PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal Staging with 'Minimally-Invasive Staged Segmental Artery Coil-Embolization' (MIS²ACE): Trial protocol for a Randomized Controlled Multicentre Trial
AUTHORS	Petroff, David; Czerny, Martin; Kölbel, Tilo; Melissano, Germano; Lonn, Lars; Haunschild, Josephina; von Aspern, Konstantin; Neuhaus, Petra; Pelz, Johann; EPSTEIN, DAVID; Romo-Avilés, Nuria; Piotrowski, Katja; Etz, Christian

VERSION 1 – REVIEW

REVIEWER	Prof Jane Blazeby University of Bristol, UK
REVIEW RETURNED	16-Aug-2018

GENERAL COMMENTS	Rationale 1. It is unclear in the background just how many of these new staged procedures have been performed, how many surgeons and centres have experience of them and what are their risks. It is uncertain whether the techniques have stabilised and that the time is right to do a full scale multi-centre study. More information is needed to convince the reader of the rationale and safely of conducting this main pragmatic trial. It is unclear whether pilot data have been obtained for example Aim 1. The primary objective could be more scientifically worded I think - rather than saying that the aim is to 'demonstrate...' which implies a certain lack of equipoise - I think i could say - that the aim is to test the hypothesis that ....MIS²ACE can greatly reduce the incidence of ischaemic SCI and mortality compared to standard open surgical or endovascular thoracoabdominal aneurysm repair alone. Outcomes I think that it would be more transparent if a definition of 'substantial SCI' is provided to improve the reliability of the assessment and reporting of SCI It is stated that 'Patients, who have not been treated within six months of randomization will be treated as failures to ensure that success/failure is defined for all randomized patients' - I think that this needs clarification - does it mean that an intention to treat analysis will be carried out? My final comment is that it would be valuable if more information about the DMC is provided - this is a high risk intervention and

	clarify about some of adverse events of the novel treatment and how this will be monitored to ensure that the 'learning curve' is not adding risk to patients is important

REVIEWER	Athanasios Saratzis NIHR Leicester BRC
REVIEW RETURNED	19-Oct-2018

GENERAL COMMENTS	This is a very interesting and ambitious study that aims to answer an important question in endovascular complex surgery. I have the following queries/comments: 1) The authors are planning to recruit 500 individuals. Even if all major EU centres are included this is still a major undertaking given that this is a fairly rare pathology. Can the authors please describe in more detail their strategies to address poor recruitment if that is the case after the trial opens? I really find it overtly optimistic to suggest that these centres will recruit 250 patients per year. Is there going to be a recruitment/attrition assessment at 1 year? 2) The authors described some safety endpoints - are these stoppage criteria? 3) One of those safety endpoints is "renal failure". Based on what definition? Is that AKI or failure requiring dialysis? 4) Can the authors please give details regarding the intra- and immediate post-operative fluid regimes? Are these left to the anaesthetists' discretion? Are there any target blood pressure levels during the procedure? 5) How are the post-operative blood pressure control and fluid regimes going to be standardised?

REVIEWER	Gustav Fraedrich Dept. of Vascular Surgery, Medical University of Innsbruck
REVIEW RETURNED	06-Nov-2018

GENERAL COMMENTS	Consequent study to follow the MISACE study. One wonders that some of the pricipal contibutors of the MISACE stdy are not authors anymore

VERSION 1 – AUTHOR RESPONSE

Reviewer 1, Prof. Jane Blazeby

Thank you for your thoughtful and helpful comments, which we have addressed below and which have led to improvements in the manuscript.

> *Rationale 1. It is unclear in the background just how many of these new staged procedures have been performed, how many surgeons and centres have experience of them and what are their risks. It is uncertain whether the techniques have stabilised and that the time is right to do a full scale multi-centre study. More information is needed to convince the reader of the rationale and safely of conducting this main pragmatic trial. It is unclear whether pilot data have been obtained for example*

We have added one citation of a recent paper containing a case series of 57 patients and also discuss this point in time for a trial of this nature.

Aim
1. The primary objective could be more scientifically worded I think - rather than saying that the aim is to 'demonstrate...' which implies a certain lack of equipoise - I think i could say - that the aim is to test the hypothesis that ....MIS²ACE can greatly reduce the incidence of ischaemic SCI and mortality compared to standard open surgical or endovascular thoracoabdominal aneurysm repair alone.

Very happy to comply.

Outcomes
I think that it would be more transparent if a definition of 'substantial SCI' is provided to improve the reliability of the assessment and reporting of SCI

We agree and have provided the modified Tarlov scale along with additional information concerning training of personnel.

It is stated that 'Patients, who have not been treated within six months of randomization will be treated as failures to ensure that success/failure is defined for all randomized patients' - I think that this needs clarification - does it mean that an intention to treat analysis will be carried out?

To explain this choice more fully, we now include the sentence “This facilitates the intention to treat analysis (see below) and reduces the amount of missing data.” In our “Statistical Analysis” section, we now stress that indeed, we will be carrying out an intention to treat analysis.

My final comment is that it would be valuable if more information about the DMC is provided - this is a high risk intervention and clarify about some of adverse events of the novel treatment and how this will be monitored to ensure that the 'learning curve' is not adding risk to patients is important

We have added more information and, at your suggestion, have added a point regarding rapid transfer of MIS^{2}ACE-related SAEs to the DMC.

Reviewer 2, Prof. Athanasios Saratzis

This is a very interesting and ambitious study that aims to answer an important question in endovascular complex surgery.

Thank you for the kind comment and the comments and questions below. They led not only to improvements in the manuscript, but also to added details in the CRFs that will certainly benefit data collection.

1) The authors are planning to recruit 500 individuals. Even if all major EU centres are included this is still a major undertaking given that this is a fairly rare pathology. Can the authors please describe in more detail their strategies to address poor recruitment if that is the case after the trial opens? I really find it overtly optimistic to suggest that these centres will recruit 250 patients per year. Is there going to be a recruitment/attrition assessment at 1 year?

This is definitely a concern we share and take very seriously. We have added the following text (and changed the heading “Sample size” to “Sample size and recruitment”):

“The planned recruitment rate is between 8 and 9 patients per site per year. This is roughly half the number of patients that meet the inclusion criteria. However, slow recruitment plagues many trials and mitigation strategies have already been developed. A list of interested recruitment sites (n>10) is being collected to expand the consortium. Statistical monitoring will be used to identify reasons for screened patients not being included in the trial so that minor and clinically justified amendments to the trial protocol can address these issues, e.g. through adjustments to the inclusion and exclusion

criteria. Finally, a newsletter including recruitment by site will be distributed at regular intervals to spawn healthy competition among the team members."

2) The authors described some safety endpoints - are these stoppage criteria?

We are now more explicit about why we define safety endpoints and how we are going to use them. The new text for "Safety Endpoints" reads:

Having identified particular safety risks in the trial aids us in collecting appropriate data, assessing and reporting these harms, as recommended by SPIRIT. [1, 2] We do not use these to define stopping criteria however, which is left at the discretion of the Data Monitoring Committee.

3) One of those safety endpoints is "renal failure". Based on what definition? Is that AKI or failure requiring dialysis?

Clinically relevant renal failure is the safety endpoint, meaning "requiring dialysis". To account for other iatrogenic kidney problems, we collect data on CKD-stages and will report all deterioration by at least two stages and also distinguish between acute and chronic. The visit schedule, unfortunately, does not permit us to collect sufficient data to assess RIFLE scores without incurring bias due to centre-effects. We have added more specific information in the manuscript.

4) Can the authors please give details regarding the intra- and immediate post-operative fluid regimes? Are these left to the anaesthetists' discretion? Are there any target blood pressure levels during the procedure?

Blood pressure management is central to the intervention and is specified in detail in "working instructions" used by the study personnel. Because of its importance, we have now added some details to the manuscript. Thank you for the good question.

5) How are the post-operative blood pressure control and fluid regimes going to be standardised?

Please see the answer to question 4 and the corresponding additions to the manuscript.

Reviewer 3, Prof. Gustav Fraedrich

One wonders that some of the pricipal contibutors of the MISACE stdy are not authors anymore

One is dumbstruck. But we shall give the reviewer the benefit of the doubt, take his proclivity for brevity as a compliment and say thank you for implicitly suggesting that not a single improvement in the substance of the manuscript is needed.
Regarding authorship: "anymore" must be a slip of the pen – there were no changes in authorship. Prof. Fraedrich correctly points out that "principal contributors to the MISACE study" qualify for authorship. All of them are listed here. The very many colleagues who are members of the trial consortium will contribute to patient recruitment, to critical discussions of the results and to writing up the manuscript when the time comes. They did not however play a substantial role in designing this trial or in preparing the current manuscript, regardless of how much they and others contributed to the technical realisation of MIS^{2}ACE itself. We went over the ICJME criteria for authorship and are unaware of any omissions.

VERSION 2 – REVIEW

REVIEWER	Athanasios Saratzis Leicester NIHR Biomedical Research Centre; Guy's and St Thomas' Foundation NHS Trust.
REVIEW RETURNED	22-Dec-2018

GENERAL COMMENTS	The authors have addressed the vast majority of comments and constructive criticism by the reviewers. I find the text informative and detailed and as per my previous comment, this is an important study for the endovascular world. I have two minor comments at this almost final stage: 1) I fully understand that the way the study has been designed AKI data as per RIFLE/AKIN/KDIGO cannot be reported accurately. Given this is an effectiveness study, can the authors at least report the COMET-suggested effectiveness renal outcomes - that is the MAKE90 criteria, as detailed here: http://www.comet-initiative.org/studies/details/893. I strongly feel that "dialysis" is not an appropriate renal outcome as it is rare. Reporting MAKE90 would be a real game changer in terms of renal outcomes in the complex endovascular aortic field. 2) I find the PPI statement rather disappointing. No patients have been involved in the design; I guess that is fine at this late stage post-funding. At the same time, however, I would urge the authors to be far more descriptive regarding the qualitative sub-study described in their protocol. How many patients? What type of interaction (surveys, focus groups, interviews)? What will they be answering? Will they be exploring study-design related issues or will they actually provide patient preferences regarding treatments and outcomes? How are the qualitative outputs going to be captured, analysed and reported? The reason why I am insistent on this is because this complex procedures may have devastating impact on the patients (e.g. paraplegia), hence patient preferences should really be explored appropriately. Finally, please note that I am not a Professor!

REVIEWER	Gustav Fraedrich Medical University of Innsbruck, Austria
REVIEW RETURNED	12-Dec-2018

GENERAL COMMENTS	no further comments

VERSION 2 – AUTHOR RESPONSE

Reviewer 2, Athanasios Saratzis

I have two minor comments at this almost final stage:

1) I fully understand that the way the study has been designed AKI data as per RIFLE/AKIN/KDIGO cannot be reported accurately. Given this is an effectiveness study, can the authors at least report the COMET-suggested effectiveness renal outcomes - that is the MAKE90 criteria, as detailed here: http://www.comet-initiative.org/studies/details/893. I strongly feel that "dialysis" is not an appropriate renal outcome as it is rare. Reporting MAKE90 would be a real game changer in terms of renal outcomes in the complex endovascular aortic field.

Thank you once again for this very constructive suggestion that we have adopted as best we could. The visit schedule permits us to determine eGFR at baseline and at the primary endpoint (30 days after the aneurysm repair). Dates of death and requirement of dialysis will be known precisely of

course. By design, there will be weeks of difference between the time interval (baseline and primary endpoint) for the control and intervention group. Moreover, the number of times contrast agents are used and the timing will differ considerably – hence the need for assessing renal outcome. All in all, this means that we shall incorporate your suggestion to use MAKE, but cannot define or record a meaningful MAKE30, MAKE60 or MAKE90. A passage to this effect has now been included in the manuscript.

2) I find the PPI statement rather disappointing. No patients have been involved in the design; I guess that is fine at this late stage post-funding. At the same time, however, I would urge the authors to be far more descriptive regarding the qualitative sub-study described in their protocol. How many patients? What type of interaction (surveys, focus groups, interviews)? What will they be answering? Will they be exploring study-design related issues or will they actually provide patient preferences regarding treatments and outcomes? How are the qualitative outputs going to be captured, analysed and reported? The reason why I am insistent on this is because this complex procedures may have devastating impact on the patients (e.g. paraplegia), hence patient preferences should really be explored appropriately.

Patient involvement is important both to us and the funding agencies and patient needs and preferences will be prominent in the publication of the main results. We are very happy to comply with your request and have added more information about the qualitative study in the text, taking into account your specific questions.

VERSION 3 – REVIEW

REVIEWER	Athanasios Saratzis NIHR Leicester Biomedical Research Centre & Department of Cardiovascular Sciences.
REVIEW RETURNED	31-Jan-2019

GENERAL COMMENTS	I have no comments to add and I am really looking forward to seeing the results of this effort in a few years.