from our manuscript and we have now revised it accordingly.
We believe this is justified in making the trial more pragmatic and more like clinical practice.5 6

To accommodate the peer reviewer's comment, we now also stratify for LVEF (EF ≥40% and EF<40%).
As this is a randomized clinical trial, the pragmatic handling of participants may lead to some heterogeneity in the composition of participants, but the randomization will level any such heterogeneity out due to the randomisation.

2) Similarly, it may be better for the authors to clearly state the type and degree of valvuar dysfunction that will be excluded in this study.
Our response: Please see our answer above.
3) The authors stated that ' pacing therapies, alone or with atrioventricular node ablation, are utilised as indicated in the view of the treatment provider.' However, the authors did not specify the treatment of this group of patients. In particular, I do not understand how patients who undergo AVN ablation can continue this study. Obviously it is not acceptable to prescribe these patients different pacing rate, since pacing itself can affect patients' symptoms and cardiac function (particularly with RV apical pacing). Do the authors have a pre-specified plan on how to manage / evaluate this group of patients?
Our response: We thank the reviewer for this important comment and agree that our intentions may have been unclear from the manuscript.
The trial aims at assessing assignment to either a strict or lenient rate control. Initially, the goal is for all participants to achieve their allocated rate control target through rate control drugs. If participants remain symptomatic, the attending physician may in cooperation with the participant decide on the best way moving forward (AV node ablation, rhythm control, etc.) and are no longer obliged to pursue the allocated rate control target. Further treatment will then be based on current European guidelines. Hence, a specific protocol for how to manage patients beyond the initial rate control drug therapy is not part of the trial. Participants will then be
analysed on an intention to treat basis. Secondly, we will perform a per protocol analysis. This has now been clarified in the manuscript.
We have now removed the sentence the peer reviewer refers to in order to avoid

confusion and added the following sentence to the section:
"These evaluations may be followed by adjustment of rate control drugs, rhythm control (electrical cardioversion, arrhythmia surgery, rhythm control medications) or atrioventricular node ablation. In case of the need for rhythm control or atrioventricular node ablation, the allocated heart rate target is no longer relevant in management."
4) Similarly, treatment of patients who undergo cardioversion (particularly those who remains in sinus rhythm afterwards) should be specified.
Our response: We thank the peer reviewer for this comment. Please, see our answer above. The heart rate targets will not apply in such cases.
5) I can understand why the authors used ECG to guide treatment and accelerometers / 6MWT to evaluate activities / exercise tolerance. However, in a research setting, holter / cardiopulmonary exercise test should be considered to provide additional information for us to interpret and understand the results.
Our response: We would like to thank the reviewer for this comment. This trial is a pragmatic trial and as the peer review said, we wish to mimic a real world setting and therefore use ECG instead of Holter. However, we have now added that we will assess the actual heart rate achieved with Holter at the end of the titration phase and after one year for documentation of the actual achieved heart rate.
Other minor comments:
1) Please state the date of study commencement and end.
Our response: We do not exactly know when we will start.
We have now added that we expect it will be in January 2021.
2) Please correct all typos in the manuscript.
Our response: We have looked through the manuscript again and hopefully, no typos remain.

Reviewer: 2
Reviewer Name: D. George Wyse
Institution and Country: University of Calgary, Department of Cardiac Sciences/Libin Cardiovascular Institute, Canada
Please state any competing interests or state 'None declared': None declared

Synopsis

The authors describe an RCT to compare the impact of strict vs. lenient rate control on quality of life in patients with a mixture of persistent and permanent AF.

Critique

Major

The authors have identified an important and under-researched aspect of the management of atrial fibrillation. In view of the large proportion of AF patients treated with rate control, it is indeed astonishing that so little research has been done to explore important unresolved issues. It is also true that the major consideration when choosing method for rhythm control in AF is symptom relief and quality of life. I would encourage them to continue with this effort to fill some gaps in knowledge but to take into consideration a number of the issues I have outlined below in planning their trial. My general sense is that these investigators would benefit from some advice by an experienced trialist or at least use of a template model from a previously successful trial.
Our response: We agree this is important work. To ensure the validity of the trial, our research group is made up of representatives from the four hospitals, where the trial will run, which includes several experienced trialists. Furthermore, we are cooperating with The Copenhagen Trial Unit, a clinical trial

unit with methodological expertise and experience in conducting randomised clinical trials for decades (www.ctu.dk). We hope that our answers give the esteemed peer reviewer confidence that we have the necessary experience to run a randomised trial.

I am not familiar with the intent of this review and the aims of this journal. It seems impossible to separate a critique of and judgement of the acceptability of the manuscript without pointing out what I perceive as difficulties with the protocol design. My comments are a mixture of both a critique of the manuscript and a critique of the protocol.

Our response: We completely agree and it was exactly the intention of our submission: to get critique of our protocol to ensure that the design of the trial is as good as it can be, ensuring maximal value for the patients from the trial results.

In general, the manuscript if fairly clear but seems lacking in brevity at times and lacks focus on detail at other times. The presentation seems scrambled and does not seem to follow a logical pattern. For example, the introduction seems too long but the description of the Data and Safety Monitoring Committee is relegated to the Supplementary material and not mentioned at all in the main manuscript.

Our response: We have tried to strike a balance between the different sections. We appreciate the comments of the peer reviewer and have now added text to both the main text and the supplementary appendix. Previously, this was already stated in the main text:

"Data monitoring

A data monitoring committee (DMC) independent from the sponsor and the investigators will be created. The DMC will be free of conflicts of interest. The DMC will be responsible for conducting an interim analysis after 50% of participants have been included. The DMC will make recommendations to the steering committee that will ultimately

decide if the trial should stop or continue (further details in supplementary file 6)."

We now write in the main manuscript:

"A data safety monitoring committee (DSMC) independent from the sponsor and the investigators will be created. The DSMC will be free of conflicts of interest. The DSMC will be responsible for conducting an interim analysis after 50% of participants have been included and monitor if the trial still holds scientific merit. The DSMC will decide when / if a new interim analysis should be performed. The DSMC will make recommendations to the steering committee whether the trial should stop or continue (further details in supplementary file 6)."

The description of obtaining informed consent makes the process seem inadequate from my experience in doing RCTs. It seems to me that research candidates should be provided with printed material, rather than a simple oral discussion as it is currently described. The consent form itself is terse and very brief. I am pretty sure it would not be approved by a REB or regulatory body with which I have ever worked. There is repeated mention of the Zealand Regional Ethics Committee throughout the manuscript but exactly what its role has been and will be is not clear.

Our response: We completely agree that only an oral discussion of the trial with a possible participant would be very inadequate. Originally, we had written the following description of the informed consent procedure:

"Procedures for informed consent

Participants will receive written information either immediately after being identified as a possible candidate or during a private, information session where verbal information is given. The information session will take place in an undisturbed environment. The information will be given by the project coordinator on site or medical personnel with equivalent prerequisites for conveying the project. Potential participants will be informed that they can bring a third party if they wish so. The participants will be given up to three weeks to consider participation depending on when they choose to schedule the information session. There will be a minimum of 48 hours from the information session to the obtaining of informed consent."

We have now added to the above, in order to further clarify that participants receive written material in addition to an oral information session:

“Participants will receive printed material containing details of each study visit, the design and rational of the trial, participant rights (such as the right to withdraw), possible adverse effects of medication, and more. The printed material will be given either immediately after being identified as a possible candidate or during a private, information session where verbal information is given and the participants can ask any questions they may have. The information session will take place in an undisturbed environment. The information will be given by the project coordinator on the site or medical personnel with equivalent prerequisites for conveying the project. Potential participants will be informed that they can bring a third party if they wish so. The participants will be given up to three weeks to consider participation depending on when they choose to schedule the information session. There will be a minimum of 48 hours from the information session to the obtaining of informed consent.”
We have also added a brief description of the process for ethical approval in Denmark. The “Regional ethics committee” is the regulatory body that approves research projects in Denmark. It approves the project after review of all material. Further, we are required to report any SAE (including SUSARs) within a week and provide a yearly report of SAE. They also have the option of conducting audits if they choose to do so.

We have now provided a further explanation of the role of the “regional ethics committee”:
“The trial protocol has been approved by the regional ethics committee which is a branch of the Danish ethics committee, which is the regulatory body approving research in Denmark. As such it is independent from the trial. The committee reviewed the full protocol, the written material for the participants, the consent form and the administered questionnaires before giving approval. The ethics committee has the option of conducting an audit of the trial if it wishes to do so. The committee must be provided with a notification of any SAE including SUSARs within a week as well as a yearly report of SAE. Any changes to the approved protocol will be submitted and approved before continuing the trial.

It is also not clear how it will interact with the DSMC (reporting of SUSAR?). An actual diagram of the committee structure and organizational aspects of the trial would be helpful in Supplementary File 8.
Our response: The regional ethics committee will not interact with the DSMC. The DSMC will report directly to the steering committee.
We have now provided a diagram of the interaction between the various parts of the trial organization as well as with regulatory bodies in supplementary file 8.
The mixing of persistent and permanent AF may not be a good idea and is a potential pitfall. If there is an unequal split in the two types of AF after randomization, the results may be confounded.
In addition to site and age, they probably also need to stratify their randomization by persistent vs. permanent AF. In fact, this may be an even more important stratum than age or site (and is probably related to age) and would then allow a prespecified subgroup analysis of the two types of AF. I would recommend confining subgroup analysis to the randomized strata. The multiple subgroups proposed later seem excessive for the proposed sample size of 350 subjects.
Our response: Based on previous evidence it is unknown whether patients with persistent and permanent AF and without heart failure respond differently to different rate targets and this is part of the motivation behind this trial. We plan to assess the validity of this hypothesis in subgroup analysis. We have previously discussed if we should instead stratify the randomization by type of atrial fibrillation and heart failure status, but decided instead to stratify for site and age. We still believe that since this is a multicenter trial, we must stratify by site. In light of the peer reviewers’ comments, we will now stratify according to type of atrial fibrillation (persistent versus permanent) instead of age, and LVEF (EF ≥40% and EF<40%.
We agree that the many subgroup analyses should not be anything but hypothesis generating, to guide future trials. We have now clarified this throughout the manuscript and have removed several subgroup analyses.

In general, the efforts to reduce bias in a study with incomplete blinding, including the analysis plan are a valiant effort. Unblinding, even partial is a greater problem when the primary outcome is quality of life, which is a largely subjective outcome. However, the study is probably not as free from bias as the investigators suggest – as treating physicians are unblinded, they will be tempted to lower the heart rate further if the subject continues to complain of symptoms (in spite of the protocol discouraging doing so). It will be important to compare actual heart rate achieved in the two groups, especially at the point in time that the primary outcome (quality of life) is assessed.
Our response: We completely agree and therefore we had added that we will perform a per-protocol analysis in addition to the intention-to-treat analysis. However, given the comment of the peer reviewer regarding the multiple analyses and subgroup analyses, we have revised, when we will conduct per protocol analyses, see below.
If the heart rates actually achieved are not substantially different between the two groups (see comment below about heart rates in RACE II), the superiority hypothesis may be doomed. Given that "lenient" in this protocol is not <110 but 80-110, that seems a likely outcome.
Our response: We completely agree with the peer reviewer that this is a risk. Hence, we already state the following in the protocol:
"If the heart rate is below 90, the treatment provider is encouraged to reduce rate limiting treatment."
However, we recognize some patients will need a rate lower than 90 to achieve adequate symptom control .
Further, we have now clarified that the target in the lenient rate control group is the highest tolerable heart rate within the interval, i.e. if the heart rate is below 110, the treatment provider is encouraged not to reduce the heart rate any further:

"The heart rate will be assessed on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. The treatment provider will target the highest tolerable resting heart rate < 110 beats per minute. Treatment providers are encouraged not to attempt to lower the heart rate if already below 110 unless symptoms or other reasons necessitates this. If the heart rate is below 90, the treatment provider is encouraged to reduce rate limiting treatment. If the patient remains symptomatic due to atrial fibrillation after achieving this definition of heart rate control, Holter monitoring or exercise tests may be deemed necessary by the treatment provider."

I think the authors need to specify a little more precisely exactly how the resting heart rate will be pursued in the strict group. A heart rate that is too low can also cause symptoms. Even better, to parallel the lenient group, why not a range to 60 to 80 rather just <80?
Our response: We have now rewritten the section on lenient rate control to the following:
"The heart rate will be assessed on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. The treatment provider will target the highest tolerable resting heart rate < 110 beats per minute. Treatment providers are encouraged not to attempt to lower the heart rate if already below 110 unless symptoms or other reasons necessitates this. If the heart rate is below 90, the treatment provider is encouraged to reduce rate limiting treatment. If the patient remains symptomatic due to atrial fibrillation after achieving this definition of heart rate control, Holter monitoring or exercise tests may be deemed necessary by the treatment provider."
And strict to the following:
"Strict rate control achieved by using rate control medication (see below) will be defined as a mean resting heart rate <80 bpm with a general recommendation of targeting 70 bpm on a 12-lead resting ECG measured over 1 minute after 5 minutes of rest. Exercise test to determine activity heart rates or Holter monitoring will only be performed if the treatment provider believes this is indicated. These evaluations may also be followed by adjustment of rate control medications, electrical cardioversion, arrhythmia surgery, or atrioventricular node ablation (treatment provider's choice)."

Given recent evidence of the advantage of rhythm control rather than rate control (EAST), the authors need to consider specifying these patients have recurrent AF and also specify the entry level age as something more like ≥50 years.
Our response: We agree that the results of the EAST trial are relevant to consider in our trial. In our view the results will indirectly affect the inclusion of participants, since it must be accepted that rate control is the main strategy going forward before a given patient is included in our trial. Hence, we expect that the results of the EAST Trial – although not yet incorporated in current European guidelines – can lead to a larger proportion of patients who will attempt rhythm control as the first treatment strategy than before the results of the EAST trial were published.
We have now clarified that relevant participants are participants where rate control is the main primary treatment strategy.

In the case of digoxin use, a therapeutic target range of serum trough digoxin level should be recommended.
Our response: It is no longer recommended in Europe to use serum digoxin levels except in cases of suspected intoxication.7 If for some reason it is warranted to measure digoxin levels, they will be prescribed by the treatment provider. We will for all patients measure renal function and adjust the dose appropriately.7

I cannot comment in a meaningful way about statistics. I think a statistical review would be helpful. However, there a number of things planned that make me generally uneasy. The sample size calculation seems overly optimistic. The selection of a clinical meaningful difference of 3 points in the SF-36 physical functioning score is rather meagre. A poll of QoL experts' opinions to buttress the choice of this number would be helpful. The estimates of dropouts and crossovers may be too optimistic as well.
Our response: We have based our sample size calculations on a mix of the anchor method (a reduction of 3 points on the PCS is described as significant in the manual, since this is associated with a 20% decrease in mortality in a cohort of 500,000 patients) and the distribution method which considers a standard deviation of 0.2 as a small change. For the latter, we used other studies to estimate the standard deviation.8 Other results supporting the reduction of 3 points are studies estimating clinically important difference using the AFEQT questionnaire, where a clinically relevant difference of 5 is actually below a 3 point difference in studies reporting both scores.9 10 We recognize that there seems to be no consensus on the approach, and hence, we have made a choice.11 12 We will discuss this potential limitation when we complete the trial.
It is an ongoing debate whether dropouts should be part of a sample size calculations. In our opinion, we should not expect a 10% drop out, since this will threaten the validity of the trial results itself, and we plan to limit the missing data to less than 5%. Furthermore, if necessary, we plan to use multiple imputation to handle missing data which will further limit the loss of power. We have now clarified in the protocol that missing data will be handled according to the recommendations by Jakobsen et al. (this article presents a detailed descriptions of how to handle missing data).13
There are other troublesome aspects with the protocol described. These include: too many "secondary/exploratory outcomes" (you cannot answer every question with a single protocol); too many subgroup analyses planned; a per protocol analysis; is the primary outcome to be analyzed as a continuous or discrete variable?
Our response: We recognize the virtue of the comments and completely agree that this is an important point. We have now added to the protocol that we will only draw conclusions on the intention to treat analysis of our primary outcome. We have further specified that we will only perform a per protocol analysis, if more than 5% of participants do not achieve the target heart rate control. All other outcomes and subgroup analyses will be considered hypothesis generating only. We have also removed several subgroup analyses.
Regarding SF-36, we will analyze it as a continuous outcome variable as it is the most

common way of analyzing the outcome and there seems to be little difference depending on the choice of analysis method despite theoretical concern from some.14-16

Minor

Page 6 Last Para Line 45: With respect to guidelines, the Canadian Cardiovascular Society recommendation is not <110 but <100. That recommendation is based on the fact that although the RACE II protocol recommended <110, the heart rate achieved in RACE II was actually much lower than 110 and over time decreased further and averaged 86 (75 for strict) at 1 year, 84 (75) at 2 years and 85 (76) at end of study (see RACE II Supplemental Material). Very few patients had a heart rate >100. I applaud the fact that resting heart rate will be measured at several time intervals (see Table 1). It will provide an estimate of protocol deviation.
Our response: We thank the peer reviewer for the kind comment and appreciate that the Canadian Cardiovascular Society has based their recommendations on heart rate target on the actual heart rates achieved in RACE II and therefore recommend below 100 instead of 110 like the American and European guidelines. We therefore completely agree that it will be important to explore the amount of protocol deviation which is why we now also measure the heart rate using 24-hour Holter monitoring at the end of the titration phase.

Further, we have now added a sentence highlighting that there are differences in heart rate target across guidelines and added the Canadian Cardiovascular Society guideline as a reference.

Page 13 Line 45: What is the correct spelling? In English I think it is amiodarone.
Our response: We thank the peer reviewer for noticing and have added an 'e' to the amiodarone.

Reviewer: 3
Reviewer Name: Dan Wright
Institution and Country: UNLV, USA
Please state any competing interests or state 'None declared': None

I am a quantitative methodologist, not a medical expert, so focused on the methods and statistical plans. Regarding the methods, the plan seems appropriate. The authors state the SF-36 is of primary interest, but presumably this is a proxy for things like mortality. There are many secondary variables. The authors need to describe how they will avoid p-fishing on these (i.e., dealing with dozens of hypothesis tests ... standard adjusting procedures would lower the power to such a degree for these to not be of value).
Our response: We thank the peer reviewer for the important comment regarding multiplicity. We recognize that we have a lot of outcomes, subgroup analyses, and assessment time points. We agree that if we were to make conclusions based on anything except the result of the primary outcome, we would need to adjust the pvalue for significance. We have now made it clearer that we will only make conclusions based on our primary outcome:
"A detailed statistical analysis plan will be published around one month after the trial has been launched. In short, our primary conclusions will be based on the results of our single primary outcome. Hence, we will consider a P value of 0.05 as our threshold for statistical significance.31 The results of secondary outcomes, exploratory outcomes, subgroup analyses, and possible per protocol analyses will be hypothesis generating only. We will assess whether the thresholds for statistical and clinical significance are crossed according to the five-step procedure proposed by Jakobsen et al.31"

We have further added small indications throughout the manuscript that no conclusions will be made based on results other than the results of the primary outcome in the intention to treat analysis.
We have further removed several subgroup analyses. Thank you.
On the statistical procedures, the authors say that they will publish the plans later. Normally with registered reports this is where I focus my review. Without this I can't say whether the authors' plans are appropriate. The author list is fairly long, so I assume there are a couple of biostatisticians on this list.
Our response: We have added further information upon the request of the editor, which the peer reviewer may review. We consider a full statistical analysis plan to be outside the scope of this assignment paper, where we will go into full detail. The statistical analysis plan will be published around 1 month after recruitment begins.

Reviewer: 4
Reviewer Name: Antonio Nenna
Institution and Country: Università Campus Bio-Medico di Roma, Rome, Italy
Please state any competing interests or state ‘None declared’: None declared

Sample size calculation is performed on the primary endpoint (SF-36/PC score).
Your sample size calculation should be performed to compare 2 scores, rather than 2 continuous outcomes (as you performed, see below). In case of ordinal data (such as those for quality of life scores), different approaches are required. Also, an "a priori" power of 80% is generally poor. Also, some patients are lost to follow up or exit the study, and should be taken into account (generally 510% in clinical trials). Sample size calculation should be revised.
Our responses: We appreciate the comment and the discussion regarding how to perform a sample size calculation using sf-36 PCS. However, we prefer to follow the conventional approach for sample size calculations considering SF-36 as a continuous outcome which is also the recommended approach in the official SF-36 manual.14-16
We hope the peer reviewer and editor will accept this conventional approach.
Estimated sample sizes for a two-sample means test t test assuming sd1 = sd2 = sd
Ho: m2 = m1 versus Ha: m2 != m1

Study parameters:

alpha = 0.0500 power = 0.8000 delta = -3.0000 m1 = 3.0000 m2 = 0.0000 sd = 10.0000

Estimated sample sizes:

N = 352
N per group = 176

Date Sent:

28-Oct-2020

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VERSION 2 – REVIEW

REVIEWER	Dr Jo Jo Hai The University of Hong Kong, Hong Kong SAR
REVIEW RETURNED	04-Jan-2021

GENERAL COMMENTS	Here are my comments: 1) Please clarify the objective in both abstract and the manuscript. You are comparing the effect of lenient vs strict rate control on the QOL of patients with persistent or permanent AF. 2) You mentioned that this will be the FIRST trial that assesses a lenient vs strict rate control strategy in patients with persistent AF. This is a bit tricky, since clinically the border between persistent and permanent AF is blurred. At its best, this study supplement the RACE II trial by providing additional information on QOL. 3) You mentioned that a per protocol analysis will be performed if >5% patients are not receiving the prescribed heart rate. You need to specify how you will manage those who are cardioverted / paced in the per-protocol analysis. Will you just remove them from the analysis?

REVIEWER	Dan Wright UNLV, USA
REVIEW RETURNED	21-Dec-2020

GENERAL COMMENTS	As the statistical reviewer my role is to judge whether the planned statistical analyses are appropriate for the research. The authors were given the opportunity to present this, and have not.

REVIEWER	Antonio Nenna Università Campus Bio-Medico di Roma
REVIEW RETURNED	12-Dec-2020

GENERAL COMMENTS	thank you for the revised version of the manuscript.

VERSION 2 – AUTHOR RESPONSE

Response
Reviewer: 1

1) Please clarify the objective in both abstract and the manuscript. You are comparing the effect of lenient vs strict rate control on the QOL of patients with persistent or permanent AF.

Our response: We thank the peer reviewer for the comment, which very concisely and precisely summarizes the main objective of the trial. We now use this more precise definition of our objective throughout the manuscript.

2) You mentioned that this will be the FIRST trial that assesses a lenient vs strict rate control strategy in patients with persistent AF. This is a bit tricky, since clinically the border between persistent and permanent AF is blurred. At its best, this study supplement the RACE II trial by providing additional

information on QOL.

Our response: We agree that the border between persistent and permanent atrial fibrillation is blurry since the historical definitions are based on the premises that the aim for management of patients with atrial fibrillation should always be to restore sinus rhythm which is no longer the case.

However, the median length of atrial fibrillation for participants in the RACE II trial was 18 months (IQR 6-60 months). We expect a significant portion with a shorter duration of atrial fibrillation and therefore wished to convey these intentions by stating we include patients with persistent atrial fibrillation (however, by definition they have 'permanent' atrial fibrillation once they enter the trial, as rate control will be the main strategy going forward.

Given the peer reviewer's thoughtful comments, we have now made changes to the description to better illustrate this tricky border between persistent and permanent atrial fibrillation.

3) You mentioned that a per protocol analysis will be performed if >5% patients are not receiving the prescribed heart rate. You need to specify how you will manage those who are cardioverted / paced in the per-protocol analysis. Will you just remove them from the analysis?

Our response: Thank you. A very good point. We agree with the peer reviewer. The per protocol analysis will only include participants who still receive a rate control strategy at our primary assessment time point.

We have now added this to the manuscript.

Reviewer: 3

Comments to the Author:
As the statistical reviewer my role is to judge whether the planned statistical analyses are appropriate for the research. The authors were given the opportunity to present this, and have not.

Our response: We hope that the editor will accept that we (before the data are collected and inspected) will submit a SAP with a detailed description of the statistical analysis, and this has now been highlighted in our revised manuscript.

Moreover, we have now added some more details regarding the general statistical analysis in our revised manuscript.

Reviewer: 4
Dr. Antonio Nenna, Universita Campus Bio-Medico di Roma

Comments to the Author:
thank you for the revised version of the manuscript.

Our response: We thank the peer reviewer for the hard work and thoughtful comments in connection with this manuscript.