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# 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

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## ABSTRACT

**Introduction** Spinal cord injury (SCI) including permanent paraplegia constitute a common complication after repair of thoracoabdominal aortic aneurysms. The staged-repair concept promises to provide protection by inducing arteriogenesis so that the collateral network can provide a robust blood supply to the spinal cord after intervention. Minimally invasive staged segmental artery coil embolization (MIS$^2$ACE) has been proved recently to be a feasible enhanced approach to staged repair.

**Methods and analysis** This RCT uses a multi-centre, multinational, parallel group design, where 500 patients will be randomized in a 1:1 ratio to standard aneurysm repair or to MIS$^2$ACE in 1-3 sessions followed by repair. Before randomization, physicians document whether open or endovascular repair is planned. The primary endpoint is successful aneurysm repair without substantial SCI 30 days after aneurysm repair. Secondary endpoints include any form of SCI, mortality (up to one year), length of stay in ICU, costs and quality of life adjusted years (QALYs). A generalized linear mixed model will be used with the logit link function and randomization arm, mode of repair (open or endovascular repair), the Crawford type and the euroSCORE II as fixed effects and the centre as a random effect. Safety endpoints include kidney failure, respiratory failure and embolic events (also from debris).

**Ethics and dissemination** This trial has been approved by the lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by each of the Ethics Committees at the trial sites. A dedicated project is coordinating communication and dissemination of the trial.

**Trial registration number** NCT03434314




**Strengths and limitations of this study**

- Large multicentre randomized controlled trial RCT in aortic surgery addressing a fundamental issue in thoracoabdominal aortic aneurysm TAAA repair
- Includes open and endovascular repair
- Provides 1-year data on SCI and mortality
- Looks at potential reductions in bleeding complications and endoleaks
- Cannot be blinded

# INTRODUCTION

This publication describes the study design and protocol of a clinical trial on Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal Staging ("PAPAartis") and follows the SPIRIT recommendations very closely ("Standard Protocol Items: Recommendations for Interventional Trials").[1, 2]

## Background

Aortic aneurysms are permanent and localized dilations of particular portions of the aorta that grow unpredictably, but with a mean estimated rate of about two millimetres per year[3] and remain asymptomatic for long periods of time. Based on the aneurysm localization, one can distinguish between thoracic, abdominal and thoracoabdominal aortic aneurysms (TAAA). The latter are complex and generally categorized according to the Crawford classification (type I-IV), based on the anatomic extent of the aneurysm.[4–6]

A study comparing a historic cohort to a matched treated population showed that the dismal five-year survival rate of 13% given the natural course of the disease could be increased to 61% with open surgical repair.[7] Although successful aortic repair cures the disease, both open and endovascular modalities can result in paraplegia from spinal cord ischaemia and mortality is high. This particularly affects patients with aneurysms extending from the thoracic to the abdominal aorta and thus involving many segmental arteries (SAs) supplying the spinal cord. It has been assumed that paraplegia in open repair arises primarily due to temporary interruption of spinal cord blood supply during the operative procedure with a duration sufficient to damage cell bodies and nerve tracts in the spinal cord irreversibly. In endovascular repair, the chronic occlusion of several segmental arteries (as well as the temporary compromising of internal iliac blood supply during the procedure) induces paraplegia with a comparable incidence.[8] Various adjunctive perioperative neuroprotective strategies, such as motor/somatosensory evoked potential monitoring, meticulous perioperative blood pressure management, cerebrospinal fluid (CSF) drainage and even local spinal cord cooling, have been introduced to minimize ischaemic spinal cord injury (SCI).[9] These methods have achieved a notable decrease in the incidence of paraplegia and paraparesis, but it remains high with an incidence of up to 20% for Crawford type II aneurysms.[10]

## Rationale

Members of the study team have found that the deliberate staged occlusion of segmental arteries leading to the paraspinous collateral network and finally supplying the spinal cord can trigger arterial collateralization, thus stabilizing blood supply to the spinal cord from alternate inflow sources and potentially preventing ischaemia.[11–16] This approach was devised after years of research that included recognition of the body's ability to tolerate segmental artery sacrifice[17] given haemodynamic stability[18, 19] along with the identification of the paraspinous arterial collateral network itself.[12, 16] One means of occluding arteries in the clinical setting has been termed 'minimally invasive staged segmental artery coil embolization' (MIS²ACE), which was proved feasible in 2015.[20]

**Objectives**

The primary objective of the PAPAartis trial is to demonstrate that MIS²ACE can greatly reduce the incidence of ischaemic SCI and mortality compared to standard open surgical or endovascular thoracoabdominal aneurysm repair alone.

**Trial Design**

PAPAartis is a multi-national, open label, randomized controlled trial. It has two parallel groups with equal allocation and the primary endpoint is to be tested in a superiority framework.

## METHODS AND ANALYSIS

### Study setting

To demonstrate the efficacy of MIS²ACE while minimizing risks, we chose participating sites with great expertise in the treatment of TAAA and tried to create a balance between those specializing in open and those in endovascular repair. The trial is jointly funded by the European Union as part of the Horizon 2020 programme and by the German Research Foundation, resulting in sites exclusively in Europe and with a strong emphasis on Germany. The recruiting sites (n=29) at commencement of the trial come from Austria (n=2), France (n=2), Germany (n=16), Italy (n=2), the Netherlands (n=1), Poland (n=2), Sweden (n=2), Switzerland (n=1) and the United Kingdom (n=1). In addition, Denmark provides an independent radiological core unit, Spain heads projects on health economics and patient satisfaction, the USA provide expert advice and Scotland heads a project on communication and dissemination. Patient recruitment will begin imminently and is planned to last two years.

### Eligibility criteria

*Inclusion criteria*

1. TAAA, Crawford type II or III (verified by radiological core unit)
2. planned open or endovascular repair of aneurysm within four months
3. ≥ 18 years old

The inclusion criteria are chosen to select a high risk (Crawford type II and III) population amenable to MIS²ACE therapy.

*Key exclusion criteria*

1. complicated (sub-) acute type B aortic dissection (but all chronic type B dissections will be included)
2. ruptured and urgent aneurysm (emergencies)
3. untreated aortic arch aneurysm (patients with a previous successful aortic arch aneurysm repair may be included independent of technique used)
4. bilaterally occluded iliac arteries or chronic total occlusion of left subclavian artery
5. pre-operative neurological deficits or spinal cord dysfunction
6. major untreated cardio-pulmonary disease
7. life-expectancy of less than one year
8. high risk for segmental artery embolism (‘shaggy’ aorta)

9. severe contrast agent allergy, severe reduction in glomerular filtration rate

The first two exclusion criteria were chosen since patients should not be subjected to additional risk as a result of the waiting time in the MIS²ACE arm before TAAA repair can be performed. The third exclusion criterion was chosen since these patients have considerable risk unrelated to the focus of the trial. Exclusion criterion 4 was chosen, since sufficient blood supply after MIS²ACE cannot be guaranteed on the one hand, and the prior occlusion implies that no additional treatment options are available in this anatomic region.

**Intervention**

An overview of the trial is provided in Fig. 1. The treating physicians choose the mode of repair, after which the patient is randomized to the interventional or the control arm.

In the interventional arm (MIS²ACE), segmental arteries will be occluded in one to three sessions some weeks before the aneurysm repair. Target SAs for coil/plug deployment will be identified considering the extent of the planned repair and individual SA anatomy. The occlusion of up to 7 SAs will be performed in a single session and conducted through a peripheral artery access (e.g. the common femoral artery) in local anaesthesia. Local anaesthesia is important so that patients can provide immediate feedback regarding potential neurological symptoms. Selected SAs will be catheterized (e.g. with a 5F catheter or 2.7F microcatheter). Microcoils or vascular plugs will be used for the occlusion itself, not however particles, which could cause unwanted microembolisms to the spinal cord directly. This will be performed in the proximal SA to ensure that the collateral network itself is not affected. The procedure may be done without spinal fluid drainage but is left at the discretion of the centre. The length of the procedure, the amount of contrast dye and the dose of radiation will be documented exactly. The recommended interval between sessions is 21 days, with a strict safety minimum of 5 days.[11] Experts in endovascular catheterization in small vessels (e.g. cardiovascular surgeons, interventionalists, endovascular surgeons, interventional radiologists, paediatric cardiologists) will perform MIS²ACE. It is essential to maintain the individual patient's blood pressure during and after the procedure (invasive monitoring) and ensure that hypotensive periods are carefully avoided. Therefore, the patient should stay in IMCU for at least 48 hours, preferably longer. Reduction or even interruption of oral anti-hypertensive medication and use of low-dose vasopressors may be utilized and are preferable to volume therapy, which increases central venous pressure and thereby also CSF pressure.

In the control arm, patients will be treated according to the optimal state-of-the art procedures at the local site. This ensures a real-world comparison in which the control arm is as strong as possible.

**Endpoints**

*Primary endpoint*

The primary endpoint is successful treatment of the aneurysm. We define "success" as (a) the patient is alive and without substantial SCI 30 days after treatment, and (b) the aneurysm did not rupture and has been excluded within six months of randomization.

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. During recruitment, the Trial Steering Committee will ensure that time lapse alone leads only very rarely to failure, otherwise this criterion will be reworked. The definition of success pertaining to mortality and SCI will be assessed 30 days after TAAA repair and "substantial SCI" means that the patient is unable to stand without assistance and is specifically defined using a modified Tarlov scale[21] and assessed by a board certified neurologist whenever possible. Treatment success for open repair is defined by complete resection and graft replacement in the absence of major related complications.

*Secondary endpoints*

For secondary endpoints, treatment success will be assessed and based on follow-up CT/MR images. Treatment success for endovascular repair is defined based on the position paper of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI)[22] and takes into account upcoming guideline papers. Failure is defined as substantial progression of the aneurysm sac (> 3mm) or the presence of major related complications (e.g. type I/III endoleaks). Completion angiography and/or follow-up MRI/CT from patients with endovascular repair will be conducted as part of clinical routine and will be sent to Copenhagen for assessment.

Note: The point in time "one year" refers to one year after TAAA repair. If patients retained in the full analysis set have not had a repair, then "30 days after TAAA repair" and "at one year" will be treated as 30 days and one year after randomization.

1. Substantial SCI at 30 days after TAAA repair and at one year

2. SCI according to the modified Tarlov scale from TAAA repair treatment to one year
3. All-cause mortality at 30 days and one year after TAAA repair
4. Length of stay in intensive care unit and intermediate care unit after TAAA repair
5. Sub-group analyses for open repair and endovascular repair separately
6. Re-operation for bleeding and drainage volumes in the first 24 h and use of blood products (only for open repair)
7. Cross-clamping times during open surgery
8. Residual aneurysm sac perfusion, i.e. type II endoleaks (only for endovascular repair)
9. Health-related quality of life will be collected using the WHOQOL-BREF[23] and the EuroQoL EQ-5D-5L instruments.[24] Hospital and other healthcare resource use will be collected. Healthcare costs, quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) over one year will be calculated.[25]

*Safety endpoints*

Beyond AE/SAE reporting and descriptive statistics on radiation exposure, the following issues will receive special attention: kidney failure, respiratory failure and embolic events (also from debris).

**Participant timeline**

Please refer to Fig. 1 for details of the visit schedule and participant timeline.

**Sample size**

Estimates of effect size are difficult for several reasons. Foremost, there are large discrepancies between outcome rates quoted in the literature. Moreover, the impact of very recent improvements in techniques on outcomes cannot yet be quantified accurately and, finally the effect size depends on the improvement due to the trial intervention, which, in turn, depends on anatomy, post-repair management and other complex factors. Taking a random effects model of the data from large recent publications for open[10, 26–28] and endovascular repair[29–31] one finds an estimated incidence of 18% (95% prediction interval 15% to 23%) for open repair and a very uncertain 24% (2 to 79)% for endovascular repair. The prediction interval as opposed to the confidence interval provides the correct bounds for what can be expected in the trial.[32] The resources and time available to the study allow for the recruitment of 500 patients. Assuming success rates of 80% in the control arm and 90% in the intervention arm and using a group-sequential design[33] with two interim analyses, this then implies a power of just over 87%.[34] The definitions of the primary endpoint and the full analysis set imply that only very few dropouts are to be expected for this analysis and that

compliance will not be a problem. The severity of the therapy and recovery times mean that loss to follow-up is not expected to be a major factor.

**Randomization**

Patients will be randomized in a 1:1 ratio to the intervention and control arms with a random number generator. Randomization will be performed online at the recruitment centres with a tool prepared and hosted by the Clinical Trial Centre Leipzig

Some of the centres are expected to recruit a very small number of patients, meaning that block randomization stratified by centre is unfeasible. Although minimization schemes could be used to attain roughly balanced allocation of patients, even at the centre level, there is controversy about the methods needed to analyse such trials. To avoid potential complexities in analysis, we have thus opted for a very simple randomization scheme, knowing that small imbalances in the number of patients per arm are to be expected.

**Selected data collection methods**

Neurological examinations will be performed by board certified neurologists whenever possible. If such an examination is made upon discharge and no signs of impairment are found, then verification that this holds at 30 days is only required by telephone. Any signs of impairment necessitate a full examination at 30 days however.

If the assessment of Crawford classification or successful treatment carried out by the radiological unit in Copenhagen should disagree with the treating physician's opinion, the blinded independent Endpoint Committee will make the final decision. The definition of success does not necessarily require that the MRI/CT be made within six months of randomization. Later verification of success is acceptable.

**Data management**

The EDC tool SecuTrial®, developed and distributed by interActive Systems GmbH, is used for creation of the study database. Data entry uses eCRF data entry masks and data changes are tracked automatically including date, time and person who entered/changed information (audit trail). Major corrections or major missing data have to be explained.

The information entered into the eCRF by the investigator or an authorised member of the study team is systematically checked for completeness, consistency and plausibility by routines implemented in the database, such that discrepancies can be dealt with at data entry. Errors and warnings are listed in a validation report and can be resolved at any time during

the data entry process. On completion of data entry, the site staff flags the eCRF-pages as 'data entry completed'.

Throughout the study, a backup of all data is made on a daily basis. Unauthorised access to patient data is prevented by the access concept of the study database, which is based on strict file system permission.

At the end of the study, once the database is complete and accurate, the database will be locked. Subsequent changes to the database are possible only by joint written agreement between co-ordinating investigator, trial statistician and data manager.

## Statistical methods

*Analysis Sets*

If patients retract informed consent before any procedure is performed (repair or SA occlusion), they will be excluded from the primary analysis, since we expect some control arm patients to be dissatisfied with their assigned treatment, retract consent, and seek MIS²ACE outside of the trial. Including them would be anti-conservative. The full analysis set (FAS) includes all randomized patients that have had a session for occluding segmental arteries (intervention arm) or have had a repair procedure (conventional arm). Randomized patients whose aneurysm ruptures or who die from any cause will be included in the FAS, irrespective of the above stipulations.

If a sufficiently large number of patients violate the trial protocol, particularly regarding the trial intervention, then a per protocol analysis will be performed using the set of patients that conformed to the major terms in the protocol. A precise definition of the per protocol set will be provided in the statistical analysis plan.

Patients are generally analysed regarding safety according to treatment received. In our case, an undue delay between randomization and treatment is a risk factor, meaning that such patients will be included in the safety analyses even if they have not yet received treatment.

*Statistical Analysis*

The primary analysis is based on the FAS and makes use of a generalized linear mixed model with the logit link function. The success/failure of treatment will be the dependent variable. The assigned randomization arm, mode of repair (open or endovascular repair), the Crawford type and the euroSCORE II are fixed effects and the centre will be treated as a random effect.

The euroSCORE II already takes age, sex and other relevant factors into account. The interaction term between the randomization arm and the other fixed effects will only be included if evidence for a strong interaction effect are seen, since this would otherwise lead to a substantial loss of power.[35, 36] As a supplementary analysis, an analogous mixed model will be performed with a unity link function to provide estimates and confidence intervals for absolute risk differences.

The definitions of the full analysis set and the primary endpoint are chosen so that almost no missing data are expected. If success cannot be ascertained with certainty, the patient will be treated as a failure. Sensitivity analyses will be used to gauge the effect of missing data on the estimates and conclusions drawn.

Analysis of binary secondary outcomes will be treated on the same footing as the primary analysis. Mortality at 30 days will be treated as binary as opposed to time-to-event, since prolonging life in the post-operative phase for a matter of days is not considered clinically relevant. Subgroup analyses of the two Crawford types and of the two modes of repair will be presented in the form of contingency tables. Mixed model Cox regression with covariates euroSCOREII, Crawford type and mode of repair will be used for one-year mortality with randomization arm as the independent variable of interest and centre as a random effect. If the assumption of proportional hazards is violated substantially, a logistic regression will be used. Kaplan-Meier curves will be used to represent the data.

In explorative analyses, the number of patent segmental arteries and the number occluded will be taken into account with respect to SCI and mortality. The anatomical position of the segmental arteries may also be used.

ICU-time and ICMU-time will be analysed with a linear mixed effects model with the same fixed and random effects as in the primary analysis and may be log transformed if warranted. Re-operation for bleeding and type II endoleaks will be presented for the subgroups of patients treated with open or endovascular repair, respectively.

Descriptive statistics will be used for further safety outcomes along with odds ratios according to treatment received, as appropriate.

Total mean cost per patient over one year will be estimated by multiplying healthcare resource use collected in the trial by unit costs from the country health system.[37] QALYs will be calculated in each treatment group using the EQ-5D-5L value set.[38] The ICER will be calculated, and will inform whether MIS²ACE is cost-effective on average for patients with

TAAA Crawford type II or III. Bootstrap methods will be used to characterize uncertainty.[25]

Further details will be provided in a statistical analysis plan.

**Statistical monitoring**

The trial conduct will be closely supervised by means of central and statistical monitoring. The objectives are a) to detect safety relevant signals as soon as possible, b) to detect non-compliance and relevant protocol violations and to prevent their future occurrence by prompt reaction, c) to prevent missing visits or measurements by prompt reminders and d) to explore means of improving on the MISACE procedure.

Statistical and central monitoring will start immediately after inclusion of the first patient. The relevant reports and descriptive statistics will be updated and discussed at the regular meetings of the Leipzig study team. Problems and abnormalities will be presented at regular intervals to the co-ordinating investigator.

**On-site monitoring**

A risk-based monitoring strategy will be implemented as required by ICH E6 (Chapter 5.0) According to the risk analysis, treatment delivery parameters, adverse events, follow-up information, data transmission and protection and informed consent documents comprise risk-bearing trial aspects and will be monitored.

Prior to recruitment, each participating centre will receive a site initiation visit, during which the trial protocol (if necessary) and the eCRFs will be reviewed with centre staff and any necessary training will be provided. During the study, trial monitors will maintain regular contact with trial centre staff (by telephone/fax/email /post) to track the progress of the trial, respond to any problems, and provide general assistance and support.

The first regular monitoring visit at a site will take place after the randomization of the site's first patient to check protocol compliance and to prevent further systematic errors due to misunderstandings. Trial site visits will take place on a regular basis. The frequency of monitoring visits will depend on the trial site's recruitment rate as well as on potential problems detected during previous on-site visits or by central monitoring.

Prior to every scheduled on-site visit, the monitor will receive summaries of the site`s patient data already documented in the database, and if applicable with data indicating possible protocol deviations or inconsistencies. During the visits, the monitor will a) check informed

consent forms of all patients enrolled, b) perform source data verification of key data in a random sample of at least 20% of the site's patients, c) perform targeted source data verification for patients with possible deviations, d) discuss open queries raised by data management or drug safety personnel, e) check essential parts of the investigator site file, f) check source data for AEs or SAEs, which have not been properly reported in the CRF/eCRF and g) check for major GCP-breaches and/or protocol violations.

**Harms**

Safety endpoints related directly to MIS$^2$ACE include kidney failure, respiratory failure and embolic events (also from debris). These endpoints will be listed according to treatment received with a breakdown according to the number of MIS$^2$ACE sessions. In addition, data on radiation exposure will be collected and presented descriptively.

## ETHICS AND DISSEMINATION

### Approval and registration

The trial protocol and the informed consent form have been reviewed and approved by the lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by each of the Ethics Committees at the trial sites. The Federal Office for Radiation Protection in Germany has also approved the additional radiation use in the intervention group (Z5-22462/2 – 2017-073). The trial has been registered with clinicaltrials.gov (NCT03434314)

### External boards

A Data Monitoring Committee (DMC) has been established to oversee patient safety and data quality in the trial. It consists of three members with expertise in aortic surgery, neurology and medical statistics. The DMC will convene at regular intervals after first-patient-in and will provide recommendations after the interim analyses as to how to proceed with the trial.

An expert advisory board consisting of four international experts on TAAA repair provide the active trial members with independent advice regarding trial design and conduct. It meets with leading members of the consortium on an annual basis and is kept abreast of the trial's progress.

### Dissemination

One project partner (MODUS Research and Innovation, Edinburgh, Scotland) has a project dedicated to communication and dissemination. Key channels, tools and target audiences for dissemination and use of project results will be identified in a Communication and Dissemination Plan. The dissemination activities will be two-fold: basic communication about the project to the public and specific dissemination to four target communities. One objective of the dissemination plan will be to support the project partners with the clinical recruitment. The other objective will be to reach out to wide audiences outside the project consortium at national, European and international levels (medical and health professionals, academics, medical and biomedical industries, policy makers, EU regulators (e.g. the European Medicines Agency), patients group, health NGOs, civil societies, scientific and lay media. The dissemination vehicles will be seminars, medical conferences and publications, project partners' individual communication streams. Dissemination material may include a project leaflet, newsletter, press releases and a trial website.

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## Authors' contributions

DP: study conception and design, statistical methods and sample size calculations, writing and reviewing of the manuscript. MC, TK, GM, KvA, JH: study design with particular focus on cardiovascular endpoints, reviewing of the manuscript. LL: study design with particular focus on radiological methods, reviewing of the manuscript. PN, KP: study design, ethics, data management, writing and reviewing of the manuscript. JP: study design with particular focus on neurological methods and endpoints, reviewing of the manuscript. DE: study design with particular focus on health economics and patient satisfaction, reviewing of the manuscript. CDE: research that lay foundation for trial, initial study conception, study design, writing and reviewing of the manuscript. All authors have read and approved the final manuscript.

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## Competing interests statement

The authors have no competing interests related to this trial.

# Figure Legends

**Figure 1:** Schematic portrayal of the participant timeline and visit schedule for the PAPAartis trial.

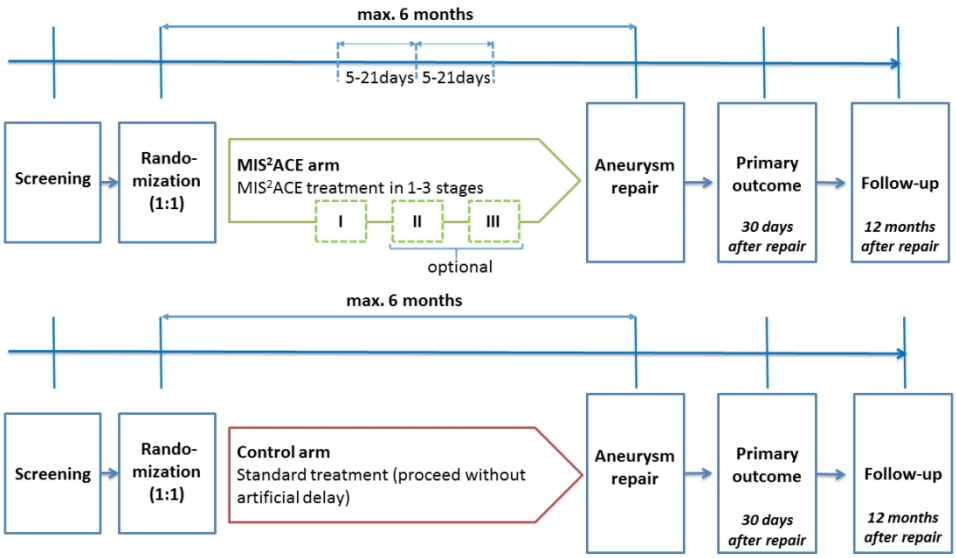


Figure 1: Schematic portrayal of the participant timeline and visit schedule for the PAPAartis trial.

338x190mm (96 x 96 DPI)

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# 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

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# 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

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## ABSTRACT

**Introduction** Spinal cord injury (SCI) including permanent paraplegia constitutes a common complication after repair of thoracoabdominal aortic aneurysms. The staged-repair concept promises to provide protection by inducing arteriogenesis so that the collateral network can provide a robust blood supply to the spinal cord after intervention. Minimally invasive staged segmental artery coil embolization (MIS$^2$ACE) has been proved recently to be a feasible enhanced approach to staged repair.

**Methods and analysis** This randomized controlled trial (RCT) uses a multi-centre, multinational, parallel group design, where 500 patients will be randomized in a 1:1 ratio to standard aneurysm repair or to MIS$^2$ACE in 1-3 sessions followed by repair. Before randomization, physicians document whether open or endovascular repair is planned. The primary endpoint is successful aneurysm repair without substantial SCI 30 days after aneurysm repair. Secondary endpoints include any form of SCI, mortality (up to one year), length of stay in the intensive care unit (ICU), costs and quality of life adjusted years (QALYs). A generalized linear mixed model will be used with the logit link function and randomization arm, mode of repair (open or endovascular repair), the Crawford type and the euroSCORE II as fixed effects and the centre as a random effect. Safety endpoints include kidney failure, respiratory failure and embolic events (also from debris). A qualitative study will explore patient perceptions.

**Ethics and dissemination** This trial has been approved by the lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by each of the Ethics Committees at the trial sites. A dedicated project is coordinating communication and dissemination of the trial.

**Trial registration number** NCT03434314


### Strengths and limitations of this study

- Large multicentre randomized controlled trial RCT in aortic surgery addressing a fundamental issue in thoracoabdominal aortic aneurysm TAAA repair
- Includes open and endovascular repair
- Provides 1-year data on SCI and mortality
- Looks at potential reductions in bleeding complications and endoleaks

- Cannot be blinded

# INTRODUCTION

This publication describes the study design and protocol of a clinical trial on Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal Staging ("PAPAartis") and follows the SPIRIT recommendations very closely ("Standard Protocol Items: Recommendations for Interventional Trials").[1, 2]

## Background

Aortic aneurysms are permanent and localized dilations of particular portions of the aorta that grow unpredictably, but with a mean estimated rate of about two millimetres per year[3] and remain asymptomatic for long periods of time. Based on the aneurysm localization, one can distinguish between thoracic, abdominal and thoracoabdominal aortic aneurysms (TAAA). The latter are complex and generally categorized according to the Crawford classification (type I-IV), based on the anatomic extent of the aneurysm.[4–6]

A study comparing a historic cohort to a matched treated population showed that the dismal five-year survival rate of 13% given the natural course of the disease could be increased to 61% with open surgical repair.[7] Although successful aortic repair cures the disease, both open and endovascular modalities can result in paraplegia from spinal cord ischaemia and mortality is high. This particularly affects patients with aneurysms extending from the thoracic to the abdominal aorta and thus involving many segmental arteries (SAs) supplying the spinal cord. It has been assumed that paraplegia in open repair arises primarily due to temporary interruption of spinal cord blood supply during the operative procedure with a duration sufficient to damage cell bodies and nerve tracts in the spinal cord irreversibly. In endovascular repair, the chronic occlusion of several segmental arteries (as well as the temporary compromising of internal iliac blood supply during the procedure) induces paraplegia with a comparable incidence.[8] Various adjunctive perioperative neuroprotective strategies, such as motor/somatosensory evoked potential monitoring, meticulous perioperative blood pressure management, cerebrospinal fluid (CSF) drainage and even local spinal cord cooling, have been introduced to minimize ischaemic spinal cord injury (SCI).[9] These methods have achieved a notable decrease in the incidence of paraplegia and paraparesis, but it remains high with an incidence of up to 20% for Crawford type II aneurysms.[10]

## Rationale

Members of the study team have found that the deliberate staged occlusion of segmental arteries leading to the paraspinous collateral network and finally supplying the spinal cord can trigger arterial collateralization, thus stabilizing blood supply to the spinal cord from alternate inflow sources and potentially preventing ischaemia.[11–16] This approach was devised after years of research that included recognition of the body's ability to tolerate segmental artery sacrifice[17] given haemodynamic stability[18, 19] along with the identification of the paraspinous arterial collateral network itself.[12, 16] One means of occluding arteries in the clinical setting has been termed 'minimally invasive staged segmental artery coil embolization' (MIS²ACE), which was proved feasible in 2015.[20] A consecutive case series of over 50 patients lends credence to its safety.[21] This is thus the ideal time to carry out such a trial – where the need to test efficacy, effectiveness and safety are paramount, but before it has gained acceptance despite lack of evidence.

## Objectives

The primary objective of the PAPAartis trial 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.

## Trial Design

PAPAartis is a multi-national, open label, randomized controlled trial. It has two parallel groups with equal allocation and the primary endpoint is to be tested in a superiority framework.

# METHODS AND ANALYSIS

## Study setting

To demonstrate the efficacy of MIS²ACE while minimizing risks, we chose participating sites with great expertise in the treatment of TAAA and tried to create a balance between those specializing in open and those in endovascular repair. The trial is jointly funded by the European Union as part of the Horizon 2020 programme and by the German Research Foundation, resulting in sites exclusively in Europe and with a strong emphasis on Germany. The recruiting sites (n=29) at commencement of the trial come from Austria (n=2), France (n=2), Germany (n=16), Italy (n=2), the Netherlands (n=1), Poland (n=2), Sweden (n=2), Switzerland (n=1) and the United Kingdom (n=1). In addition, Denmark provides an independent radiological core unit, Spain heads projects on health economics and patient satisfaction, the USA provide expert advice and Scotland heads a project on communication and dissemination. Patient recruitment will begin imminently and is planned to last two years.

## Eligibility criteria

*Inclusion criteria*

1. TAAA, Crawford type II or III (verified by radiological core unit)
2. planned open or endovascular repair of aneurysm within four months
3. ≥ 18 years old

The inclusion criteria are chosen to select a high risk (Crawford type II and III) population amenable to MIS²ACE therapy.

*Key exclusion criteria*

1. complicated (sub-) acute type B aortic dissection (but all chronic type B dissections will be included)
2. ruptured and urgent aneurysm (emergencies)
3. untreated aortic arch aneurysm (patients with a previous successful aortic arch aneurysm repair may be included independent of technique used)
4. bilaterally occluded iliac arteries or chronic total occlusion of left subclavian artery
5. pre-operative neurological deficits or spinal cord dysfunction
6. major untreated cardio-pulmonary disease
7. life-expectancy of less than one year
8. high risk for segmental artery embolism (‘shaggy’ aorta)

9. severe contrast agent allergy, severe reduction in glomerular filtration rate

The first two exclusion criteria were chosen since patients should not be subjected to additional risk as a result of the waiting time in the MIS²ACE arm before TAAA repair can be performed. The third exclusion criterion was chosen since these patients have considerable risk unrelated to the focus of the trial. Exclusion criterion 4 was chosen, since sufficient blood supply after MIS²ACE cannot be guaranteed on the one hand, and the prior occlusion implies that no additional treatment options are available in this anatomic region.

**Intervention**

An overview of the trial is provided in Fig. 1. The treating physicians choose the mode of repair, after which the patient is randomized to the interventional or the control arm.

In the interventional arm (MIS²ACE), segmental arteries (SAs) will be occluded in one to three sessions some weeks before the aneurysm repair. Target SAs for coil/plug deployment will be identified considering the extent of the planned repair and individual SA anatomy. The occlusion of up to 7 SAs will be performed in a single session and conducted through a peripheral artery access (e.g. the common femoral artery) in local anaesthesia. Local anaesthesia is important so that patients can provide immediate feedback regarding potential neurological symptoms. Selected SAs will be catheterized (e.g. with a 5F catheter or 2.7F microcatheter). Microcoils or vascular plugs will be used for the occlusion itself, not however particles, which could cause unwanted microembolisms to the spinal cord directly. This will be performed in the proximal SA to ensure that the collateral network itself is not affected. The procedure may be done without spinal fluid drainage but this is left at the discretion of the centre. The length of the procedure, the amount of contrast dye and the dose of radiation will be documented exactly. The recommended interval between sessions is 21 days, with a strict safety minimum of 5 days.[11] Experts in endovascular catheterization in small vessels (e.g. cardiovascular surgeons, interventionalists, endovascular surgeons, interventional radiologists, paediatric cardiologists) will perform MIS²ACE. It is essential to maintain blood pressure above 140 mmHg, but for hypertensive patients, it is imperative that the post-operative pressure should not fall below their individual pre-operative systolic blood pressure during and after the procedure (invasive monitoring), ideally for at least 2 days. Anti-hypertensive drugs have to be adjusted accordingly. Therefore, the patient should stay in the IMCU for at least 48 hours, preferably longer. Reduction or even interruption of oral anti-hypertensive medication and use of low-dose vasopressors may be utilized and are preferable to volume therapy, which increases central venous pressure and thereby also CSF pressure.

In the control arm, treatment will be according to the optimal state-of-the art procedures at the local site. This ensures a real-world comparison in which the control arm is as strong as possible.

As the trial proceeds, statistical monitoring and concomitant projects may identify need for revisions to the intervention. These alterations will then be adopted with protocol amendments to optimize patient safety.

**Endpoints**

*Primary endpoint*

The primary endpoint is successful treatment of the aneurysm. We define "success" as (a) the patient is alive and without substantial SCI 30 days after treatment, and (b) the aneurysm did not rupture and was excluded within six months of randomization.

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. This facilitates the intention to treat analysis (see below) and reduces the amount of missing data. During recruitment, the Trial Steering Committee will ensure that time lapse alone leads only very rarely to failure, otherwise this criterion will be reworked. The definition of success pertaining to mortality and SCI will be assessed 30 days after TAAA repair and "substantial SCI" means that the patient is unable to stand without assistance and is defined using the modified Tarlov scale[22] (see below) and assessed by a board certified neurologist whenever possible:

0 – No lower extremity movement

1 – Lower extremity motion without gravity

2 – Lower extremity motion against gravity

3 – Able to stand with assistance

4 – Able to walk with assistance

5 – Normal

A training video describing this scale is provided for study personnel.

Treatment success for open repair is defined by complete resection and graft replacement in the absence of major related complications.

*Secondary endpoints*

For secondary endpoints, treatment success will be assessed and based on follow-up CT/MR images. Treatment success for endovascular repair is defined based on the position paper of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI)[23] and takes into account upcoming guideline papers. Failure is defined as substantial progression of the aneurysm sac (> 3 mm) or the presence of major related complications (e.g. type I/III endoleaks). Completion angiography and/or follow-up MRI/CT from patients with endovascular repair will be conducted as part of clinical routine and will be sent to Copenhagen for assessment.

Note: The point in time "one year" refers to one year after TAAA repair. If patients retained in the full analysis set have not had a repair, then "30 days after TAAA repair" and "at one year" will be treated as 30 days and one year after randomization.

1. Substantial SCI at 30 days after TAAA repair and at one year
2. SCI according to the modified Tarlov scale from TAAA repair treatment to one year
3. All-cause mortality at 30 days and one year after TAAA repair
4. Length of stay in intensive care unit and intermediate care unit after TAAA repair
5. Sub-group analyses for open repair and endovascular repair separately
6. Re-operation for bleeding and drainage volumes in the first 24 h and use of blood products (only for open repair)
7. Cross-clamping times during open surgery
8. Residual aneurysm sac perfusion, i.e. type II endoleaks (only for endovascular repair)
9. Health-related quality of life will be collected using the WHOQOL-BREF[24] and the EuroQoL EQ-5D-5L instruments.[25] Hospital and other healthcare resource use will be collected. Healthcare costs, quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) over one year will be calculated.[26]

*Safety endpoints*

Beyond AE/SAE reporting and descriptive statistics on radiation exposure, the following issues will receive special attention: kidney failure, respiratory failure and embolic events (also from debris). Kidney failure is defined as requiring dialysis and or deterioration in chronic kidney disease (CKD) stage by at least two stages. Acute and chronic kidney disease will be distinguished. 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.

**Participant timeline**

Please refer to Fig. 1 for details of the visit schedule and participant timeline.

**Sample size and recruitment**

Estimates of effect size are difficult for several reasons. Foremost, there are large discrepancies between outcome rates quoted in the literature. Moreover, the impact of recent improvements in techniques on outcomes cannot yet be quantified accurately and, finally the effect size depends on the improvement due to the trial intervention, which, in turn, depends on anatomy, post-repair management and other complex factors. Taking a random effects model of the data from large recent publications for open [10, 27–29] and endovascular repair [30–32] one finds an estimated incidence of 18% (95% prediction interval 15% to 23%) for open repair and a very uncertain 24% (2 to 79)% for endovascular repair. The prediction interval as opposed to the confidence interval provides the correct bounds for what can be expected in the trial.[33] The resources and time available to the study allow for the recruitment of 500 patients. Assuming success rates of 80% in the control arm and 90% in the intervention arm and using a group-sequential design [34] with two interim analyses, this then implies a power of just over 87%.[35] The definitions of the primary endpoint and the full analysis set imply that only very few dropouts are to be expected for this analysis and that compliance will not be a problem. The severity of the therapy and recovery times mean that loss to follow-up is not expected to be a major factor.

The planned recruitment 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.

**Randomization**

Patients will be randomized in a 1:1 ratio to the intervention and control arms with a random number generator. Randomization will be performed online at the recruitment centres with a tool prepared and hosted by the Clinical Trial Centre Leipzig

Some of the centres are expected to recruit a very small number of patients, meaning that block randomization stratified by centre is unfeasible. Although minimization schemes could be used to attain roughly balanced allocation of patients, even at the centre level, there is controversy about the methods needed to analyse such trials. To avoid potential complexities in analysis, we have thus opted for a very simple randomization scheme, knowing that small imbalances in the number of patients per arm are to be expected.

**Selected data collection methods**

Neurological examinations will be performed by board certified neurologists whenever possible. If such an examination is made upon discharge and no signs of impairment are found, then verification that this holds at 30 days is only required by telephone. Any signs of impairment necessitate a full examination at 30 days however.

If the assessment of Crawford classification or successful treatment carried out by the radiological unit in Copenhagen should disagree with the treating physician's opinion, the blinded independent Endpoint Committee will make the final decision. The definition of success does not necessarily require that the MRI/CT be made within six months of randomization. Later verification of success is acceptable.

**Data management**

The EDC tool SecuTrial®, developed and distributed by interActive Systems GmbH, is used for creation of the study database. Data entry uses eCRF data entry masks and data changes are tracked automatically including date, time and person who entered/changed information (audit trail). Major corrections or major missing data have to be explained.

The information entered into the eCRF by the investigator or an authorised member of the study team is systematically checked for completeness, consistency and plausibility by routines implemented in the database, such that discrepancies can be dealt with at data entry. Errors and warnings are listed in a validation report and can be resolved at any time during the data entry process. On completion of data entry, the site staff flags the eCRF-pages as 'data entry completed'.

Throughout the study, a backup of all data is made daily. Unauthorised access to patient data is prevented by the access concept of the study database, which is based on strict file system permission.

At the end of the study, once the database is complete and accurate, the database will be locked. Subsequent changes to the database are possible only by joint written agreement between co-ordinating investigator, trial statistician and data manager.

**Statistical methods**

*Analysis Sets*

If patients retract informed consent before any procedure is performed (repair or SA occlusion), they will be excluded from the primary analysis, since we expect some control arm patients to be dissatisfied with their assigned treatment, retract consent, and seek MIS²ACE outside of the trial. Including them would be anti-conservative. The full analysis set (FAS) includes all randomized patients that have had a session for occluding segmental arteries (intervention arm) or have had a repair procedure (conventional arm). Randomized patients whose aneurysm ruptures or who die from any cause will be included in the FAS, irrespective of the above stipulations.

If a sufficiently large number of patients violate the trial protocol, particularly regarding the trial intervention, then a per protocol analysis will be performed using the set of patients that conformed to the major terms in the protocol. A precise definition of the per protocol set will be provided in the statistical analysis plan.

Patients are generally analysed regarding safety according to treatment received. In our case, an undue delay between randomization and treatment is a risk factor, meaning that such patients will be included in the safety analyses even if they have not yet received treatment.

*Statistical Analysis*

The primary analysis is an intention to treat (ITT) analysis based on the FAS and makes use of a generalized linear mixed model with the logit link function. The success/failure of treatment will be the dependent variable. The assigned randomization arm, mode of repair (open or endovascular repair), the Crawford type and the euroSCORE II are fixed effects and the centre will be treated as a random effect. The euroSCORE II already takes age, sex and other relevant factors into account. The interaction term between the randomization arm and the other fixed effects will only be included if evidence for a strong interaction effect are seen,

since this would otherwise lead to a substantial loss of power.[36, 37] As a supplementary analysis, an analogous mixed model will be performed with a unity link function to provide estimates and confidence intervals for absolute risk differences.

The definitions of the full analysis set and the primary endpoint are chosen so that almost no missing data are expected. If success cannot be ascertained with certainty, the patient will be treated as a failure. Sensitivity analyses will be used to gauge the effect of missing data on the estimates and conclusions drawn.

Interim analyses are planned 30 days after 50% of patients (n=250) and 75% (n=375) have been treated for the aneurysm. The primary endpoint will be analysed and randomization can be terminated for efficacy if a p-value of 0.0030 (first interim analysis) or 0.018 (second interim analysis) is reached. The p-value for demonstrating efficacy in the final analysis is 0.044.

Analysis of binary secondary outcomes will be treated on the same footing as the primary analysis. Mortality at 30 days will be treated as binary as opposed to time-to-event, since prolonging life in the post-operative phase for a matter of days is not considered clinically relevant. Subgroup analyses of the two Crawford types and of the two modes of repair will be presented in the form of contingency tables. Mixed model Cox regression with covariates euroSCOREII, Crawford type and mode of repair will be used for one-year mortality with randomization arm as the independent variable of interest and centre as a random effect. If the assumption of proportional hazards is violated substantially, a logistic regression will be used. Kaplan-Meier curves will be used to represent the data.

In explorative analyses, the number of patent segmental arteries and the number occluded will be taken into account with respect to SCI and mortality. The anatomical position of the segmental arteries may also be used.

ICU-time and ICMU-time will be analysed with a linear mixed effects model with the same fixed and random effects as in the primary analysis and may be log transformed if warranted. Re-operation for bleeding and type II endoleaks will be presented for the subgroups of patients treated with open or endovascular repair, respectively.

Descriptive statistics will be used for further safety outcomes along with odds ratios according to treatment received, as appropriate.

Total mean cost per patient over one year will be estimated by multiplying healthcare resource use collected in the trial by unit costs from the country health system.[38] QALYs

will be calculated in each treatment group using the EQ-5D-5L value set.[39] The ICER will be calculated, and will inform whether MIS²ACE is cost-effective on average for patients with TAAA Crawford type II or III. Bootstrap methods will be used to characterize uncertainty.[26]

Further details will be provided in a statistical analysis plan.

**Statistical monitoring**

The trial conduct will be closely supervised by means of central and statistical monitoring. The objectives are a) to detect safety relevant signals as soon as possible, b) to detect non-compliance and relevant protocol violations and to prevent their future occurrence by prompt reaction, c) to prevent missing visits or measurements by prompt reminders and d) to explore means of improving on the MIS²ACE procedure.

Statistical and central monitoring will start immediately after inclusion of the first patient. The relevant reports and descriptive statistics will be updated and discussed at the regular meetings of the Leipzig study team. Problems and abnormalities will be presented at regular intervals to the co-ordinating investigator.

**On-site monitoring**

A risk-based monitoring strategy will be implemented as required by ICH E6 (Chapter 5.0) According to the risk analysis, treatment delivery parameters, adverse events, follow-up information, data transmission and protection and informed consent documents comprise risk-bearing trial aspects and will be monitored.

Prior to recruitment, each participating centre will receive a site initiation visit, during which the trial protocol (if necessary) and the eCRFs will be reviewed with centre staff and any necessary training will be provided. During the study, trial monitors will maintain regular contact with trial centre staff (by telephone/fax/email/post) to track the progress of the trial, respond to any problems, and provide general assistance and support.

The first regular monitoring visit at a site will take place after the randomization of the site's first patient to check protocol compliance and to prevent further systematic errors due to misunderstandings. Trial site visits will take place on a regular basis. The frequency of monitoring visits will depend on the trial site's recruitment rate as well as on potential problems detected during previous on-site visits or by central monitoring.

Prior to every scheduled on-site visit, the monitor will receive summaries of the site`s patient data already documented in the database, and if applicable with data indicating possible protocol deviations or inconsistencies. During the visits, the monitor will a) check informed consent forms of all patients enrolled, b) perform source data verification of key data in a random sample of at least 20% of the site's patients, c) perform targeted source data verification for patients with possible deviations, d) discuss open queries raised by data management or drug safety personnel, e) check essential parts of the investigator site file, f) check source data for AEs or SAEs, which have not been properly reported in the CRF/eCRF and g) check for major GCP-breaches and/or protocol violations.

**Harms**

Safety endpoints related directly to MIS$^2$ACE include kidney failure, respiratory failure and embolic events (also from debris). These endpoints will be listed according to treatment received with a breakdown according to the number of MIS$^2$ACE sessions. In addition, data on radiation exposure will be collected and presented descriptively.

**Patient and Public Involvement**

The trial protocol was developed in part by physicians with years of experience in treating TAAA patients. Their experience indicated that paraplegia is the greatest concern that patients have when deliberating on whether or not to be treated, and was thus chosen along with mortality for the primary outcome. A qualitative study will recruit a small number of patients for one-on-one in-depth interviews in different sites of the trial. The goal is for the patient to express in his or her own words the impact on their life of diagnosis and treatment, and look at changes that occur in quality of life, family, work, lifestyle and social environment from an ethnographic standpoint. Patients and the public have not yet been involved directly in the trial.

# ETHICS AND DISSEMINATION

## Approval and registration

The trial protocol and the informed consent form have been reviewed and approved by the lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by each of the Ethics Committees at the trial sites. The Federal Office for Radiation Protection in Germany has also approved the additional radiation use in the intervention group (Z5-22462/2 – 2017-073). The trial has been registered with clinicaltrials.gov (NCT03434314). Amendments to the protocol will be reviewed by Ethics Committees. Informed consent will be obtained before collecting any patient data and patient information.

## External boards

A Data Monitoring Committee (DMC) has been established to oversee patient safety and data quality in the trial. It consists of three members with expertise in aortic surgery, neurology and medical statistics. The DMC charter states that its role is to "safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and assist and advise the trial steering committee to protect the validity and credibility of the trial. In order to do this, the DMC evaluates the results of the regular reports and their influence on the risk assessment for the patients as well as for the integrity of the trial. The DMC gives its recommendations at regular intervals as to whether the continuation of the trial is justifiable." Only the trial statistician and the DMC members will have access to the interim analyses until the end of the trial. At the inaugural meeting the members of the DMC will be asked to discuss whether SAEs related to the MIS$^2$ACE procedure should be sent to them without delay.

An expert advisory board consisting of four international experts on TAAA repair provide the active trial members with independent advice regarding trial design and conduct. It meets with leading members of the consortium on an annual basis and is kept abreast of the trial's progress.

## Dissemination

One project partner (MODUS Research and Innovation, Edinburgh, Scotland) has a project dedicated to communication and dissemination. Key channels, tools and target audiences for dissemination and use of project results will be identified in a Communication and Dissemination Plan. The dissemination activities will be two-fold: basic communication about

the project to the public and specific dissemination to four target communities. One objective of the dissemination plan will be to support the project partners with the clinical recruitment. The other objective will be to reach out to wide audiences outside the project consortium at national, European and international levels (medical and health professionals, academics, medical and biomedical industries, policy makers, EU regulators (e.g. the European Medicines Agency), patients groups, health NGOs, civil societies, scientific and lay media. The dissemination vehicles will be seminars, medical conferences and publications, project partners' individual communication streams. Dissemination material may include a project leaflet, newsletter, press releases and a trial website.

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### Authors' contributions

DP: study conception and design, statistical methods and sample size calculations, writing and reviewing of the manuscript. MC, TK, GM, KvA, JH: study design with particular focus on cardiovascular endpoints, reviewing of the manuscript. LL: study design with particular focus on radiological methods, reviewing of the manuscript. PN, KP: study design, ethics, data management, writing and reviewing of the manuscript. JP: study design with particular focus on neurological methods and endpoints, reviewing of the manuscript. DE: study design with particular focus on health economics and patient satisfaction, reviewing of the manuscript. NR: study design for portion on qualitative patient satisfaction, reviewing of the manuscript. CDE: research that lay foundation for trial, initial study conception, study design, writing and reviewing of the manuscript. All authors have read and approved the final manuscript.

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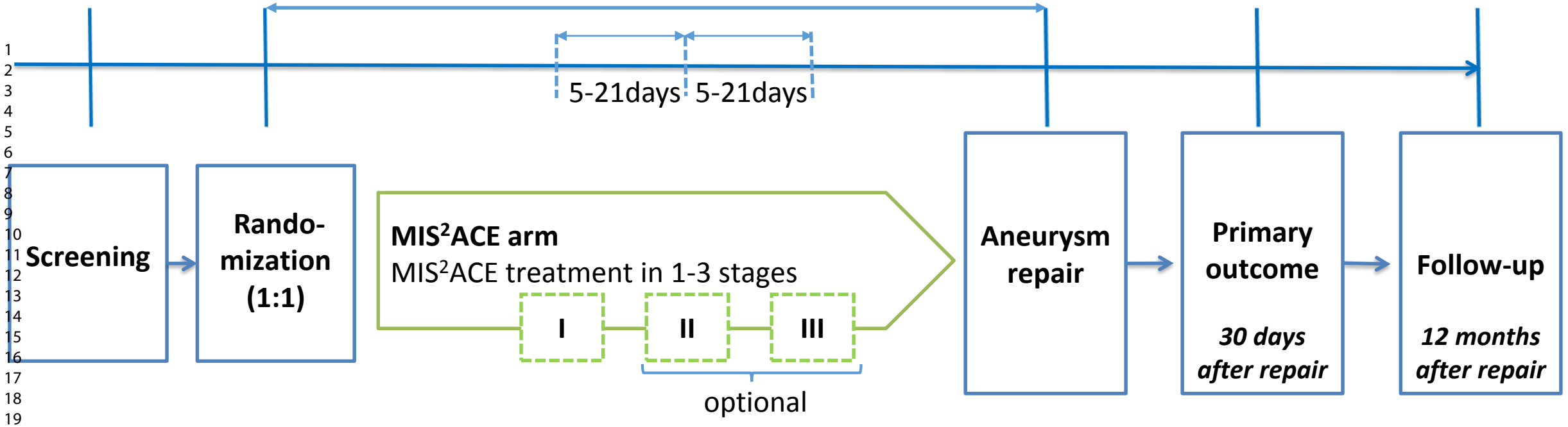
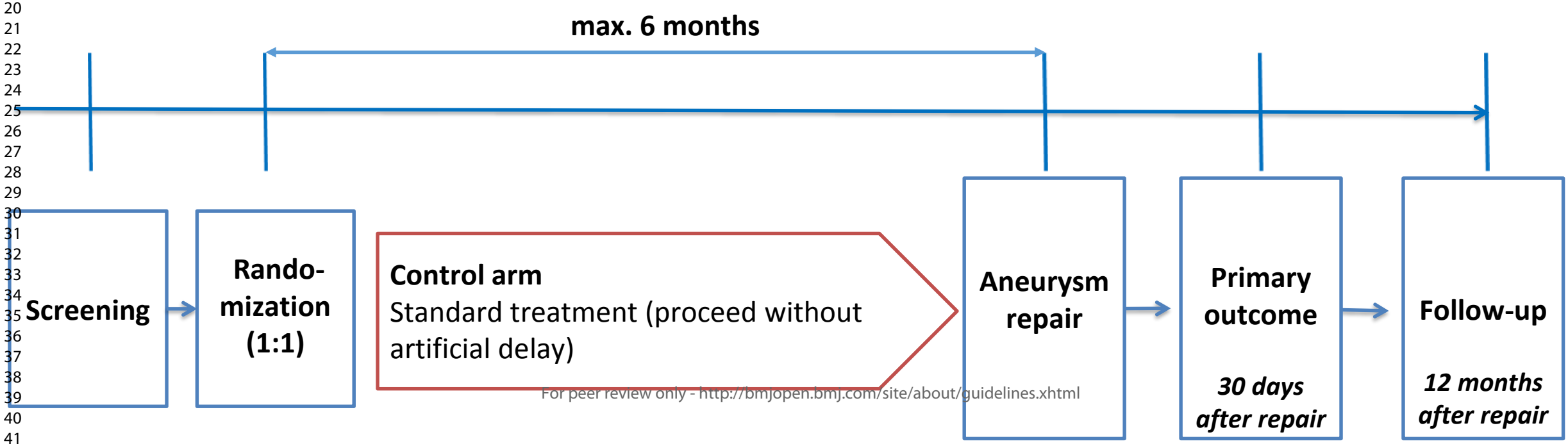
### Competing interests statement

The authors have no competing interests related to this trial.

## Figure Legends

**Figure 1:** Schematic portrayal of the participant timeline and visit schedule for the PAPAartis trial.



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym<br><br>*Title page* |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry<br><br>*End of Abstract* |
| | 2b | All items from the World Health Organization Trial Registration Data Set<br><br>*Available through the clinicaltrial.gov website and in the full trial protocol* |
| Protocol version | 3 | Date and version identifier<br><br>*Not applicable* |
| Funding | 4 | Sources and types of financial, material, and other support<br><br>*Lines 508-510* |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors<br><br>*Lines 496-506* |
| | 5b | Name and contact information for the trial sponsor<br><br>*Not applicable (there is no legal "sponsor" function, but the coordinating investigator was named)* |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities<br><br>*Not applicable* |

| | | |
|---|---|---|
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)<br><br>*Described throughout paper* |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention<br><br>*Line 32-44* |
| | 6b | Explanation for choice of comparators<br><br>*Lines 116-119* |
| Objectives | 7 | Specific objectives or hypotheses<br><br>*Lines 45-47* |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)<br><br>*Lines 49-51* |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained<br><br>*Lines 54-64* |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)<br><br>*Lines 66-89* |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered<br><br>*Lines 91-118* |

| | | |
|---|---|---|
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) |
| | | *Lines 119-121* |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) |
| | | *Lines 309-317* |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial |
| | | *Not applicable* |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended |
| | | *Lines 124-176* |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) |
| | | *Figure 1* |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
| | | *Lines 184-198* |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size |
| | | *Lines 199-207* |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions<br><br>*Lines 209-211* |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned<br><br>*Lines 213-214* |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions<br><br>*Line 211* |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how<br><br>*Not applicable (discussed as limitation)* |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial<br><br>*Not applicable* |

**Methods: Data collection, management, and analysis**

| | | |
|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol<br><br>*Lines 142, 219-227* |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols<br><br>*Not applicable (since intervention always well documented and short-term and mortality data are expected to be very complete)* |

| | | |
|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol<br><br>*Lines 229-244* |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol<br><br>*Lines 263-276* |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)<br><br>*Lines 282-305* |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)<br><br>*Lines 247-261* |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed<br><br>*Lines 365-376* |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial<br><br>*Lines 194, 277-281, 371-372* |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct<br><br>*Lines 172-179, 342-345* |

| | | |
|---|---|---|
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor<br><br>*Lines 318-340, 365-380* |

**Ethics and dissemination**

| | | |
|---|---|---|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval<br><br>*Lines 357-361* |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)<br><br>*Line 362.* |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)<br><br>*Not applicable (part of trial protocol and delegation lists, but too technical for manuscript)* |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable<br><br>*Not applicable* |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site<br><br>*Not applicable (site contracts are confidential).* |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators<br><br>*Not applicable (not regulated contractually).* |

| | | |
|---|---|---|
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation<br><br>*Not applicable (insurance provided for all patients however).* |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions<br><br>*Lines 382-394* |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers<br><br>*Not applicable (will be decided within consortium at later date).* |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code<br><br>*Not applicable (will be decided within consortium at later date).* |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# 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

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| | |

# 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

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## ABSTRACT

**Introduction** Spinal cord injury (SCI) including permanent paraplegia constitutes a common complication after repair of thoracoabdominal aortic aneurysms. The staged-repair concept promises to provide protection by inducing arteriogenesis so that the collateral network can provide a robust blood supply to the spinal cord after intervention. Minimally invasive staged segmental artery coil embolization (MIS$^2$ACE) has been proved recently to be a feasible enhanced approach to staged repair.

**Methods and analysis** This randomized controlled trial (RCT) uses a multi-centre, multinational, parallel group design, where 500 patients will be randomized in a 1:1 ratio to standard aneurysm repair or to MIS$^2$ACE in 1-3 sessions followed by repair. Before randomization, physicians document whether open or endovascular repair is planned. The primary endpoint is successful aneurysm repair without substantial SCI 30 days after aneurysm repair. Secondary endpoints include any form of SCI, mortality (up to one year), length of stay in the intensive care unit (ICU), costs and quality of life adjusted years (QALYs). A generalized linear mixed model will be used with the logit link function and randomization arm, mode of repair (open or endovascular repair), the Crawford type and the euroSCORE II as fixed effects and the centre as a random effect. Safety endpoints include kidney failure, respiratory failure and embolic events (also from debris). A qualitative study will explore patient perceptions.

**Ethics and dissemination** This trial has been approved by the lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by each of the Ethics Committees at the trial sites. A dedicated project is coordinating communication and dissemination of the trial.

**Trial registration number** NCT03434314


### Strengths and limitations of this study

- Large multicentre randomized controlled trial RCT in aortic surgery addressing a fundamental issue in thoracoabdominal aortic aneurysm TAAA repair
- Includes open and endovascular repair
- Provides 1-year data on SCI and mortality
- Looks at potential reductions in bleeding complications and endoleaks

- Cannot be blinded

# INTRODUCTION

This publication describes the study design and protocol of a clinical trial on Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal Staging ("PAPAartis") and follows the SPIRIT recommendations very closely ("Standard Protocol Items: Recommendations for Interventional Trials").[1, 2]

## Background

Aortic aneurysms are permanent and localized dilations of particular portions of the aorta that grow unpredictably, but with a mean estimated rate of about two millimetres per year[3] and remain asymptomatic for long periods of time. Based on the aneurysm localization, one can distinguish between thoracic, abdominal and thoracoabdominal aortic aneurysms (TAAA). The latter are complex and generally categorized according to the Crawford classification (type I-IV), based on the anatomic extent of the aneurysm.[4–6]

A study comparing a historic cohort to a matched treated population showed that the dismal five-year survival rate of 13% given the natural course of the disease could be increased to 61% with open surgical repair.[7] Although successful aortic repair cures the disease, both open and endovascular modalities can result in paraplegia from spinal cord ischaemia and mortality is high. This particularly affects patients with aneurysms extending from the thoracic to the abdominal aorta and thus involving many segmental arteries (SAs) supplying the spinal cord. It has been assumed that paraplegia in open repair arises primarily due to temporary interruption of spinal cord blood supply during the operative procedure with a duration sufficient to damage cell bodies and nerve tracts in the spinal cord irreversibly. In endovascular repair, the chronic occlusion of several segmental arteries (as well as the temporary compromising of internal iliac blood supply during the procedure) induces paraplegia with a comparable incidence.[8] Various adjunctive perioperative neuroprotective strategies, such as motor/somatosensory evoked potential monitoring, meticulous perioperative blood pressure management, cerebrospinal fluid (CSF) drainage and even local spinal cord cooling, have been introduced to minimize ischaemic spinal cord injury (SCI).[9] These methods have achieved a notable decrease in the incidence of paraplegia and paraparesis, but it remains high with an incidence of up to 20% for Crawford type II aneurysms.[10]

## Rationale

Members of the study team have found that the deliberate staged occlusion of segmental arteries leading to the paraspinous collateral network and finally supplying the spinal cord can trigger arterial collateralization, thus stabilizing blood supply to the spinal cord from alternate inflow sources and potentially preventing ischaemia.[11–16] This approach was devised after years of research that included recognition of the body's ability to tolerate segmental artery sacrifice[17] given haemodynamic stability[18, 19] along with the identification of the paraspinous arterial collateral network itself.[12, 16] One means of occluding arteries in the clinical setting has been termed 'minimally invasive staged segmental artery coil embolization' (MIS²ACE), which was proved feasible in 2015.[20] A consecutive case series of over 50 patients lends credence to its safety.[21] This is thus the ideal time to carry out such a trial – where the need to test efficacy, effectiveness and safety are paramount, but before it has gained acceptance despite lack of evidence.

## Objectives

The primary objective of the PAPAartis trial 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.

## Trial Design

PAPAartis is a multi-national, open label, randomized controlled trial. It has two parallel groups with equal allocation and the primary endpoint is to be tested in a superiority framework.

# METHODS AND ANALYSIS

## Study setting

To demonstrate the efficacy of MIS²ACE while minimizing risks, we chose participating sites with great expertise in the treatment of TAAA and tried to create a balance between those specializing in open and those in endovascular repair. The trial is jointly funded by the European Union as part of the Horizon 2020 programme and by the German Research Foundation, resulting in sites exclusively in Europe and with a strong emphasis on Germany. The recruiting sites (n=29) at commencement of the trial come from Austria (n=2), France (n=2), Germany (n=16), Italy (n=2), the Netherlands (n=1), Poland (n=2), Sweden (n=2), Switzerland (n=1) and the United Kingdom (n=1). In addition, Denmark provides an independent radiological core unit, Spain heads projects on health economics and patient satisfaction, the USA provide expert advice and Scotland heads a project on communication and dissemination. Patient recruitment will begin imminently and is planned to last two years.

## Eligibility criteria

*Inclusion criteria*

1. TAAA, Crawford type II or III (verified by radiological core unit)
2. planned open or endovascular repair of aneurysm within four months
3. ≥ 18 years old

The inclusion criteria are chosen to select a high risk (Crawford type II and III) population amenable to MIS²ACE therapy.

*Key exclusion criteria*

1. complicated (sub-) acute type B aortic dissection (but all chronic type B dissections will be included)
2. ruptured and urgent aneurysm (emergencies)
3. untreated aortic arch aneurysm (patients with a previous successful aortic arch aneurysm repair may be included independent of technique used)
4. bilaterally occluded iliac arteries or chronic total occlusion of left subclavian artery
5. pre-operative neurological deficits or spinal cord dysfunction
6. major untreated cardio-pulmonary disease
7. life-expectancy of less than one year
8. high risk for segmental artery embolism (‘shaggy’ aorta)

9. severe contrast agent allergy, severe reduction in glomerular filtration rate

The first two exclusion criteria were chosen since patients should not be subjected to additional risk as a result of the waiting time in the MIS²ACE arm before TAAA repair can be performed. The third exclusion criterion was chosen since these patients have considerable risk unrelated to the focus of the trial. Exclusion criterion 4 was chosen, since sufficient blood supply after MIS²ACE cannot be guaranteed on the one hand, and the prior occlusion implies that no additional treatment options are available in this anatomic region.

**Intervention**

An overview of the trial is provided in Fig. 1. The treating physicians choose the mode of repair, after which the patient is randomized to the interventional or the control arm.

In the interventional arm (MIS²ACE), segmental arteries (SAs) will be occluded in one to three sessions some weeks before the aneurysm repair. Target SAs for coil/plug deployment will be identified considering the extent of the planned repair and individual SA anatomy. The occlusion of up to 7 SAs will be performed in a single session and conducted through a peripheral artery access (e.g. the common femoral artery) in local anaesthesia. Local anaesthesia is important so that patients can provide immediate feedback regarding potential neurological symptoms. Selected SAs will be catheterized (e.g. with a 5F catheter or 2.7F microcatheter). Microcoils or vascular plugs will be used for the occlusion itself, not however particles, which could cause unwanted microembolisms to the spinal cord directly. This will be performed in the proximal SA to ensure that the collateral network itself is not affected. The procedure may be done without spinal fluid drainage but this is left at the discretion of the centre. The length of the procedure, the amount of contrast dye and the dose of radiation will be documented exactly. The recommended interval between sessions is 21 days, with a strict safety minimum of 5 days.[11] Experts in endovascular catheterization in small vessels (e.g. cardiovascular surgeons, interventionalists, endovascular surgeons, interventional radiologists, paediatric cardiologists) will perform MIS²ACE. It is essential to maintain blood pressure above 140 mmHg, but for hypertensive patients, it is imperative that the post-operative pressure should not fall below their individual pre-operative systolic blood pressure during and after the procedure (invasive monitoring), ideally for at least 2 days. Anti-hypertensive drugs have to be adjusted accordingly. Therefore, the patient should stay in the IMCU for at least 48 hours, preferably longer. Reduction or even interruption of oral anti-hypertensive medication and use of low-dose vasopressors may be utilized and are preferable to volume therapy, which increases central venous pressure and thereby also CSF pressure.

In the control arm, treatment will be according to the optimal state-of-the art procedures at the local site. This ensures a real-world comparison in which the control arm is as strong as possible.

As the trial proceeds, statistical monitoring and concomitant projects may identify need for revisions to the intervention. These alterations will then be adopted with protocol amendments to optimize patient safety.

**Endpoints**

*Primary endpoint*

The primary endpoint is successful treatment of the aneurysm. We define "success" as (a) the patient is alive and without substantial SCI 30 days after treatment, and (b) the aneurysm did not rupture and was excluded within six months of randomization.

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. This facilitates the intention to treat analysis (see below) and reduces the amount of missing data. During recruitment, the Trial Steering Committee will ensure that time lapse alone leads only very rarely to failure, otherwise this criterion will be reworked. The definition of success pertaining to mortality and SCI will be assessed 30 days after TAAA repair and "substantial SCI" means that the patient is unable to stand without assistance and is defined using the modified Tarlov scale[22] (see below) and assessed by a board certified neurologist whenever possible:

0 – No lower extremity movement

1 – Lower extremity motion without gravity

2 – Lower extremity motion against gravity

3 – Able to stand with assistance

4 – Able to walk with assistance

5 – Normal

A training video describing this scale is provided for study personnel.

Treatment success for open repair is defined by complete resection and graft replacement in the absence of major related complications.

*Secondary endpoints*

For secondary endpoints, treatment success will be assessed and based on follow-up CT/MR images. Treatment success for endovascular repair is defined based on the position paper of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI)[23] and takes into account upcoming guideline papers. Failure is defined as substantial progression of the aneurysm sac (> 3 mm) or the presence of major related complications (e.g. type I/III endoleaks). Completion angiography and/or follow-up MRI/CT from patients with endovascular repair will be conducted as part of clinical routine and will be sent to Copenhagen for assessment.

Note: The point in time "one year" refers to one year after TAAA repair. If patients retained in the full analysis set have not had a repair, then "30 days after TAAA repair" and "at one year" will be treated as 30 days and one year after randomization.

1. Substantial SCI at 30 days after TAAA repair and at one year
2. SCI according to the modified Tarlov scale from TAAA repair treatment to one year
3. All-cause mortality at 30 days and one year after TAAA repair
4. Length of stay in intensive care unit and intermediate care unit after TAAA repair
5. Sub-group analyses for open repair and endovascular repair separately
6. Re-operation for bleeding and drainage volumes in the first 24 h and use of blood products (only for open repair)
7. Cross-clamping times during open surgery
8. Residual aneurysm sac perfusion, i.e. type II endoleaks (only for endovascular repair)
9. Health-related quality of life will be collected using the WHOQOL-BREF[24] and the EuroQoL EQ-5D-5L instruments.[25] Hospital and other healthcare resource use will be collected. Healthcare costs, quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) over one year will be calculated.[26]

*Safety endpoints*

Beyond AE/SAE reporting and descriptive statistics on radiation exposure, the following issues will receive special attention: acute kidney injury (AKI), respiratory failure and embolic events (also from debris). AKI is defined using the MAKE criteria [27], comparing baseline to the time-point of the primary outcome, where we note that the nature of the trial and logistics of the visits preclude the use of MAKE at precisely 90 days (MAKE90). We also record new dialysis separately and deterioration in chronic kidney disease (CKD) stage by at

least two stages. Acute and chronic kidney disease will be distinguished. 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.

**Participant timeline**

Please refer to Fig. 1 for details of the visit schedule and participant timeline.

**Sample size and recruitment**

Estimates of effect size are difficult for several reasons. Foremost, there are large discrepancies between outcome rates quoted in the literature. Moreover, the impact of recent improvements in techniques on outcomes cannot yet be quantified accurately and, finally the effect size depends on the improvement due to the trial intervention, which, in turn, depends on anatomy, post-repair management and other complex factors. Taking a random effects model of the data from large recent publications for open [10, 28–30] and endovascular repair [31–33] one finds an estimated incidence of 18% (95% prediction interval 15% to 23%) for open repair and a very uncertain 24% (2 to 79)% for endovascular repair. The prediction interval as opposed to the confidence interval provides the correct bounds for what can be expected in the trial.[34] The resources and time available to the study allow for the recruitment of 500 patients. Assuming success rates of 80% in the control arm and 90% in the intervention arm and using a group-sequential design [35] with two interim analyses, this then implies a power of just over 87%.[36] The definitions of the primary endpoint and the full analysis set imply that only very few dropouts are to be expected for this analysis and that compliance will not be a problem. The severity of the therapy and recovery times mean that loss to follow-up is not expected to be a major factor.

The planned recruitment 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.

## Randomization

Patients will be randomized in a 1:1 ratio to the intervention and control arms with a random number generator. Randomization will be performed online at the recruitment centres with a tool prepared and hosted by the Clinical Trial Centre Leipzig

Some of the centres are expected to recruit a very small number of patients, meaning that block randomization stratified by centre is unfeasible. Although minimization schemes could be used to attain roughly balanced allocation of patients, even at the centre level, there is controversy about the methods needed to analyse such trials. To avoid potential complexities in analysis, we have thus opted for a very simple randomization scheme, knowing that small imbalances in the number of patients per arm are to be expected.

## Selected data collection methods

Neurological examinations will be performed by board certified neurologists whenever possible. If such an examination is made upon discharge and no signs of impairment are found, then verification that this holds at 30 days is only required by telephone. Any signs of impairment necessitate a full examination at 30 days however.

If the assessment of Crawford classification or successful treatment carried out by the radiological unit in Copenhagen should disagree with the treating physician's opinion, the blinded independent Endpoint Committee will make the final decision. The definition of success does not necessarily require that the MRI/CT be made within six months of randomization. Later verification of success is acceptable.

## Data management

The EDC tool SecuTrial®, developed and distributed by interActive Systems GmbH, is used for creation of the study database. Data entry uses eCRF data entry masks and data changes are tracked automatically including date, time and person who entered/changed information (audit trail). Major corrections or major missing data have to be explained.

The information entered into the eCRF by the investigator or an authorised member of the study team is systematically checked for completeness, consistency and plausibility by routines implemented in the database, such that discrepancies can be dealt with at data entry. Errors and warnings are listed in a validation report and can be resolved at any time during the data entry process. On completion of data entry, the site staff flags the eCRF-pages as 'data entry completed'.

Throughout the study, a backup of all data is made daily. Unauthorised access to patient data is prevented by the access concept of the study database, which is based on strict file system permission.

At the end of the study, once the database is complete and accurate, the database will be locked. Subsequent changes to the database are possible only by joint written agreement between co-ordinating investigator, trial statistician and data manager.

**Statistical methods**

*Analysis Sets*

If patients retract informed consent before any procedure is performed (repair or SA occlusion), they will be excluded from the primary analysis, since we expect some control arm patients to be dissatisfied with their assigned treatment, retract consent, and seek MIS²ACE outside of the trial. Including them would be anti-conservative. The full analysis set (FAS) includes all randomized patients that have had a session for occluding segmental arteries (intervention arm) or have had a repair procedure (conventional arm). Randomized patients whose aneurysm ruptures or who die from any cause will be included in the FAS, irrespective of the above stipulations.

If a sufficiently large number of patients violate the trial protocol, particularly regarding the trial intervention, then a per protocol analysis will be performed using the set of patients that conformed to the major terms in the protocol. A precise definition of the per protocol set will be provided in the statistical analysis plan.

Patients are generally analysed regarding safety according to treatment received. In our case, an undue delay between randomization and treatment is a risk factor, meaning that such patients will be included in the safety analyses even if they have not yet received treatment.

*Statistical Analysis*

The primary analysis is an intention to treat (ITT) analysis based on the FAS and makes use of a generalized linear mixed model with the logit link function. The success/failure of treatment will be the dependent variable. The assigned randomization arm, mode of repair (open or endovascular repair), the Crawford type and the euroSCORE II are fixed effects and the centre will be treated as a random effect. The euroSCORE II already takes age, sex and other relevant factors into account. The interaction term between the randomization arm and the other fixed effects will only be included if evidence for a strong interaction effect are seen,

since this would otherwise lead to a substantial loss of power.[37, 38] As a supplementary analysis, an analogous mixed model will be performed with a unity link function to provide estimates and confidence intervals for absolute risk differences.

The definitions of the full analysis set and the primary endpoint are chosen so that almost no missing data are expected. If success cannot be ascertained with certainty, the patient will be treated as a failure. Sensitivity analyses will be used to gauge the effect of missing data on the estimates and conclusions drawn.

Interim analyses are planned 30 days after 50% of patients (n=250) and 75% (n=375) have been treated for the aneurysm. The primary endpoint will be analysed and randomization can be terminated for efficacy if a p-value of 0.0030 (first interim analysis) or 0.018 (second interim analysis) is reached. The p-value for demonstrating efficacy in the final analysis is 0.044.

Analysis of binary secondary outcomes will be treated on the same footing as the primary analysis. Mortality at 30 days will be treated as binary as opposed to time-to-event, since prolonging life in the post-operative phase for a matter of days is not considered clinically relevant. Subgroup analyses of the two Crawford types and of the two modes of repair will be presented in the form of contingency tables. Mixed model Cox regression with covariates euroSCOREII, Crawford type and mode of repair will be used for one-year mortality with randomization arm as the independent variable of interest and centre as a random effect. If the assumption of proportional hazards is violated substantially, a logistic regression will be used. Kaplan-Meier curves will be used to represent the data.

In explorative analyses, the number of patent segmental arteries and the number occluded will be taken into account with respect to SCI and mortality. The anatomical position of the segmental arteries may also be used.

ICU-time and ICMU-time will be analysed with a linear mixed effects model with the same fixed and random effects as in the primary analysis and may be log transformed if warranted. Re-operation for bleeding and type II endoleaks will be presented for the subgroups of patients treated with open or endovascular repair, respectively.

Descriptive statistics will be used for further safety outcomes along with odds ratios according to treatment received, as appropriate.

Total mean cost per patient over one year will be estimated by multiplying healthcare resource use collected in the trial by unit costs from the country health system.[39] QALYs

will be calculated in each treatment group using the EQ-5D-5L value set.[40] The ICER will be calculated, and will inform whether MIS²ACE is cost-effective on average for patients with TAAA Crawford type II or III. Bootstrap methods will be used to characterize uncertainty.[26]

Further details will be provided in a statistical analysis plan.

**Statistical monitoring**

The trial conduct will be closely supervised by means of central and statistical monitoring. The objectives are a) to detect safety relevant signals as soon as possible, b) to detect non-compliance and relevant protocol violations and to prevent their future occurrence by prompt reaction, c) to prevent missing visits or measurements by prompt reminders and d) to explore means of improving on the MIS²ACE procedure.

Statistical and central monitoring will start immediately after inclusion of the first patient. The relevant reports and descriptive statistics will be updated and discussed at the regular meetings of the Leipzig study team. Problems and abnormalities will be presented at regular intervals to the co-ordinating investigator.

**On-site monitoring**

A risk-based monitoring strategy will be implemented as required by ICH E6 (Chapter 5.0) According to the risk analysis, treatment delivery parameters, adverse events, follow-up information, data transmission and protection and informed consent documents comprise risk-bearing trial aspects and will be monitored.

Prior to recruitment, each participating centre will receive a site initiation visit, during which the trial protocol (if necessary) and the eCRFs will be reviewed with centre staff and any necessary training will be provided. During the study, trial monitors will maintain regular contact with trial centre staff (by telephone/fax/email/post) to track the progress of the trial, respond to any problems, and provide general assistance and support.

The first regular monitoring visit at a site will take place after the randomization of the site's first patient to check protocol compliance and to prevent further systematic errors due to misunderstandings. Trial site visits will take place on a regular basis. The frequency of monitoring visits will depend on the trial site's recruitment rate as well as on potential problems detected during previous on-site visits or by central monitoring.

Prior to every scheduled on-site visit, the monitor will receive summaries of the site`s patient data already documented in the database, and if applicable with data indicating possible protocol deviations or inconsistencies. During the visits, the monitor will a) check informed consent forms of all patients enrolled, b) perform source data verification of key data in a random sample of at least 20% of the site's patients, c) perform targeted source data verification for patients with possible deviations, d) discuss open queries raised by data management or drug safety personnel, e) check essential parts of the investigator site file, f) check source data for AEs or SAEs, which have not been properly reported in the CRF/eCRF and g) check for major GCP-breaches and/or protocol violations.

**Harms**

Safety endpoints related directly to MIS$^2$ACE include kidney failure, respiratory failure and embolic events (also from debris). These endpoints will be listed according to treatment received with a breakdown according to the number of MIS$^2$ACE sessions. In addition, data on radiation exposure will be collected and presented descriptively.

**Patient and Public Involvement**

The trial protocol was developed in part by physicians with years of experience in treating TAAA patients. Their experience indicated that paraplegia is the greatest concern that patients have when deliberating on whether or not to be treated, and was thus chosen along with mortality for the primary outcome. A qualitative study will recruit about 30 patients after surgical wound healing for one-on-one in-depth interviews in different sites of the trial. Purposive sampling will be used to select information-rich cases to be interviewed, according to criteria of clinical outcome, age, gender and other patient social variables as social class or ethnicity. The finalization of the data collection process will be determined following the principle of theoretical saturation. Interviews will take place with an experienced qualitative researcher in the patient's own language in a mutually convenient, private comfortable place. A literature review will be conducted to broadly inform the interview guide, though patients will be encouraged to speak freely. The goal is for the patient to express in his or her own words the impact on their life of diagnosis and treatment, and look at changes that occur in quality of life, family, work, lifestyle and social environment from an ethnographic standpoint. The interviews will be recorded and transcribed literally. Summative content analysis will be performed using NVivo$^{TM}$ software (QSR International, Melbourne, Australia). Patients and the public have not yet been involved directly in the trial.

# ETHICS AND DISSEMINATION

## Approval and registration

The trial protocol and the informed consent form have been reviewed and approved by the lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by each of the Ethics Committees at the trial sites. The Federal Office for Radiation Protection in Germany has also approved the additional radiation use in the intervention group (Z5-22462/2 – 2017-073). The trial has been registered with clinicaltrials.gov (NCT03434314). Amendments to the protocol will be reviewed by Ethics Committees. Informed consent will be obtained before collecting any patient data and patient information.

## External boards

A Data Monitoring Committee (DMC) has been established to oversee patient safety and data quality in the trial. It consists of three members with expertise in aortic surgery, neurology and medical statistics. The DMC charter states that its role is to "safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and assist and advise the trial steering committee to protect the validity and credibility of the trial. In order to do this, the DMC evaluates the results of the regular reports and their influence on the risk assessment for the patients as well as for the integrity of the trial. The DMC gives its recommendations at regular intervals as to whether the continuation of the trial is justifiable." Only the trial statistician and the DMC members will have access to the interim analyses until the end of the trial. At the inaugural meeting the members of the DMC will be asked to discuss whether SAEs related to the MIS$^2$ACE procedure should be sent to them without delay.

An expert advisory board consisting of four international experts on TAAA repair provide the active trial members with independent advice regarding trial design and conduct. It meets with leading members of the consortium on an annual basis and is kept abreast of the trial's progress.

## Dissemination

One project partner (MODUS Research and Innovation, Edinburgh, Scotland) has a project dedicated to communication and dissemination. Key channels, tools and target audiences for dissemination and use of project results will be identified in a Communication and Dissemination Plan. The dissemination activities will be two-fold: basic communication about

the project to the public and specific dissemination to four target communities. One objective of the dissemination plan will be to support the project partners with the clinical recruitment. The other objective will be to reach out to wide audiences outside the project consortium at national, European and international levels (medical and health professionals, academics, medical and biomedical industries, policy makers, EU regulators (e.g. the European Medicines Agency), patients groups, health NGOs, civil societies, scientific and lay media. The dissemination vehicles will be seminars, medical conferences and publications, project partners' individual communication streams. Dissemination material may include a project leaflet, newsletter, press releases and a trial website.

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## Authors' contributions

DP: study conception and design, statistical methods and sample size calculations, writing and reviewing of the manuscript. MC, TK, GM, KvA, JH: study design with particular focus on cardiovascular endpoints, reviewing of the manuscript. LL: study design with particular focus on radiological methods, reviewing of the manuscript. PN, KP: study design, ethics, data management, writing and reviewing of the manuscript. JP: study design with particular focus on neurological methods and endpoints, reviewing of the manuscript. DE: study design with particular focus on health economics and patient satisfaction, reviewing of the manuscript. NR: study design for portion on qualitative patient satisfaction, reviewing of the manuscript. CDE: research that lay foundation for trial, initial study conception, study design, writing and reviewing of the manuscript. All authors have read and approved the final manuscript.

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## Competing interests statement

The authors have no competing interests related to this trial.

## License statement

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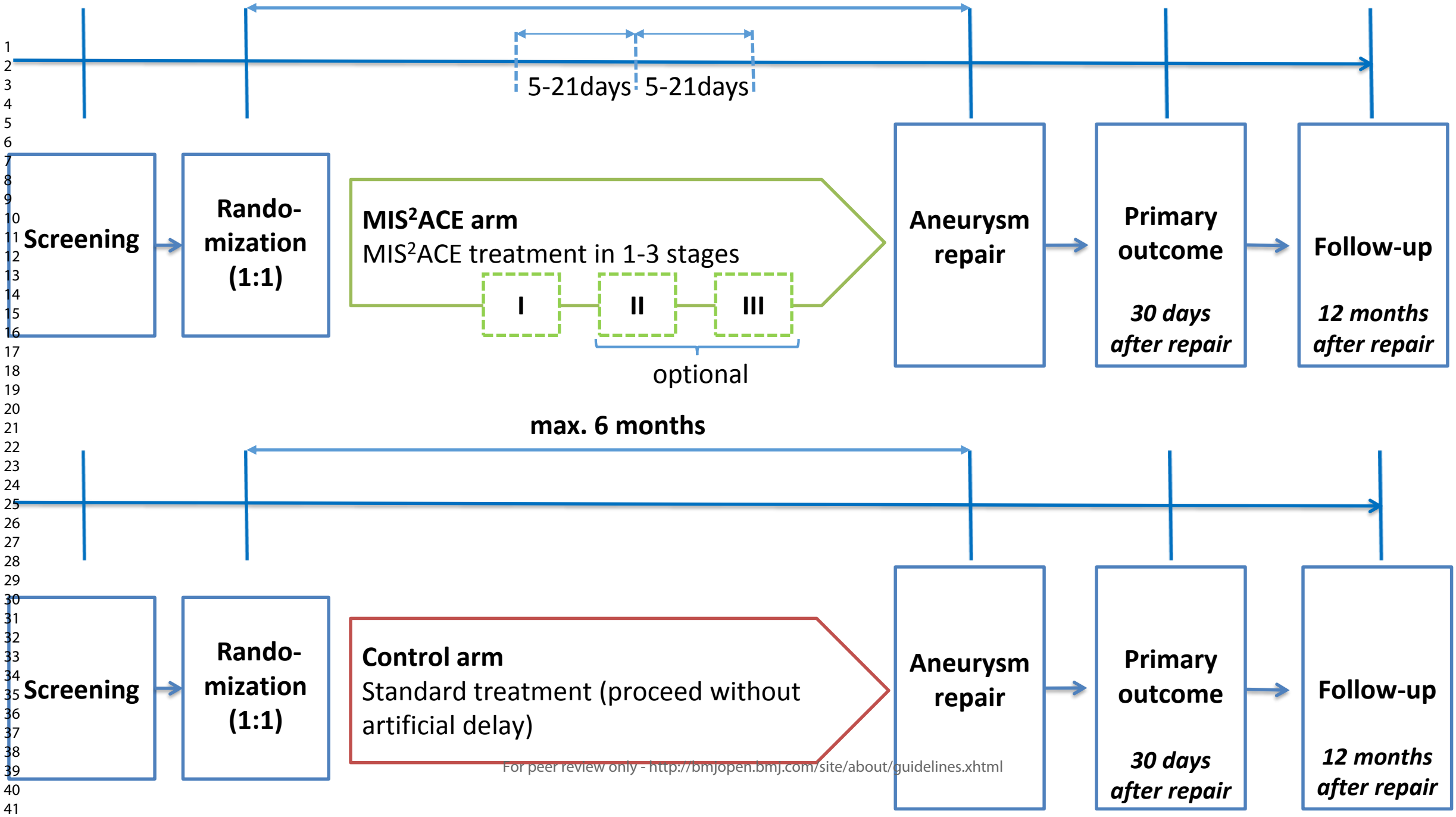
## Figure Legends

**Figure 1:** Schematic portrayal of the participant timeline and visit schedule for the PAPAartis trial.



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym<br><br>*Title page* |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry<br><br>*End of Abstract* |
| | 2b | All items from the World Health Organization Trial Registration Data Set<br><br>*Available through the clinicaltrial.gov website and in the full trial protocol* |
| Protocol version | 3 | Date and version identifier<br><br>*Not applicable* |
| Funding | 4 | Sources and types of financial, material, and other support<br><br>*Lines 508-510* |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors<br><br>*Lines 496-506* |
| | 5b | Name and contact information for the trial sponsor<br><br>*Not applicable (there is no legal "sponsor" function, but the coordinating investigator was named)* |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities<br><br>*Not applicable* |

| | | |
|---|---|---|
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)<br><br>*Described throughout paper* |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention<br><br>*Line 32-44* |
| | 6b | Explanation for choice of comparators<br><br>*Lines 116-119* |
| Objectives | 7 | Specific objectives or hypotheses<br><br>*Lines 45-47* |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)<br><br>*Lines 49-51* |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained<br><br>*Lines 54-64* |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)<br><br>*Lines 66-89* |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered<br><br>*Lines 91-118* |

| | | |
|---|---|---|
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)<br><br>*Lines 119-121* |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)<br><br>*Lines 309-317* |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial<br><br>*Not applicable* |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended<br><br>*Lines 124-176* |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)<br><br>*Figure 1* |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations<br><br>*Lines 184-198* |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size<br><br>*Lines 199-207* |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions<br><br>*Lines 209-211* |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned<br><br>*Lines 213-214* |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions<br><br>*Line 211* |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how<br><br>*Not applicable (discussed as limitation)* |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial<br><br>*Not applicable* |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol<br><br>*Lines 142, 219-227* |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols<br><br>*Not applicable (since intervention always well documented and short-term and mortality data are expected to be very complete)* |

| | | |
|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol<br><br>*Lines 229-244* |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol<br><br>*Lines 263-276* |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)<br><br>*Lines 282-305* |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)<br><br>*Lines 247-261* |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed<br><br>*Lines 365-376* |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial<br><br>*Lines 194, 277-281, 371-372* |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct<br><br>*Lines 172-179, 342-345* |

| | | |
|---|---|---|
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor<br><br>*Lines 318-340, 365-380* |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval<br><br>*Lines 357-361* |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)<br><br>*Line 362.* |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)<br><br>*Not applicable (part of trial protocol and delegation lists, but too technical for manuscript)* |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable<br><br>*Not applicable* |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site<br><br>*Not applicable (site contracts are confidential).* |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators<br><br>*Not applicable (not regulated contractually).* |

| | | |
|---|---|---|
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation<br><br>*Not applicable (insurance provided for all patients however).* |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions<br><br>*Lines 382-394* |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers<br><br>*Not applicable (will be decided within consortium at later date).* |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code<br><br>*Not applicable (will be decided within consortium at later date).* |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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# 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



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# 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

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## ABSTRACT

**Introduction** Spinal cord injury (SCI) including permanent paraplegia constitutes a common complication after repair of thoracoabdominal aortic aneurysms. The staged-repair concept promises to provide protection by inducing arteriogenesis so that the collateral network can provide a robust blood supply to the spinal cord after intervention. Minimally invasive staged segmental artery coil embolization (MIS$^2$ACE) has been proved recently to be a feasible enhanced approach to staged repair.

**Methods and analysis** This randomized controlled trial (RCT) uses a multi-centre, multinational, parallel group design, where 500 patients will be randomized in a 1:1 ratio to standard aneurysm repair or to MIS$^2$ACE in 1-3 sessions followed by repair. Before randomization, physicians document whether open or endovascular repair is planned. The primary endpoint is successful aneurysm repair without substantial SCI 30 days after aneurysm repair. Secondary endpoints include any form of SCI, mortality (up to one year), length of stay in the intensive care unit (ICU), costs and quality of life adjusted years (QALYs). A generalized linear mixed model will be used with the logit link function and randomization arm, mode of repair (open or endovascular repair), the Crawford type and the euroSCORE II as fixed effects and the centre as a random effect. Safety endpoints include kidney failure, respiratory failure and embolic events (also from debris). A qualitative study will explore patient perceptions.

**Ethics and dissemination** This trial has been approved by the lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by each of the Ethics Committees at the trial sites. A dedicated project is coordinating communication and dissemination of the trial.

**Trial registration number** NCT03434314


### Strengths and limitations of this study

- This is a particularly large multicentre randomized controlled trial (RCT) in aortic surgery addressing a fundamental issue in thoracoabdominal aortic aneurysm (TAAA) repair.
- The trial includes open and endovascular repair.
- It provides important 1-year data on SCI and mortality.

- PAPAartis looks at potential reductions in bleeding complications and endoleaks.
- Because of the nature of the intervention, it cannot be blinded.

# INTRODUCTION

This publication describes the study design and protocol of a clinical trial on Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal Staging ("PAPAartis") and follows the SPIRIT recommendations very closely ("Standard Protocol Items: Recommendations for Interventional Trials").[1, 2]

## Background

Aortic aneurysms are permanent and localized dilations of particular portions of the aorta that grow unpredictably, but with a mean estimated rate of about two millimetres per year[3] and remain asymptomatic for long periods of time. Based on the aneurysm localization, one can distinguish between thoracic, abdominal and thoracoabdominal aortic aneurysms (TAAA). The latter are complex and generally categorized according to the Crawford classification (type I-IV), based on the anatomic extent of the aneurysm.[4–6]

A study comparing a historic cohort to a matched treated population showed that the dismal five-year survival rate of 13% given the natural course of the disease could be increased to 61% with open surgical repair.[7] Although successful aortic repair cures the disease, both open and endovascular modalities can result in paraplegia from spinal cord ischaemia and mortality is high. This particularly affects patients with aneurysms extending from the thoracic to the abdominal aorta and thus involving many segmental arteries (SAs) supplying the spinal cord. It has been assumed that paraplegia in open repair arises primarily due to temporary interruption of spinal cord blood supply during the operative procedure with a duration sufficient to damage cell bodies and nerve tracts in the spinal cord irreversibly. In endovascular repair, the chronic occlusion of several segmental arteries (as well as the temporary compromising of internal iliac blood supply during the procedure) induces paraplegia with a comparable incidence.[8] Various adjunctive perioperative neuroprotective strategies, such as motor/somatosensory evoked potential monitoring, meticulous perioperative blood pressure management, cerebrospinal fluid (CSF) drainage and even local spinal cord cooling, have been introduced to minimize ischaemic spinal cord injury (SCI).[9] These methods have achieved a notable decrease in the incidence of paraplegia and

paraparesis, but it remains high with an incidence of up to 20% for Crawford type II aneurysms.[10]

**Rationale**

Members of the study team have found that the deliberate staged occlusion of segmental arteries leading to the paraspinous collateral network and finally supplying the spinal cord can trigger arterial collateralization, thus stabilizing blood supply to the spinal cord from alternate inflow sources and potentially preventing ischaemia.[11–16] This approach was devised after years of research that included recognition of the body's ability to tolerate segmental artery sacrifice[17] given haemodynamic stability[18, 19] along with the identification of the paraspinous arterial collateral network itself.[12, 16] One means of occluding arteries in the clinical setting has been termed 'minimally invasive staged segmental artery coil embolization' (MIS²ACE), which was proved feasible in 2015.[20] A consecutive case series of over 50 patients lends credence to its safety.[21] This is thus the ideal time to carry out such a trial – where the need to test efficacy, effectiveness and safety are paramount, but before it has gained acceptance despite lack of evidence.

**Objectives**

The primary objective of the PAPAartis trial 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.

**Trial Design**

PAPAartis is a multi-national, open label, randomized controlled trial. It has two parallel groups with equal allocation and the primary endpoint is to be tested in a superiority framework.

# METHODS AND ANALYSIS

## Study setting

To demonstrate the efficacy of MIS²ACE while minimizing risks, we chose participating sites with great expertise in the treatment of TAAA and tried to create a balance between those specializing in open and those in endovascular repair. The trial is jointly funded by the European Union as part of the Horizon 2020 programme and by the German Research Foundation, resulting in sites exclusively in Europe and with a strong emphasis on Germany. The recruiting sites (n=29) at commencement of the trial come from Austria (n=2), France (n=2), Germany (n=16), Italy (n=2), the Netherlands (n=1), Poland (n=2), Sweden (n=2), Switzerland (n=1) and the United Kingdom (n=1). In addition, Denmark provides an independent radiological core unit, Spain heads projects on health economics and patient satisfaction, the USA provide expert advice and Scotland heads a project on communication and dissemination. Patient recruitment will begin imminently and is planned to last two years.

## Eligibility criteria

*Inclusion criteria*

1. TAAA, Crawford type II or III (verified by radiological core unit)
2. planned open or endovascular repair of aneurysm within four months
3. ≥ 18 years old

The inclusion criteria are chosen to select a high risk (Crawford type II and III) population amenable to MIS²ACE therapy.

*Key exclusion criteria*

1. complicated (sub-) acute type B aortic dissection (but all chronic type B dissections will be included)
2. ruptured and urgent aneurysm (emergencies)
3. untreated aortic arch aneurysm (patients with a previous successful aortic arch aneurysm repair may be included independent of technique used)
4. bilaterally occluded iliac arteries or chronic total occlusion of left subclavian artery
5. pre-operative neurological deficits or spinal cord dysfunction
6. major untreated cardio-pulmonary disease
7. life-expectancy of less than one year
8. high risk for segmental artery embolism (‘shaggy’ aorta)

9. severe contrast agent allergy, severe reduction in glomerular filtration rate

The first two exclusion criteria were chosen since patients should not be subjected to additional risk as a result of the waiting time in the MIS²ACE arm before TAAA repair can be performed. The third exclusion criterion was chosen since these patients have considerable risk unrelated to the focus of the trial. Exclusion criterion 4 was chosen, since sufficient blood supply after MIS²ACE cannot be guaranteed on the one hand, and the prior occlusion implies that no additional treatment options are available in this anatomic region.

**Intervention**

An overview of the trial is provided in Fig. 1. The treating physicians choose the mode of repair, after which the patient is randomized to the interventional or the control arm.

In the interventional arm (MIS²ACE), segmental arteries (SAs) will be occluded in one to three sessions some weeks before the aneurysm repair. Target SAs for coil/plug deployment will be identified considering the extent of the planned repair and individual SA anatomy. The occlusion of up to 7 SAs will be performed in a single session and conducted through a peripheral artery access (e.g. the common femoral artery) in local anaesthesia. Local anaesthesia is important so that patients can provide immediate feedback regarding potential neurological symptoms. Selected SAs will be catheterized (e.g. with a 5F catheter or 2.7F microcatheter). Microcoils or vascular plugs will be used for the occlusion itself, not however particles, which could cause unwanted microembolisms to the spinal cord directly. This will be performed in the proximal SA to ensure that the collateral network itself is not affected. The procedure may be done without spinal fluid drainage but this is left at the discretion of the centre. The length of the procedure, the amount of contrast dye and the dose of radiation will be documented exactly. The recommended interval between sessions is 21 days, with a strict safety minimum of 5 days.[11] Experts in endovascular catheterization in small vessels (e.g. cardiovascular surgeons, interventionalists, endovascular surgeons, interventional radiologists, paediatric cardiologists) will perform MIS²ACE. It is essential to maintain blood pressure above 140 mmHg, but for hypertensive patients, it is imperative that the post-operative pressure should not fall below their individual pre-operative systolic blood pressure during and after the procedure (invasive monitoring), ideally for at least 2 days. Anti-hypertensive drugs have to be adjusted accordingly. Therefore, the patient should stay in the IMCU for at least 48 hours, preferably longer. Reduction or even interruption of oral anti-hypertensive medication and use of low-dose vasopressors may be utilized and are preferable to volume therapy, which increases central venous pressure and thereby also CSF pressure.

In the control arm, treatment will be according to the optimal state-of-the art procedures at the local site. This ensures a real-world comparison in which the control arm is as strong as possible.

As the trial proceeds, statistical monitoring and concomitant projects may identify need for revisions to the intervention. These alterations will then be adopted with protocol amendments to optimize patient safety.

**Endpoints**

*Primary endpoint*

The primary endpoint is successful treatment of the aneurysm. We define "success" as (a) the patient is alive and without substantial SCI 30 days after treatment, and (b) the aneurysm did not rupture and was excluded within six months of randomization.

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. This facilitates the intention to treat analysis (see below) and reduces the amount of missing data. During recruitment, the Trial Steering Committee will ensure that time lapse alone leads only very rarely to failure, otherwise this criterion will be reworked. The definition of success pertaining to mortality and SCI will be assessed 30 days after TAAA repair and "substantial SCI" means that the patient is unable to stand without assistance and is defined using the modified Tarlov scale[22] (see below) and assessed by a board certified neurologist whenever possible:

0 – No lower extremity movement

1 – Lower extremity motion without gravity

2 – Lower extremity motion against gravity

3 – Able to stand with assistance

4 – Able to walk with assistance

5 – Normal

A training video describing this scale is provided for study personnel.

Treatment success for open repair is defined by complete resection and graft replacement in the absence of major related complications.

*Secondary endpoints*

For secondary endpoints, treatment success will be assessed and based on follow-up CT/MR images. Treatment success for endovascular repair is defined based on the position paper of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI)[23] and takes into account upcoming guideline papers. Failure is defined as substantial progression of the aneurysm sac (> 3 mm) or the presence of major related complications (e.g. type I/III endoleaks). Completion angiography and/or follow-up MRI/CT from patients with endovascular repair will be conducted as part of clinical routine and will be sent to Copenhagen for assessment.

Note: The point in time "one year" refers to one year after TAAA repair. If patients retained in the full analysis set have not had a repair, then "30 days after TAAA repair" and "at one year" will be treated as 30 days and one year after randomization.

1. Substantial SCI at 30 days after TAAA repair and at one year
2. SCI according to the modified Tarlov scale from TAAA repair treatment to one year
3. All-cause mortality at 30 days and one year after TAAA repair
4. Length of stay in intensive care unit and intermediate care unit after TAAA repair
5. Sub-group analyses for open repair and endovascular repair separately
6. Re-operation for bleeding and drainage volumes in the first 24 h and use of blood products (only for open repair)
7. Cross-clamping times during open surgery
8. Residual aneurysm sac perfusion, i.e. type II endoleaks (only for endovascular repair)
9. Health-related quality of life will be collected using the WHOQOL-BREF[24] and the EuroQoL EQ-5D-5L instruments.[25] Hospital and other healthcare resource use will be collected. Healthcare costs, quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) over one year will be calculated.[26]

*Safety endpoints*

Beyond AE/SAE reporting and descriptive statistics on radiation exposure, the following issues will receive special attention: acute kidney injury (AKI), respiratory failure and embolic events (also from debris). AKI is defined using the MAKE criteria [27], comparing baseline to the time-point of the primary outcome, where we note that the nature of the trial and logistics of the visits preclude the use of MAKE at precisely 90 days (MAKE90). We also record new dialysis separately and deterioration in chronic kidney disease (CKD) stage by at

least two stages. Acute and chronic kidney disease will be distinguished. 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.

**Participant timeline**

Please refer to Fig. 1 for details of the visit schedule and participant timeline.

**Sample size and recruitment**

Estimates of effect size are difficult for several reasons. Foremost, there are large discrepancies between outcome rates quoted in the literature. Moreover, the impact of recent improvements in techniques on outcomes cannot yet be quantified accurately and, finally the effect size depends on the improvement due to the trial intervention, which, in turn, depends on anatomy, post-repair management and other complex factors. Taking a random effects model of the data from large recent publications for open [10, 28–30] and endovascular repair [31–33] one finds an estimated incidence of 18% (95% prediction interval 15% to 23%) for open repair and a very uncertain 24% (2 to 79)% for endovascular repair. The prediction interval as opposed to the confidence interval provides the correct bounds for what can be expected in the trial.[34] The resources and time available to the study allow for the recruitment of 500 patients. Assuming success rates of 80% in the control arm and 90% in the intervention arm and using a group-sequential design [35] with two interim analyses, this then implies a power of just over 87%.[36] The definitions of the primary endpoint and the full analysis set imply that only very few dropouts are to be expected for this analysis and that compliance will not be a problem. The severity of the therapy and recovery times mean that loss to follow-up is not expected to be a major factor.

The planned recruitment 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.

## Randomization

Patients will be randomized in a 1:1 ratio to the intervention and control arms with a random number generator. Randomization will be performed online at the recruitment centres with a tool prepared and hosted by the Clinical Trial Centre Leipzig

Some of the centres are expected to recruit a very small number of patients, meaning that block randomization stratified by centre is unfeasible. Although minimization schemes could be used to attain roughly balanced allocation of patients, even at the centre level, there is controversy about the methods needed to analyse such trials. To avoid potential complexities in analysis, we have thus opted for a very simple randomization scheme, knowing that small imbalances in the number of patients per arm are to be expected.

## Selected data collection methods

Neurological examinations will be performed by board certified neurologists whenever possible. If such an examination is made upon discharge and no signs of impairment are found, then verification that this holds at 30 days is only required by telephone. Any signs of impairment necessitate a full examination at 30 days however.

If the assessment of Crawford classification or successful treatment carried out by the radiological unit in Copenhagen should disagree with the treating physician's opinion, the blinded independent Endpoint Committee will make the final decision. The definition of success does not necessarily require that the MRI/CT be made within six months of randomization. Later verification of success is acceptable.

## Data management

The EDC tool SecuTrial®, developed and distributed by interActive Systems GmbH, is used for creation of the study database. Data entry uses eCRF data entry masks and data changes are tracked automatically including date, time and person who entered/changed information (audit trail). Major corrections or major missing data have to be explained.

The information entered into the eCRF by the investigator or an authorised member of the study team is systematically checked for completeness, consistency and plausibility by routines implemented in the database, such that discrepancies can be dealt with at data entry. Errors and warnings are listed in a validation report and can be resolved at any time during the data entry process. On completion of data entry, the site staff flags the eCRF-pages as 'data entry completed'.

Throughout the study, a backup of all data is made daily. Unauthorised access to patient data is prevented by the access concept of the study database, which is based on strict file system permission.

At the end of the study, once the database is complete and accurate, the database will be locked. Subsequent changes to the database are possible only by joint written agreement between co-ordinating investigator, trial statistician and data manager.

**Statistical methods**

*Analysis Sets*

If patients retract informed consent before any procedure is performed (repair or SA occlusion), they will be excluded from the primary analysis, since we expect some control arm patients to be dissatisfied with their assigned treatment, retract consent, and seek MIS²ACE outside of the trial. Including them would be anti-conservative. The full analysis set (FAS) includes all randomized patients that have had a session for occluding segmental arteries (intervention arm) or have had a repair procedure (conventional arm). Randomized patients whose aneurysm ruptures or who die from any cause will be included in the FAS, irrespective of the above stipulations.

If a sufficiently large number of patients violate the trial protocol, particularly regarding the trial intervention, then a per protocol analysis will be performed using the set of patients that conformed to the major terms in the protocol. A precise definition of the per protocol set will be provided in the statistical analysis plan.

Patients are generally analysed regarding safety according to treatment received. In our case, an undue delay between randomization and treatment is a risk factor, meaning that such patients will be included in the safety analyses even if they have not yet received treatment.

*Statistical Analysis*

The primary analysis is an intention to treat (ITT) analysis based on the FAS and makes use of a generalized linear mixed model with the logit link function. The success/failure of treatment will be the dependent variable. The assigned randomization arm, mode of repair (open or endovascular repair), the Crawford type and the euroSCORE II are fixed effects and the centre will be treated as a random effect. The euroSCORE II already takes age, sex and other relevant factors into account. The interaction term between the randomization arm and the other fixed effects will only be included if evidence for a strong interaction effect are seen,

since this would otherwise lead to a substantial loss of power.[37, 38] As a supplementary analysis, an analogous mixed model will be performed with a unity link function to provide estimates and confidence intervals for absolute risk differences.

The definitions of the full analysis set and the primary endpoint are chosen so that almost no missing data are expected. If success cannot be ascertained with certainty, the patient will be treated as a failure. Sensitivity analyses will be used to gauge the effect of missing data on the estimates and conclusions drawn.

Interim analyses are planned 30 days after 50% of patients (n=250) and 75% (n=375) have been treated for the aneurysm. The primary endpoint will be analysed and randomization can be terminated for efficacy if a p-value of 0.0030 (first interim analysis) or 0.018 (second interim analysis) is reached. The p-value for demonstrating efficacy in the final analysis is 0.044.

Analysis of binary secondary outcomes will be treated on the same footing as the primary analysis. Mortality at 30 days will be treated as binary as opposed to time-to-event, since prolonging life in the post-operative phase for a matter of days is not considered clinically relevant. Subgroup analyses of the two Crawford types and of the two modes of repair will be presented in the form of contingency tables. Mixed model Cox regression with covariates euroSCOREII, Crawford type and mode of repair will be used for one-year mortality with randomization arm as the independent variable of interest and centre as a random effect. If the assumption of proportional hazards is violated substantially, a logistic regression will be used. Kaplan-Meier curves will be used to represent the data.

In explorative analyses, the number of patent segmental arteries and the number occluded will be taken into account with respect to SCI and mortality. The anatomical position of the segmental arteries may also be used.

ICU-time and ICMU-time will be analysed with a linear mixed effects model with the same fixed and random effects as in the primary analysis and may be log transformed if warranted. Re-operation for bleeding and type II endoleaks will be presented for the subgroups of patients treated with open or endovascular repair, respectively.

Descriptive statistics will be used for further safety outcomes along with odds ratios according to treatment received, as appropriate.

Total mean cost per patient over one year will be estimated by multiplying healthcare resource use collected in the trial by unit costs from the country health system.[39] QALYs

will be calculated in each treatment group using the EQ-5D-5L value set.[40] The ICER will be calculated, and will inform whether MIS²ACE is cost-effective on average for patients with TAAA Crawford type II or III. Bootstrap methods will be used to characterize uncertainty.[26]

Further details will be provided in a statistical analysis plan.

**Statistical monitoring**

The trial conduct will be closely supervised by means of central and statistical monitoring. The objectives are a) to detect safety relevant signals as soon as possible, b) to detect non-compliance and relevant protocol violations and to prevent their future occurrence by prompt reaction, c) to prevent missing visits or measurements by prompt reminders and d) to explore means of improving on the MIS²ACE procedure.

Statistical and central monitoring will start immediately after inclusion of the first patient. The relevant reports and descriptive statistics will be updated and discussed at the regular meetings of the Leipzig study team. Problems and abnormalities will be presented at regular intervals to the co-ordinating investigator.

**On-site monitoring**

A risk-based monitoring strategy will be implemented as required by ICH E6 (Chapter 5.0) According to the risk analysis, treatment delivery parameters, adverse events, follow-up information, data transmission and protection and informed consent documents comprise risk-bearing trial aspects and will be monitored.

Prior to recruitment, each participating centre will receive a site initiation visit, during which the trial protocol (if necessary) and the eCRFs will be reviewed with centre staff and any necessary training will be provided. During the study, trial monitors will maintain regular contact with trial centre staff (by telephone/fax/email/post) to track the progress of the trial, respond to any problems, and provide general assistance and support.

The first regular monitoring visit at a site will take place after the randomization of the site's first patient to check protocol compliance and to prevent further systematic errors due to misunderstandings. Trial site visits will take place on a regular basis. The frequency of monitoring visits will depend on the trial site's recruitment rate as well as on potential problems detected during previous on-site visits or by central monitoring.

Prior to every scheduled on-site visit, the monitor will receive summaries of the site`s patient data already documented in the database, and if applicable with data indicating possible protocol deviations or inconsistencies. During the visits, the monitor will a) check informed consent forms of all patients enrolled, b) perform source data verification of key data in a random sample of at least 20% of the site's patients, c) perform targeted source data verification for patients with possible deviations, d) discuss open queries raised by data management or drug safety personnel, e) check essential parts of the investigator site file, f) check source data for AEs or SAEs, which have not been properly reported in the CRF/eCRF and g) check for major GCP-breaches and/or protocol violations.

**Harms**

Safety endpoints related directly to MIS$^2$ACE include kidney failure, respiratory failure and embolic events (also from debris). These endpoints will be listed according to treatment received with a breakdown according to the number of MIS$^2$ACE sessions. In addition, data on radiation exposure will be collected and presented descriptively.

**Patient and Public Involvement**

The trial protocol was developed in part by physicians with years of experience in treating TAAA patients. Their experience indicated that paraplegia is the greatest concern that patients have when deliberating on whether or not to be treated, and was thus chosen along with mortality for the primary outcome. A qualitative study will recruit about 30 patients after surgical wound healing for one-on-one in-depth interviews in different sites of the trial. Purposive sampling will be used to select information-rich cases to be interviewed, according to criteria of clinical outcome, age, gender and other patient social variables as social class or ethnicity. The finalization of the data collection process will be determined following the principle of theoretical saturation. Interviews will take place with an experienced qualitative researcher in the patient's own language in a mutually convenient, private comfortable place. A literature review will be conducted to broadly inform the interview guide, though patients will be encouraged to speak freely. The goal is for the patient to express in his or her own words the impact on their life of diagnosis and treatment, and look at changes that occur in quality of life, family, work, lifestyle and social environment from an ethnographic standpoint. The interviews will be recorded and transcribed literally. Summative content analysis will be performed using NVivo$^{TM}$ software (QSR International, Melbourne, Australia). Patients and the public have not yet been involved directly in the trial.

# ETHICS AND DISSEMINATION

## Approval and registration

The trial protocol and the informed consent form have been reviewed and approved by the lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by each of the Ethics Committees at the trial sites. The Federal Office for Radiation Protection in Germany has also approved the additional radiation use in the intervention group (Z5-22462/2 – 2017-073). The trial has been registered with clinicaltrials.gov (NCT03434314). Amendments to the protocol will be reviewed by Ethics Committees. Informed consent will be obtained before collecting any patient data and patient information.

## External boards

A Data Monitoring Committee (DMC) has been established to oversee patient safety and data quality in the trial. It consists of three members with expertise in aortic surgery, neurology and medical statistics. The DMC charter states that its role is to "safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and assist and advise the trial steering committee to protect the validity and credibility of the trial. In order to do this, the DMC evaluates the results of the regular reports and their influence on the risk assessment for the patients as well as for the integrity of the trial. The DMC gives its recommendations at regular intervals as to whether the continuation of the trial is justifiable." Only the trial statistician and the DMC members will have access to the interim analyses until the end of the trial. At the inaugural meeting the members of the DMC will be asked to discuss whether SAEs related to the MIS$^2$ACE procedure should be sent to them without delay.

An expert advisory board consisting of four international experts on TAAA repair provide the active trial members with independent advice regarding trial design and conduct. It meets with leading members of the consortium on an annual basis and is kept abreast of the trial's progress.

## Dissemination

One project partner (MODUS Research and Innovation, Edinburgh, Scotland) has a project dedicated to communication and dissemination. Key channels, tools and target audiences for dissemination and use of project results will be identified in a Communication and Dissemination Plan. The dissemination activities will be two-fold: basic communication about

the project to the public and specific dissemination to four target communities. One objective of the dissemination plan will be to support the project partners with the clinical recruitment. The other objective will be to reach out to wide audiences outside the project consortium at national, European and international levels (medical and health professionals, academics, medical and biomedical industries, policy makers, EU regulators (e.g. the European Medicines Agency), patients groups, health NGOs, civil societies, scientific and lay media. The dissemination vehicles will be seminars, medical conferences and publications, project partners' individual communication streams. Dissemination material may include a project leaflet, newsletter, press releases and a trial website.

**Data Sharing Statement**

We are committed to transparent research and are aware of the International Committee of Medical Journal Editors (ICMJE) recommendations on data sharing. After publication of the major results and upon reasonable request from researchers performing an individual patient data meta-analysis, individual patient data that underlie published results will be shared after de-identification. This requires approval by the local Institutional Review Board (IRB) of the researcher requesting the data along with public registration of the meta-analysis. Summary statistics that go beyond the scope of published material will be made available to researchers for meta-analysis upon reasonable request and if the necessary data analysis is not unduly time-consuming. Together with publication of the main results, the trial protocol in full will be made publically available as well as the statistical analysis plan.

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## Authors' contributions

DP: study conception and design, statistical methods and sample size calculations, writing and reviewing of the manuscript. MC, TK, GM, KvA, JH: study design with particular focus on cardiovascular endpoints, reviewing of the manuscript. LL: study design with particular focus on radiological methods, reviewing of the manuscript. PN, KP: study design, ethics, data management, writing and reviewing of the manuscript. JP: study design with particular focus on neurological methods and endpoints, reviewing of the manuscript. DE: study design with particular focus on health economics and patient satisfaction, reviewing of the manuscript. NR: study design for portion on qualitative patient satisfaction, reviewing of the manuscript. CDE: research that lay foundation for trial, initial study conception, study design, writing and reviewing of the manuscript. All authors have read and approved the final manuscript.

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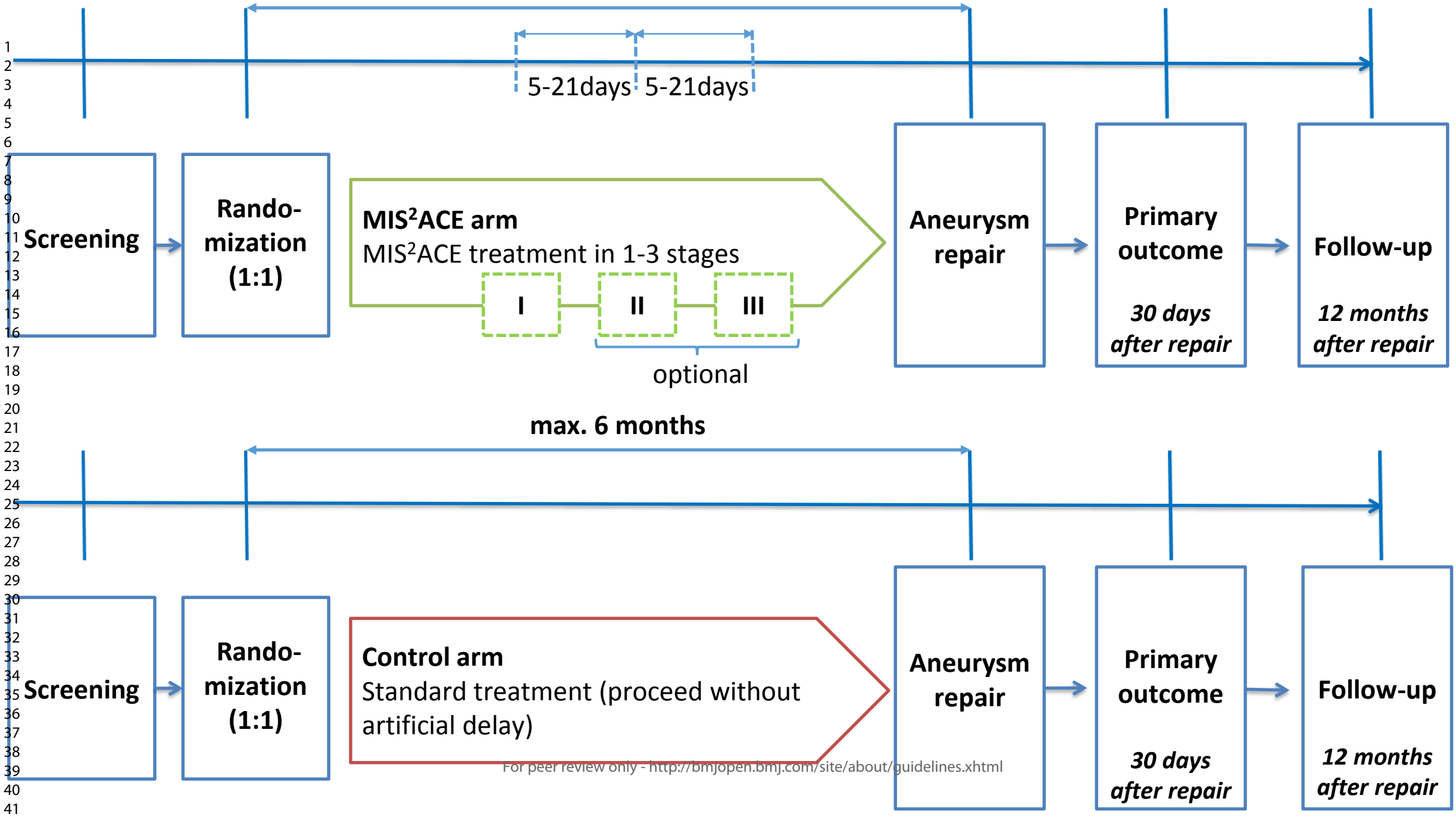
## Competing interests statement

The authors have no competing interests related to this trial.

## Figure Legends

**Figure 1:** Schematic portrayal of the participant timeline and visit schedule for the PAPAartis trial.



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym<br><br>*Title page* |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry<br><br>*End of Abstract* |
| | 2b | All items from the World Health Organization Trial Registration Data Set<br><br>*Available through the clinicaltrial.gov website and in the full trial protocol* |
| Protocol version | 3 | Date and version identifier<br><br>*Not applicable* |
| Funding | 4 | Sources and types of financial, material, and other support<br><br>*Lines 508-510* |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors<br><br>*Lines 496-506* |
| | 5b | Name and contact information for the trial sponsor<br><br>*Not applicable (there is no legal "sponsor" function, but the coordinating investigator was named)* |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities<br><br>*Not applicable* |

| | | |
|---|---|---|
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)<br><br>*Described throughout paper* |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention<br><br>*Line 32-44* |
| | 6b | Explanation for choice of comparators<br><br>*Lines 116-119* |
| Objectives | 7 | Specific objectives or hypotheses<br><br>*Lines 45-47* |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)<br><br>*Lines 49-51* |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained<br><br>*Lines 54-64* |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)<br><br>*Lines 66-89* |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered<br><br>*Lines 91-118* |

| | | |
|---|---|---|
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)<br><br>*Lines 119-121* |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)<br><br>*Lines 309-317* |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial<br><br>*Not applicable* |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended<br><br>*Lines 124-176* |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)<br><br>*Figure 1* |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations<br><br>*Lines 184-198* |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size<br><br>*Lines 199-207* |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions<br><br>*Lines 209-211* |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned<br><br>*Lines 213-214* |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions<br><br>*Line 211* |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how<br><br>*Not applicable (discussed as limitation)* |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial<br><br>*Not applicable* |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol<br><br>*Lines 142, 219-227* |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols<br><br>*Not applicable (since intervention always well documented and short-term and mortality data are expected to be very complete)* |

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| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol<br><br>*Lines 229-244* |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol<br><br>*Lines 263-276* |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)<br><br>*Lines 282-305* |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)<br><br>*Lines 247-261* |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed<br><br>*Lines 365-376* |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial<br><br>*Lines 194, 277-281, 371-372* |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct<br><br>*Lines 172-179, 342-345* |

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| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor<br><br>*Lines 318-340, 365-380* |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval<br><br>*Lines 357-361* |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)<br><br>*Line 362.* |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)<br><br>*Not applicable (part of trial protocol and delegation lists, but too technical for manuscript)* |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable<br><br>*Not applicable* |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site<br><br>*Not applicable (site contracts are confidential).* |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators<br><br>*Not applicable (not regulated contractually).* |

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| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation<br><br>*Not applicable (insurance provided for all patients however).* |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions<br><br>*Lines 382-394* |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers<br><br>*Not applicable (will be decided within consortium at later date).* |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code<br><br>*Not applicable (will be decided within consortium at later date).* |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable<br><br>*Not applicable (part of full protocol, but too technical and detailed for this manuscript).* |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.