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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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Keywords:	Thoracoabdominal aortic aneurysms, TAAA, spinal cord injury, SCI, segmental artery coil embolization, MISACE

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3 **Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal**
4 **Staging with ‘Minimally-Invasive Staged Segmental Artery Coil-**
5 **Embolization’ (MIS²ACE): Trial protocol for a Randomized Controlled**
6 **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 (MIS²ACE) 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 MIS²ACE 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

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3 Members of the study team have found that the deliberate staged occlusion of segmental
4 arteries leading to the paraspinous collateral network and finally supplying the spinal cord can
5 trigger arterial collateralization, thus stabilizing blood supply to the spinal cord from alternate
6 inflow sources and potentially preventing ischaemia.[11–16] This approach was devised after
7
8 35 years of research that included recognition of the body’s ability to tolerate segmental artery
9 sacrifice[17] given haemodynamic stability[18, 19] along with the identification of the
10 paraspinous arterial collateral network itself.[12, 16] One means of occluding arteries in the
11 clinical setting has been termed ‘minimally invasive staged segmental artery coil
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16 40 embolization’ (MIS²ACE), which was proved feasible in 2015.[20]

17 18 **Objectives**

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20 The primary objective of the PAPAartis trial is to demonstrate that MIS²ACE can greatly
21 reduce the incidence of ischaemic SCI and mortality compared to standard open surgical or
22 endovascular thoracoabdominal aneurysm repair alone.
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25 26 45 **Trial Design**

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

50 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)
- 65 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

- 70 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)
- 75 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)

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3 80 9. severe contrast agent allergy, severe reduction in glomerular filtration rate
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5 The first two exclusion criteria were chosen since patients should not be subjected to
6 additional risk as a result of the waiting time in the MIS²ACE arm before TAAA repair can be
7 performed. The third exclusion criterion was chosen since these patients have considerable
8 risk unrelated to the focus of the trial. Exclusion criterion 4 was chosen, since sufficient blood
9
10 supply after MIS²ACE cannot be guaranteed on the one hand, and the prior occlusion implies
11 85 that no additional treatment options are available in this anatomic region.
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15 **Intervention**

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17 An overview of the trial is provided in Fig. 1. The treating physicians choose the mode of
18 repair, after which the patient is randomized to the interventional or the control arm.
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21 90 In the interventional arm (MIS²ACE), segmental arteries will be occluded in one to three
22 sessions some weeks before the aneurysm repair. Target SAs for coil/plug deployment will be
23 identified considering the extent of the planned repair and individual SA anatomy. The
24 occlusion of up to 7 SAs will be performed in a single session and conducted through a
25 peripheral artery access (e.g. the common femoral artery) in local anaesthesia. Local
26 anaesthesia is important so that patients can provide immediate feedback regarding potential
27 neurological symptoms. Selected SAs will be catheterized (e.g. with a 5F catheter or 2.7F
28 microcatheter). Microcoils or vascular plugs will be used for the occlusion itself, not however
29 particles, which could cause unwanted microembolisms to the spinal cord directly. This will
30 95 be performed in the proximal SA to ensure that the collateral network itself is not affected.
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37 100 The procedure may be done without spinal fluid drainage but is left at the discretion of the
38 centre. The length of the procedure, the amount of contrast dye and the dose of radiation will
39 be documented exactly. The recommended interval between sessions is 21 days, with a strict
40 safety minimum of 5 days.[11] Experts in endovascular catheterization in small vessels (e.g.
41 cardiovascular surgeons, interventionalists, endovascular surgeons, interventional
42 radiologists, paediatric cardiologists) will perform MIS²ACE. It is essential to maintain the
43 individual patient's blood pressure during and after the procedure (invasive monitoring) and
44 ensure that hypotensive periods are carefully avoided. Therefore, the patient should stay in
45 IMCU for at least 48 hours, preferably longer. Reduction or even interruption of oral anti-
46 hypertensive medication and use of low-dose vasopressors may be utilized and are preferable
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51 110 to volume therapy, which increases central venous pressure and thereby also CSF pressure.
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3 In the control arm, patients will be treated according to the optimal state-of-the art procedures
4 at the local site. This ensures a real-world comparison in which the control arm is as strong as
5 possible.
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8 **Endpoints**

10 115 *Primary endpoint*

12 The primary endpoint is successful treatment of the aneurysm. We define “success” as (a) the
13 patient is alive and without substantial SCI 30 days after treatment, and (b) the aneurysm did
14 not rupture and has been excluded within six months of randomization.
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18 Patients, who have not been treated within six months of randomization will be treated as
19 failures to ensure that success/failure is defined for all randomized patients. During
20 120 recruitment, the Trial Steering Committee will ensure that time lapse alone leads only very
21 rarely to failure, otherwise this criterion will be reworked. The definition of success
22 pertaining to mortality and SCI will be assessed 30 days after TAAA repair and “substantial
23 SCI” means that the patient is unable to stand without assistance and is specifically defined
24 using a modified Tarlov scale[21] and assessed by a board certified neurologist whenever
25 125 possible. Treatment success for open repair is defined by complete resection and graft
26 replacement in the absence of major related complications.
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33 *Secondary endpoints*

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35 For secondary endpoints, treatment success will be assessed and based on follow-up CT/MR
36 130 images. Treatment success for endovascular repair is defined based on the position paper of
37 the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of
38 Cardiology (ESC), in collaboration with the European Association of Percutaneous
39 Cardiovascular Interventions (EAPCI)[22] and takes into account upcoming guideline papers.
40 Failure is defined as substantial progression of the aneurysm sac (> 3mm) or the presence of
41 135 major related complications (e.g. type I/III endoleaks). Completion angiography and/or
42 follow-up MRI/CT from patients with endovascular repair will be conducted as part of
43 clinical routine and will be sent to Copenhagen for assessment.
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51 Note: The point in time “one year” refers to one year after TAAA repair. If patients retained
52 in the full analysis set have not had a repair, then “30 days after TAAA repair” and “at one
53 140 year” will be treated as 30 days and one year after randomization.
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55

- 56 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
- 145 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)
- 150 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

- 155 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.

160 **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

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3 175 compliance will not be a problem. The severity of the therapy and recovery times mean that
4 loss to follow-up is not expected to be a major factor.
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6 7 **Randomization**

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9 Patients will be randomized in a 1:1 ratio to the intervention and control arms with a random
10 number generator. Randomization will be performed online at the recruitment centres with a
11
12 180 tool prepared and hosted by the Clinical Trial Centre Leipzig
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14 Some of the centres are expected to recruit a very small number of patients, meaning that
15 block randomization stratified by centre is unfeasible. Although minimization schemes could
16 be used to attain roughly balanced allocation of patients, even at the centre level, there is
17 controversy about the methods needed to analyse such trials. To avoid potential complexities
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21 185 in analysis, we have thus opted for a very simple randomization scheme, knowing that small
22 imbalances in the number of patients per arm are to be expected.
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24 25 **Selected data collection methods**

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27 Neurological examinations will be performed by board certified neurologists whenever
28 possible. If such an examination is made upon discharge and no signs of impairment are
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30 190 found, then verification that this holds at 30 days is only required by telephone. Any signs of
31 impairment necessitate a full examination at 30 days however.
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34 If the assessment of Crawford classification or successful treatment carried out by the
35 radiological unit in Copenhagen should disagree with the treating physician's opinion, the
36 blinded independent Endpoint Committee will make the final decision. The definition of
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39 195 success does not necessarily require that the MRI/CT be made within six months of
40 randomization. Later verification of success is acceptable.
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42 43 **Data management**

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45 The EDC tool SecuTrial®, developed and distributed by interActive Systems GmbH, is used
46 for creation of the study database. Data entry uses eCRF data entry masks and data changes
47
48 200 are tracked automatically including date, time and person who entered/changed information
49 (audit trail). Major corrections or major missing data have to be explained.
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52 The information entered into the eCRF by the investigator or an authorised member of the
53 study team is systematically checked for completeness, consistency and plausibility by
54 routines implemented in the database, such that discrepancies can be dealt with at data entry.
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57 205 Errors and warnings are listed in a validation report and can be resolved at any time during
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3 the data entry process. On completion of data entry, the site staff flags the eCRF-pages as
4 'data entry completed'.
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7 Throughout the study, a backup of all data is made on a daily basis. Unauthorised access to
8 patient data is prevented by the access concept of the study database, which is based on strict
9
10 210 file system permission.

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12 At the end of the study, once the database is complete and accurate, the database will be
13 locked. Subsequent changes to the database are possible only by joint written agreement
14 between co-ordinating investigator, trial statistician and data manager.
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19 215 **Statistical methods**

20 21 *Analysis Sets*

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23 If patients retract informed consent before any procedure is performed (repair or SA
24 occlusion), they will be excluded from the primary analysis, since we expect some control
25 arm patients to be dissatisfied with their assigned treatment, retract consent, and seek
26
27 220 MIS²ACE outside of the trial. Including them would be anti-conservative. The full analysis
28 set (FAS) includes all randomized patients that have had a session for occluding segmental
29 arteries (intervention arm) or have had a repair procedure (conventional arm). Randomized
30 patients whose aneurysm ruptures or who die from any cause will be included in the FAS,
31 irrespective of the above stipulations.
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37 225 If a sufficiently large number of patients violate the trial protocol, particularly regarding the
38 trial intervention, then a per protocol analysis will be performed using the set of patients that
39 conformed to the major terms in the protocol. A precise definition of the per protocol set will
40 be provided in the statistical analysis plan.
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45 Patients are generally analysed regarding safety according to treatment received. In our case,
46 230 an undue delay between randomization and treatment is a risk factor, meaning that such
47 patients will be included in the safety analyses even if they have not yet received treatment.
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50 *Statistical Analysis*

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52 The primary analysis is based on the FAS and makes use of a generalized linear mixed model
53 with the logit link function. The success/failure of treatment will be the dependent variable.
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55 235 The assigned randomization arm, mode of repair (open or endovascular repair), the Crawford
56 type and the euroSCORE II are fixed effects and the centre will be treated as a random effect.
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3 The euroSCORE II already takes age, sex and other relevant factors into account. The
4 interaction term between the randomization arm and the other fixed effects will only be
5 included if evidence for a strong interaction effect are seen, since this would otherwise lead to
6 a substantial loss of power.[35, 36] As a supplementary analysis, an analogous mixed model
7 240 will be performed with a unity link function to provide estimates and confidence intervals for
8 absolute risk differences.
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13 The definitions of the full analysis set and the primary endpoint are chosen so that almost no
14 missing data are expected. If success cannot be ascertained with certainty, the patient will be
15 245 treated as a failure. Sensitivity analyses will be used to gauge the effect of missing data on the
16 estimates and conclusions drawn.
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21 Analysis of binary secondary outcomes will be treated on the same footing as the primary
22 analysis. Mortality at 30 days will be treated as binary as opposed to time-to-event, since
23 prolonging life in the post-operative phase for a matter of days is not considered clinically
24 250 relevant. Subgroup analyses of the two Crawford types and of the two modes of repair will be
25 presented in the form of contingency tables. Mixed model Cox regression with covariates
26 euroSCOREII, Crawford type and mode of repair will be used for one-year mortality with
27 randomization arm as the independent variable of interest and centre as a random effect. If the
28 assumption of proportional hazards is violated substantially, a logistic regression will be used.
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33 255 Kaplan-Meier curves will be used to represent the data.
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36 In explorative analyses, the number of patent segmental arteries and the number occluded will
37 be taken into account with respect to SCI and mortality. The anatomical position of the
38 segmental arteries may also be used.
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42 ICU-time and ICMU-time will be analysed with a linear mixed effects model with the same
43 260 fixed and random effects as in the primary analysis and may be log transformed if warranted.
44 Re-operation for bleeding and type II endoleaks will be presented for the subgroups of
45 patients treated with open or endovascular repair, respectively.
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49 Descriptive statistics will be used for further safety outcomes along with odds ratios
50 according to treatment received, as appropriate.
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52 265 Total mean cost per patient over one year will be estimated by multiplying healthcare
53 resource use collected in the trial by unit costs from the country health system.[37] QALYs
54 will be calculated in each treatment group using the EQ-5D-5L value set.[38] The ICER will
55 be calculated, and will inform whether MIS²ACE is cost-effective on average for patients with
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3 TAAA Crawford type II or III. Bootstrap methods will be used to characterize
4 270 uncertainty.[25]
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6 Further details will be provided in a statistical analysis plan.
7

8 **Statistical monitoring**

9
10 The trial conduct will be closely supervised by means of central and statistical monitoring.
11 The objectives are a) to detect safety relevant signals as soon as possible, b) to detect non-
12 275 compliance and relevant protocol violations and to prevent their future occurrence by prompt
13 reaction, c) to prevent missing visits or measurements by prompt reminders and d) to explore
14 means of improving on the MISACE procedure.
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19 Statistical and central monitoring will start immediately after inclusion of the first patient. The
20 relevant reports and descriptive statistics will be updated and discussed at the regular
21 280 meetings of the Leipzig study team. Problems and abnormalities will be presented at regular
22 intervals to the co-ordinating investigator.
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26 **On-site monitoring**

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28 A risk-based monitoring strategy will be implemented as required by ICH E6 (Chapter 5.0)
29 According to the risk analysis, treatment delivery parameters, adverse events, follow-up
30 285 information, data transmission and protection and informed consent documents comprise risk-
31 bearing trial aspects and will be monitored.
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36 Prior to recruitment, each participating centre will receive a site initiation visit, during which
37 the trial protocol (if necessary) and the eCRFs will be reviewed with centre staff and any
38 necessary training will be provided. During the study, trial monitors will maintain regular
39 290 contact with trial centre staff (by telephone/fax/email /post) to track the progress of the trial,
40 respond to any problems, and provide general assistance and support.
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45 The first regular monitoring visit at a site will take place after the randomization of the site's
46 first patient to check protocol compliance and to prevent further systematic errors due to
47 misunderstandings. Trial site visits will take place on a regular basis. The frequency of
48 295 monitoring visits will depend on the trial site's recruitment rate as well as on potential
49 problems detected during previous on-site visits or by central monitoring.
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53 Prior to every scheduled on-site visit, the monitor will receive summaries of the site's patient
54 data already documented in the database, and if applicable with data indicating possible
55 protocol deviations or inconsistencies. During the visits, the monitor will a) check informed
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3 300 consent forms of all patients enrolled, b) perform source data verification of key data in a
4 random sample of at least 20% of the site's patients, c) perform targeted source data
5 verification for patients with possible deviations, d) discuss open queries raised by data
6 management or drug safety personnel, e) check essential parts of the investigator site file, f)
7 check source data for AEs or SAEs, which have not been properly reported in the CRF/eCRF
8 and g) check for major GCP-breaches and/or protocol violations.
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12 **Harms**

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15 Safety endpoints related directly to MIS²ACE include kidney failure, respiratory failure and
16 embolic events (also from debris). These endpoints will be listed according to treatment
17 received with a breakdown according to the number of MIS²ACE sessions. In addition, data
18 on radiation exposure will be collected and presented descriptively.
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ETHICS AND DISSEMINATION

Approval and registration

315 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

320 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.

325 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

330 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.

335 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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3 445 **Authors' contributions**
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5 DP: study conception and design, statistical methods and sample size calculations, writing and
6 reviewing of the manuscript. MC, TK, GM, KvA, JH: study design with particular focus on
7 cardiovascular endpoints, reviewing of the manuscript. LL: study design with particular focus
8 on radiological methods, reviewing of the manuscript. PN, KP: study design, ethics, data
9 management, writing and reviewing of the manuscript. JP: study design with particular focus
10 on neurological methods and endpoints, reviewing of the manuscript. DE: study design with
11 450 particular focus on health economics and patient satisfaction, reviewing of the manuscript.
12 CDE: research that lay foundation for trial, initial study conception, study design, writing and
13 reviewing of the manuscript. All authors have read and approved the final manuscript.
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28 **Competing interests statement**
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30 460 The authors have no competing interests related to this trial.
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37 **Figure Legends**
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39 **Figure 1:** Schematic portrayal of the participant timeline and visit schedule for the PAPAartis
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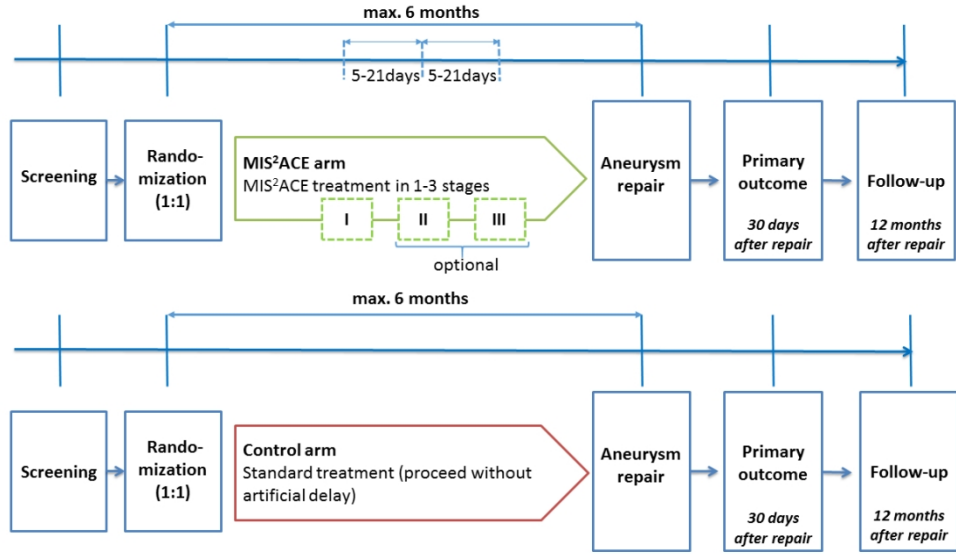


Figure 1: Schematic portrayal of the participant timeline and visit schedule for the PAPAartis trial.

338x190mm (96 x 96 DPI)

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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Keywords:	Thoracoabdominal aortic aneurysms, TAAA, spinal cord injury, SCI, segmental artery coil embolization, MISACE

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3 **Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal**
4 **Staging with ‘Minimally-Invasive Staged Segmental Artery Coil-**
5 **Embolization’ (MIS²ACE): Trial protocol for a Randomized Controlled**
6 **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 (MIS²ACE) 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 MIS²ACE 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)

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3 9. severe contrast agent allergy, severe reduction in glomerular filtration rate
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6 The first two exclusion criteria were chosen since patients should not be subjected to
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8 85 additional risk as a result of the waiting time in the MIS²ACE arm before TAAA repair can be
9 performed. The third exclusion criterion was chosen since these patients have considerable
10 risk unrelated to the focus of the trial. Exclusion criterion 4 was chosen, since sufficient blood
11 supply after MIS²ACE cannot be guaranteed on the one hand, and the prior occlusion implies
12 that no additional treatment options are available in this anatomic region.
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17 90 **Intervention**

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19 An overview of the trial is provided in Fig. 1. The treating physicians choose the mode of
20 repair, after which the patient is randomized to the interventional or the control arm.
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23 In the interventional arm (MIS²ACE), segmental arteries (SAs) will be occluded in one to
24 three sessions some weeks before the aneurysm repair. Target SAs for coil/plug deployment
25 will be identified considering the extent of the planned repair and individual SA anatomy. The
26 95 occlusion of up to 7 SAs will be performed in a single session and conducted through a
27 peripheral artery access (e.g. the common femoral artery) in local anaesthesia. Local
28 anaesthesia is important so that patients can provide immediate feedback regarding potential
29 neurological symptoms. Selected SAs will be catheterized (e.g. with a 5F catheter or 2.7F
30 microcatheter). Microcoils or vascular plugs will be used for the occlusion itself, not however
31 particles, which could cause unwanted microembolisms to the spinal cord directly. This will
32 be performed in the proximal SA to ensure that the collateral network itself is not affected.
33 The procedure may be done without spinal fluid drainage but this is left at the discretion of
34 the centre. The length of the procedure, the amount of contrast dye and the dose of radiation
35 100 will be documented exactly. The recommended interval between sessions is 21 days, with a
36 strict safety minimum of 5 days.[11] Experts in endovascular catheterization in small vessels
37 (e.g. cardiovascular surgeons, interventionalists, endovascular surgeons, interventional
38 radiologists, paediatric cardiologists) will perform MIS²ACE. It is essential to maintain blood
39 pressure above 140 mmHg, but for hypertensive patients, it is imperative that the post-
40 operative pressure should not fall below their individual pre-operative systolic blood pressure
41 during and after the procedure (invasive monitoring), ideally for at least 2 days. Anti-
42 hypertensive drugs have to be adjusted accordingly. Therefore, the patient should stay in the
43 IMCU for at least 48 hours, preferably longer. Reduction or even interruption of oral anti-
44 105 hypertensive medication and use of low-dose vasopressors may be utilized and are preferable
45 to volume therapy, which increases central venous pressure and thereby also CSF pressure.
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3 In the control arm, treatment will be according to the optimal state-of-the art procedures at the
4 local site. This ensures a real-world comparison in which the control arm is as strong as
5 possible.
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9 As the trial proceeds, statistical monitoring and concomitant projects may identify need for
10 revisions to the intervention. These alterations will then be adopted with protocol
11 120 amendments to optimize patient safety.
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14 **Endpoints**

15 *Primary endpoint*

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17 The primary endpoint is successful treatment of the aneurysm. We define “success” as (a) the
18 patient is alive and without substantial SCI 30 days after treatment, and (b) the aneurysm did
19 not rupture and was excluded within six months of randomization.
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24 Patients, who have not been treated within six months of randomization will be treated as
25 failures to ensure that success/failure is defined for all randomized patients. This facilitates
26 the intention to treat analysis (see below) and reduces the amount of missing data. During
27 recruitment, the Trial Steering Committee will ensure that time lapse alone leads only very
28 rarely to failure, otherwise this criterion will be reworked. The definition of success
29 pertaining to mortality and SCI will be assessed 30 days after TAAA repair and “substantial
30 130 SCI” means that the patient is unable to stand without assistance and is defined using the
31 modified Tarlov scale[22] (see below) and assessed by a board certified neurologist whenever
32 possible:
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41 0 – No lower extremity movement

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43 1 – Lower extremity motion without gravity

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45 2 – Lower extremity motion against gravity

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47 3 – Able to stand with assistance

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49 4 – Able to walk with assistance
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52 5 – Normal
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55 A training video describing this scale is provided for study personnel.
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58 Treatment success for open repair is defined by complete resection and graft replacement in
59 the absence of major related complications.
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3 145 *Secondary endpoints*
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5 For secondary endpoints, treatment success will be assessed and based on follow-up CT/MR
6 images. Treatment success for endovascular repair is defined based on the position paper of
7 the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of
8 Cardiology (ESC), in collaboration with the European Association of Percutaneous
9 Cardiovascular Interventions (EAPCI)[23] and takes into account upcoming guideline papers.
10 Failure is defined as substantial progression of the aneurysm sac (> 3 mm) or the presence of
11 major related complications (e.g. type I/III endoleaks). Completion angiography and/or
12 follow-up MRI/CT from patients with endovascular repair will be conducted as part of
13 clinical routine and will be sent to Copenhagen for assessment.
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22 155 Note: The point in time “one year” refers to one year after TAAA repair. If patients retained
23 in the full analysis set have not had a repair, then “30 days after TAAA repair” and “at one
24 year” will be treated as 30 days and one year after randomization.
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- 27 1. Substantial SCI at 30 days after TAAA repair and at one year
- 28 2. SCI according to the modified Tarlov scale from TAAA repair treatment to one year
- 29 30 3. All-cause mortality at 30 days and one year after TAAA repair
- 31 32 4. Length of stay in intensive care unit and intermediate care unit after TAAA repair
- 33 34 5. Sub-group analyses for open repair and endovascular repair separately
- 35 36 6. Re-operation for bleeding and drainage volumes in the first 24 h and use of blood
37 products (only for open repair)
- 38 39 7. Cross-clamping times during open surgery
- 40 41 8. Residual aneurysm sac perfusion, i.e. type II endoleaks (only for endovascular repair)
- 42 43 9. Health-related quality of life will be collected using the WHOQOL-BREF[24] and the
44 EuroQoL EQ-5D-5L instruments.[25] Hospital and other healthcare resource use will
45 be collected. Healthcare costs, quality-adjusted life years (QALYs) and the
46 incremental cost-effectiveness ratio (ICER) over one year will be calculated.[26]
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50 *Safety endpoints*
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52 Beyond AE/SAE reporting and descriptive statistics on radiation exposure, the following
53 issues will receive special attention: kidney failure, respiratory failure and embolic events
54 (also from debris). Kidney failure is defined as requiring dialysis and or deterioration in
55 chronic kidney disease (CKD) stage by at least two stages. Acute and chronic kidney disease
56 175 will be distinguished. Having identified particular safety risks in the trial aids us in collecting
57 appropriate data, assessing and reporting these harms, as recommended by SPIRIT. [1, 2] We
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2
3 do not use these to define stopping criteria however, which is left at the discretion of the Data
4 Monitoring Committee.

6 180 **Participant timeline**

8
9 Please refer to Fig. 1 for details of the visit schedule and participant timeline.

11 **Sample size and recruitment**

13
14 Estimates of effect size are difficult for several reasons. Foremost, there are large
15 discrepancies between outcome rates quoted in the literature. Moreover, the impact of recent
16 improvements in techniques on outcomes cannot yet be quantified accurately and, finally the
17 185 effect size depends on the improvement due to the trial intervention, which, in turn, depends
18 on anatomy, post-repair management and other complex factors. Taking a random effects
19 model of the data from large recent publications for open [10, 27–29] and endovascular repair
20 [30–32] one finds an estimated incidence of 18% (95% prediction interval 15% to 23%) for
21 open repair and a very uncertain 24% (2 to 79)% for endovascular repair. The prediction
22 interval as opposed to the confidence interval provides the correct bounds for what can be
23 expected in the trial.[33] The resources and time available to the study allow for the
24 recruitment of 500 patients. Assuming success rates of 80% in the control arm and 90% in the
25 190 intervention arm and using a group-sequential design [34] with two interim analyses, this then
26 implies a power of just over 87%.[35] The definitions of the primary endpoint and the full
27 analysis set imply that only very few dropouts are to be expected for this analysis and that
28 compliance will not be a problem. The severity of the therapy and recovery times mean that
29 loss to follow-up is not expected to be a major factor.

31
32 The planned recruitment is between 8 and 9 patients per site per year. This is roughly half the
33 number of patients that meet the inclusion criteria. However, slow recruitment plagues many
34 200 trials and mitigation strategies have already been developed. A list of interested recruitment
35 sites ($n > 10$) is being collected to expand the consortium. Statistical monitoring will be used
36 to identify reasons for screened patients not being included in the trial so that minor and
37 clinically justified amendments to the trial protocol can address these issues, e.g. through
38 adjustments to the inclusion and exclusion criteria. Finally, a newsletter including recruitment
39 205 by site will be distributed at regular intervals to spawn healthy competition among the team
40 members.

58 **Randomization**

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2
3 Patients will be randomized in a 1:1 ratio to the intervention and control arms with a random
4
5 210 number generator. Randomization will be performed online at the recruitment centres with a
6
7 tool prepared and hosted by the Clinical Trial Centre Leipzig

8
9 Some of the centres are expected to recruit a very small number of patients, meaning that
10
11 block randomization stratified by centre is unfeasible. Although minimization schemes could
12
13 be used to attain roughly balanced allocation of patients, even at the centre level, there is
14 215 controversy about the methods needed to analyse such trials. To avoid potential complexities
15
16 in analysis, we have thus opted for a very simple randomization scheme, knowing that small
17
18 imbalances in the number of patients per arm are to be expected.

20 **Selected data collection methods**

21
22 Neurological examinations will be performed by board certified neurologists whenever
23
24 220 possible. If such an examination is made upon discharge and no signs of impairment are
25
26 found, then verification that this holds at 30 days is only required by telephone. Any signs of
27
28 impairment necessitate a full examination at 30 days however.

29
30 If the assessment of Crawford classification or successful treatment carried out by the
31
32 radiological unit in Copenhagen should disagree with the treating physician's opinion, the
33 225 blinded independent Endpoint Committee will make the final decision. The definition of
34
35 success does not necessarily require that the MRI/CT be made within six months of
36
37 randomization. Later verification of success is acceptable.

38 **Data management**

39
40 The EDC tool SecuTrial®, developed and distributed by interActive Systems GmbH, is used
41
42 230 for creation of the study database. Data entry uses eCRF data entry masks and data changes
43
44 are tracked automatically including date, time and person who entered/changed information
45
46 (audit trail). Major corrections or major missing data have to be explained.

47
48 The information entered into the eCRF by the investigator or an authorised member of the
49
50 study team is systematically checked for completeness, consistency and plausibility by
51
52 235 routines implemented in the database, such that discrepancies can be dealt with at data entry.
53
54 Errors and warnings are listed in a validation report and can be resolved at any time during
55
56 the data entry process. On completion of data entry, the site staff flags the eCRF-pages as
57
58 'data entry completed'.
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3 Throughout the study, a backup of all data is made daily. Unauthorised access to patient data
4
5 240 is prevented by the access concept of the study database, which is based on strict file system
6 permission.
7

8
9 At the end of the study, once the database is complete and accurate, the database will be
10 locked. Subsequent changes to the database are possible only by joint written agreement
11 between co-ordinating investigator, trial statistician and data manager.
12
13

14 15 245 **Statistical methods**

16 17 *Analysis Sets*

18
19 If patients retract informed consent before any procedure is performed (repair or SA
20 occlusion), they will be excluded from the primary analysis, since we expect some control
21 arm patients to be dissatisfied with their assigned treatment, retract consent, and seek
22 MIS²ACE outside of the trial. Including them would be anti-conservative. The full analysis
23 set (FAS) includes all randomized patients that have had a session for occluding segmental
24 250 arteries (intervention arm) or have had a repair procedure (conventional arm). Randomized
25 patients whose aneurysm ruptures or who die from any cause will be included in the FAS,
26 irrespective of the above stipulations.
27
28

29
30 If a sufficiently large number of patients violate the trial protocol, particularly regarding the
31 trial intervention, then a per protocol analysis will be performed using the set of patients that
32 conformed to the major terms in the protocol. A precise definition of the per protocol set will
33 be provided in the statistical analysis plan.
34 255

35
36 Patients are generally analysed regarding safety according to treatment received. In our case,
37 an undue delay between randomization and treatment is a risk factor, meaning that such
38 260 patients will be included in the safety analyses even if they have not yet received treatment.
39

40 41 *Statistical Analysis*

42
43 The primary analysis is an intention to treat (ITT) analysis based on the FAS and makes use
44 of a generalized linear mixed model with the logit link function. The success/failure of
45 265 treatment will be the dependent variable. The assigned randomization arm, mode of repair
46 (open or endovascular repair), the Crawford type and the euroSCORE II are fixed effects and
47 the centre will be treated as a random effect. The euroSCORE II already takes age, sex and
48 other relevant factors into account. The interaction term between the randomization arm and
49 the other fixed effects will only be included if evidence for a strong interaction effect are seen,
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3 270 since this would otherwise lead to a substantial loss of power.[36, 37] As a supplementary
4 analysis, an analogous mixed model will be performed with a unity link function to provide
5 estimates and confidence intervals for absolute risk differences.
6
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8
9 The definitions of the full analysis set and the primary endpoint are chosen so that almost no
10 missing data are expected. If success cannot be ascertained with certainty, the patient will be
11
12 275 treated as a failure. Sensitivity analyses will be used to gauge the effect of missing data on the
13 estimates and conclusions drawn.
14
15

16 Interim analyses are planned 30 days after 50% of patients (n=250) and 75% (n=375) have
17 been treated for the aneurysm. The primary endpoint will be analysed and randomization can
18 be terminated for efficacy if a p-value of 0.0030 (first interim analysis) or 0.018 (second
19
20 280 interim analysis) is reached. The p-value for demonstrating efficacy in the final analysis is
21 0.044.
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26 Analysis of binary secondary outcomes will be treated on the same footing as the primary
27 analysis. Mortality at 30 days will be treated as binary as opposed to time-to-event, since
28 prolonging life in the post-operative phase for a matter of days is not considered clinically
29 relevant. Subgroup analyses of the two Crawford types and of the two modes of repair will be
30
31 285 presented in the form of contingency tables. Mixed model Cox regression with covariates
32 euroSCOREII, Crawford type and mode of repair will be used for one-year mortality with
33 randomization arm as the independent variable of interest and centre as a random effect. If the
34 assumption of proportional hazards is violated substantially, a logistic regression will be used.
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39 290 Kaplan-Meier curves will be used to represent the data.
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42 In explorative analyses, the number of patent segmental arteries and the number occluded will
43 be taken into account with respect to SCI and mortality. The anatomical position of the
44 segmental arteries may also be used.
45
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48 ICU-time and ICMU-time will be analysed with a linear mixed effects model with the same
49
50 295 fixed and random effects as in the primary analysis and may be log transformed if warranted.
51 Re-operation for bleeding and type II endoleaks will be presented for the subgroups of
52 patients treated with open or endovascular repair, respectively.
53
54

55 Descriptive statistics will be used for further safety outcomes along with odds ratios
56 according to treatment received, as appropriate.
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59 300 Total mean cost per patient over one year will be estimated by multiplying healthcare
60 resource use collected in the trial by unit costs from the country health system.[38] QALYs

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3 will be calculated in each treatment group using the EQ-5D-5L value set.[39] The ICER will
4 be calculated, and will inform whether MIS²ACE is cost-effective on average for patients with
5 TAAA Crawford type II or III. Bootstrap methods will be used to characterize
6
7
8 305 uncertainty.[26]

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10 Further details will be provided in a statistical analysis plan.

11 12 13 **Statistical monitoring**

14
15 The trial conduct will be closely supervised by means of central and statistical monitoring.

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17 The objectives are a) to detect safety relevant signals as soon as possible, b) to detect non-
18
19 310 compliance and relevant protocol violations and to prevent their future occurrence by prompt
20 reaction, c) to prevent missing visits or measurements by prompt reminders and d) to explore
21 means of improving on the MIS²ACE procedure.

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25 Statistical and central monitoring will start immediately after inclusion of the first patient. The
26 relevant reports and descriptive statistics will be updated and discussed at the regular
27
28 315 meetings of the Leipzig study team. Problems and abnormalities will be presented at regular
29 intervals to the co-ordinating investigator.

30 31 32 **On-site monitoring**

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34 A risk-based monitoring strategy will be implemented as required by ICH E6 (Chapter 5.0)
35 According to the risk analysis, treatment delivery parameters, adverse events, follow-up
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37 320 information, data transmission and protection and informed consent documents comprise risk-
38 bearing trial aspects and will be monitored.

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42 Prior to recruitment, each participating centre will receive a site initiation visit, during which
43 the trial protocol (if necessary) and the eCRFs will be reviewed with centre staff and any
44 necessary training will be provided. During the study, trial monitors will maintain regular
45
46 325 contact with trial centre staff (by telephone/fax/email/post) to track the progress of the trial,
47 respond to any problems, and provide general assistance and support.

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51 The first regular monitoring visit at a site will take place after the randomization of the site's
52 first patient to check protocol compliance and to prevent further systematic errors due to
53 misunderstandings. Trial site visits will take place on a regular basis. The frequency of
54
55 330 monitoring visits will depend on the trial site's recruitment rate as well as on potential
56 problems detected during previous on-site visits or by central monitoring.

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2
3 Prior to every scheduled on-site visit, the monitor will receive summaries of the site's patient
4 data already documented in the database, and if applicable with data indicating possible
5 protocol deviations or inconsistencies. During the visits, the monitor will a) check informed
6
7
8 335 consent forms of all patients enrolled, b) perform source data verification of key data in a
9 random sample of at least 20% of the site's patients, c) perform targeted source data
10 verification for patients with possible deviations, d) discuss open queries raised by data
11 management or drug safety personnel, e) check essential parts of the investigator site file, f)
12 check source data for AEs or SAEs, which have not been properly reported in the CRF/eCRF
13 and g) check for major GCP-breaches and/or protocol violations.
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18 19 **Harms**

20
21 Safety endpoints related directly to MIS²ACE include kidney failure, respiratory failure and
22 embolic events (also from debris). These endpoints will be listed according to treatment
23 received with a breakdown according to the number of MIS²ACE sessions. In addition, data
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25
26
27 345 on radiation exposure will be collected and presented descriptively.
28

29 **Patient and Public Involvement**

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31 The trial protocol was developed in part by physicians with years of experience in treating
32 TAAA patients. Their experience indicated that paraplegia is the greatest concern that patients
33 have when deliberating on whether or not to be treated, and was thus chosen along with
34 mortality for the primary outcome. A qualitative study will recruit a small number of patients
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37 350 for one-on-one in-depth interviews in different sites of the trial. The goal is for the patient to
38 express in his or her own words the impact on their life of diagnosis and treatment, and look at
39 changes that occur in quality of life, family, work, lifestyle and social environment from an
40 ethnographic standpoint. Patients and the public have not yet been involved directly in the trial.
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355 **ETHICS AND DISSEMINATION**

Approval and registration

8 The trial protocol and the informed consent form have been reviewed and approved by the
9 lead Ethics Committee from the University of Leipzig (435/17-ek) and will be reviewed by
10 each of the Ethics Committees at the trial sites. The Federal Office for Radiation Protection in
11 Germany has also approved the additional radiation use in the intervention group (Z5-22462/2
12 – 2017-073). The trial has been registered with clinicaltrials.gov (NCT03434314).
13
14 360

15 Amendments to the protocol will be reviewed by Ethics Committees. Informed consent will
16 be obtained before collecting any patient data and patient information.
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External boards

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23 365 A Data Monitoring Committee (DMC) has been established to oversee patient safety and data
24 quality in the trial. It consists of three members with expertise in aortic surgery, neurology
25 and medical statistics. The DMC charter states that its role is to “safeguard the interests of
26 trial participants, assess the safety and efficacy of the interventions during the trial, and assist
27 and advise the trial steering committee to protect the validity and credibility of the trial. In
28 order to do this, the DMC evaluates the results of the regular reports and their influence on the
29 risk assessment for the patients as well as for the integrity of the trial. The DMC gives its
30 recommendations at regular intervals as to whether the continuation of the trial is justifiable.”
31
32 370 Only the trial statistician and the DMC members will have access to the interim analyses until
33 the end of the trial. At the inaugural meeting the members of the DMC will be asked to
34 discuss whether SAEs related to the MIS²ACE procedure should be sent to them without
35 delay.
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45 An expert advisory board consisting of four international experts on TAAA repair provide the
46 active trial members with independent advice regarding trial design and conduct. It meets
47 with leading members of the consortium on an annual basis and is kept abreast of the trial’s
48 progress.
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50 380

Dissemination

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54 One project partner (MODUS Research and Innovation, Edinburgh, Scotland) has a project
55 dedicated to communication and dissemination. Key channels, tools and target audiences for
56 dissemination and use of project results will be identified in a Communication and
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59 385
60 Dissemination Plan. The dissemination activities will be two-fold: basic communication about

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2
3 the project to the public and specific dissemination to four target communities. One objective
4 of the dissemination plan will be to support the project partners with the clinical recruitment.
5 The other objective will be to reach out to wide audiences outside the project consortium at
6 national, European and international levels (medical and health professionals, academics,
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10 390 medical and biomedical industries, policy makers, EU regulators (e.g. the European
11 Medicines Agency), patients groups, health NGOs, civil societies, scientific and lay media.
12 The dissemination vehicles will be seminars, medical conferences and publications, project
13 partners' individual communication streams. Dissemination material may include a project
14 leaflet, newsletter, press releases and a trial website.
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Authors' contributions

495 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
500 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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innovation programme under grant agreement 733203 and from the German Research
Foundation under grant number ET 127/2-1.

Competing interests statement

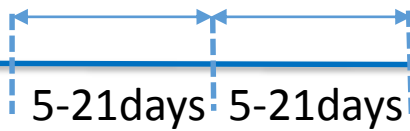
510 The authors have no competing interests related to this trial.

Figure Legends

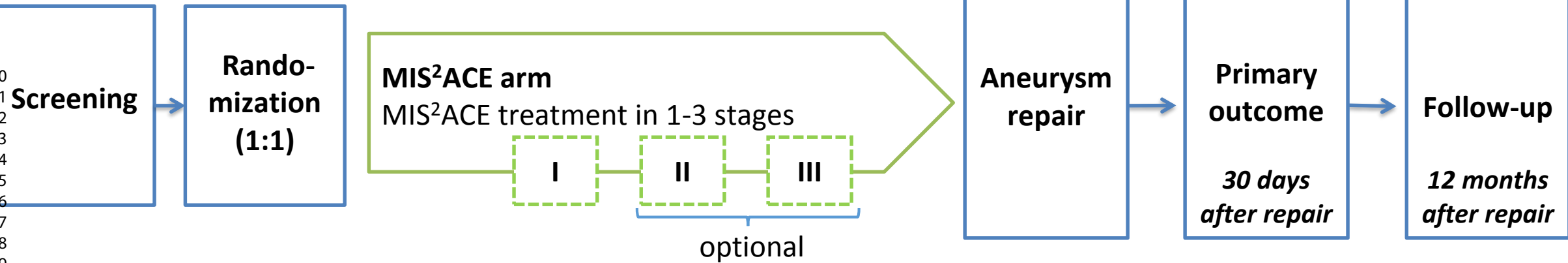
515 **Figure 1:** Schematic portrayal of the participant timeline and visit schedule for the PAPAartis
trial.

max. 6 months

BMJ Open



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max. 6 months





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 <i>Title page</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <i>End of Abstract</i>
	2b	All items from the World Health Organization Trial Registration Data Set <i>Available through the clinicaltrials.gov website and in the full trial protocol</i>
Protocol version	3	Date and version identifier <i>Not applicable</i>
Funding	4	Sources and types of financial, material, and other support <i>Lines 508-510</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <i>Lines 496-506</i>
	5b	Name and contact information for the trial sponsor <i>Not applicable (there is no legal "sponsor" function, but the coordinating investigator was named)</i>
	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 <i>Not applicable</i>

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- 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)

Described throughout paper

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Introduction

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16
- 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

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Line 32-44

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- 6b Explanation for choice of comparators

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Lines 116-119

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- Objectives 7 Specific objectives or hypotheses

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Lines 45-47

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- 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)

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Lines 49-51

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36

Methods: Participants, interventions, and outcomes

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- 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

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Lines 54-64

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- 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)

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Lines 66-89

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- Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

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Lines 91-118

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- 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:

1
2 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

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11 *Lines 209-211*

12 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

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19 *Lines 213-214*

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

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25 *Line 211*

26 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

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31
32 *Not applicable (discussed as limitation)*

33 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

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37
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39 *Not applicable*

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

41
42 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

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52 *Lines 142, 219-227*

53 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

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60 *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
- 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
- Lines 263-276*
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)
- 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)
- 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
- 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
- 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
- Lines 172-179, 342-345*

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2 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
3 whether the process will be independent from investigators and the
4 sponsor
5

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7 *Lines 318-340, 365-380*
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9 **Ethics and dissemination**

10
11 Research ethics 24 Plans for seeking research ethics committee/institutional review board
12 approval (REC/IRB) approval
13

14
15 *Lines 357-361*
16

17 Protocol amendments 25 Plans for communicating important protocol modifications (eg,
18 changes to eligibility criteria, outcomes, analyses) to relevant parties
19 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
20 regulators)
21

22
23 *Line 362.*
24

25 Consent or assent 26a Who will obtain informed consent or assent from potential trial
26 participants or authorised surrogates, and how (see Item 32)
27

28
29 *Not applicable (part of trial protocol and delegation lists, but too
30 technical for manuscript)*
31

32 26b Additional consent provisions for collection and use of participant data
33 and biological specimens in ancillary studies, if applicable
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35
36 *Not applicable*
37

38 Confidentiality 27 How personal information about potential and enrolled participants will
39 be collected, shared, and maintained in order to protect confidentiality
40 before, during, and after the trial
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42
43 *Not applicable (part of full protocol, but too technical and detailed for
44 this manuscript).*
45

46 Declaration of interests 28 Financial and other competing interests for principal investigators for
47 the overall trial and each study site
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49
50 *Not applicable (site contracts are confidential).*
51

52 Access to data 29 Statement of who will have access to the final trial dataset, and
53 disclosure of contractual agreements that limit such access for
54 investigators
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57 *Not applicable (not regulated contractually).*
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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5			<i>Not applicable (insurance provided for all patients however).</i>
6			
7	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
8	policy		participants, healthcare professionals, the public, and other relevant
9			groups (eg, via publication, reporting in results databases, or other
10			data sharing arrangements), including any publication restrictions
11			
12			<i>Lines 382-394</i>
13			
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15		31b	Authorship eligibility guidelines and any intended use of professional
16			writers
17			
18			<i>Not applicable (will be decided within consortium at later date).</i>
19			
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21		31c	Plans, if any, for granting public access to the full protocol, participant-
22			level dataset, and statistical code
23			
24			<i>Not applicable (will be decided within consortium at later date).</i>
25			
26			
27	Appendices		
28			
29	Informed consent	32	Model consent form and other related documentation given to
30	materials		participants and authorised surrogates
31			
32			<i>Not applicable (part of full protocol, but too technical and detailed for</i>
33			<i>this manuscript).</i>
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36	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
37	specimens		specimens for genetic or molecular analysis in the current trial and for
38			future use in ancillary studies, if applicable
39			
40			<i>Not applicable (part of full protocol, but too technical and detailed for</i>
41			<i>this manuscript).</i>
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*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Neurology
Keywords:	Thoracoabdominal aortic aneurysms, TAAA, spinal cord injury, SCI, segmental artery coil embolization, MISACE

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Manuscripts

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3 **Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal**
4 **Staging with ‘Minimally-Invasive Staged Segmental Artery Coil-**
5 **Embolization’ (MIS²ACE): Trial protocol for a Randomized Controlled**
6 **Multicentre Trial**
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56 **Word count:** 3956

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58 **Keywords:** Thoracoabdominal aortic aneurysms, TAAA, spinal cord injury, SCI, segmental
59 artery coil embolization, MIS²ACE
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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 (MIS²ACE) 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 MIS²ACE 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)

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3 9. severe contrast agent allergy, severe reduction in glomerular filtration rate
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6 The first two exclusion criteria were chosen since patients should not be subjected to
7 85 additional risk as a result of the waiting time in the MIS²ACE arm before TAAA repair can be
8 performed. The third exclusion criterion was chosen since these patients have considerable
9 risk unrelated to the focus of the trial. Exclusion criterion 4 was chosen, since sufficient blood
10 supply after MIS²ACE cannot be guaranteed on the one hand, and the prior occlusion implies
11 that no additional treatment options are available in this anatomic region.
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16 90 **Intervention**
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18 An overview of the trial is provided in Fig. 1. The treating physicians choose the mode of
19 repair, after which the patient is randomized to the interventional or the control arm.
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22 In the interventional arm (MIS²ACE), segmental arteries (SAs) will be occluded in one to
23 three sessions some weeks before the aneurysm repair. Target SAs for coil/plug deployment
24 will be identified considering the extent of the planned repair and individual SA anatomy. The
25 95 occlusion of up to 7 SAs will be performed in a single session and conducted through a
26 peripheral artery access (e.g. the common femoral artery) in local anaesthesia. Local
27 anaesthesia is important so that patients can provide immediate feedback regarding potential
28 neurological symptoms. Selected SAs will be catheterized (e.g. with a 5F catheter or 2.7F
29 microcatheter). Microcoils or vascular plugs will be used for the occlusion itself, not however
30 100 particles, which could cause unwanted microembolisms to the spinal cord directly. This will
31 be performed in the proximal SA to ensure that the collateral network itself is not affected.
32 The procedure may be done without spinal fluid drainage but this is left at the discretion of
33 the centre. The length of the procedure, the amount of contrast dye and the dose of radiation
34 105 will be documented exactly. The recommended interval between sessions is 21 days, with a
35 strict safety minimum of 5 days.[11] Experts in endovascular catheterization in small vessels
36 (e.g. cardiovascular surgeons, interventionalists, endovascular surgeons, interventional
37 radiologists, paediatric cardiologists) will perform MIS²ACE. It is essential to maintain blood
38 pressure above 140 mmHg, but for hypertensive patients, it is imperative that the post-
39 110 operative pressure should not fall below their individual pre-operative systolic blood pressure
40 during and after the procedure (invasive monitoring), ideally for at least 2 days. Anti-
41 hypertensive drugs have to be adjusted accordingly. Therefore, the patient should stay in the
42 IMCU for at least 48 hours, preferably longer. Reduction or even interruption of oral anti-
43 hypertensive medication and use of low-dose vasopressors may be utilized and are preferable
44 115 to volume therapy, which increases central venous pressure and thereby also CSF pressure.
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3 In the control arm, treatment will be according to the optimal state-of-the art procedures at the
4 local site. This ensures a real-world comparison in which the control arm is as strong as
5 possible.
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9 As the trial proceeds, statistical monitoring and concomitant projects may identify need for
10
11 120 revisions to the intervention. These alterations will then be adopted with protocol
12 amendments to optimize patient safety.
13

14 **Endpoints**

15 *Primary endpoint*

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19 The primary endpoint is successful treatment of the aneurysm. We define “success” as (a) the
20
21 125 patient is alive and without substantial SCI 30 days after treatment, and (b) the aneurysm did
22 not rupture and was excluded within six months of randomization.
23

24
25 Patients, who have not been treated within six months of randomization will be treated as
26 failures to ensure that success/failure is defined for all randomized patients. This facilitates
27 the intention to treat analysis (see below) and reduces the amount of missing data. During
28
29 recruitment, the Trial Steering Committee will ensure that time lapse alone leads only very
30
31 130 rarely to failure, otherwise this criterion will be reworked. The definition of success
32 pertaining to mortality and SCI will be assessed 30 days after TAAA repair and “substantial
33 SCI” means that the patient is unable to stand without assistance and is defined using the
34 modified Tarlov scale[22] (see below) and assessed by a board certified neurologist whenever
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36 possible:
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41 0 – No lower extremity movement

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43 1 – Lower extremity motion without gravity

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45 2 – Lower extremity motion against gravity

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47 3 – Able to stand with assistance

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49 4 – Able to walk with assistance

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51 140 5 – Normal
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55 A training video describing this scale is provided for study personnel.

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58 Treatment success for open repair is defined by complete resection and graft replacement in
59 the absence of major related complications.
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3 145 *Secondary endpoints*
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5 For secondary endpoints, treatment success will be assessed and based on follow-up CT/MR
6 images. Treatment success for endovascular repair is defined based on the position paper of
7 the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of
8 Cardiology (ESC), in collaboration with the European Association of Percutaneous
9 Cardiovascular Interventions (EAPCI)[23] and takes into account upcoming guideline papers.
10 Failure is defined as substantial progression of the aneurysm sac (> 3 mm) or the presence of
11 major related complications (e.g. type I/III endoleaks). Completion angiography and/or
12 follow-up MRI/CT from patients with endovascular repair will be conducted as part of
13 clinical routine and will be sent to Copenhagen for assessment.
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21 155 Note: The point in time “one year” refers to one year after TAAA repair. If patients retained
22 in the full analysis set have not had a repair, then “30 days after TAAA repair” and “at one
23 year” will be treated as 30 days and one year after randomization.
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25
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- 27 1. Substantial SCI at 30 days after TAAA repair and at one year
- 28 2. SCI according to the modified Tarlov scale from TAAA repair treatment to one year
- 29 3. All-cause mortality at 30 days and one year after TAAA repair
- 30 31 160 4. Length of stay in intensive care unit and intermediate care unit after TAAA repair
- 32 5. Sub-group analyses for open repair and endovascular repair separately
- 33 6. Re-operation for bleeding and drainage volumes in the first 24 h and use of blood
- 34 products (only for open repair)
- 35 7. Cross-clamping times during open surgery
- 36 8. Residual aneurysm sac perfusion, i.e. type II endoleaks (only for endovascular repair)
- 37 9. Health-related quality of life will be collected using the WHOQOL-BREF[24] and the
- 38 EuroQoL EQ-5D-5L instruments.[25] Hospital and other healthcare resource use will
- 39 be collected. Healthcare costs, quality-adjusted life years (QALYs) and the
- 40 165 incremental cost-effectiveness ratio (ICER) over one year will be calculated.[26]
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50 *Safety endpoints*

51 Beyond AE/SAE reporting and descriptive statistics on radiation exposure, the following
52 issues will receive special attention: acute kidney injury (AKI), respiratory failure and
53 embolic events (also from debris). AKI is defined using the MAKE criteria [27], comparing
54 baseline to the time-point of the primary outcome, where we note that the nature of the trial
55 and logistics of the visits preclude the use of MAKE at precisely 90 days (MAKE90). We also
56 175 record new dialysis separately and deterioration in chronic kidney disease (CKD) stage by at
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3 least two stages. Acute and chronic kidney disease will be distinguished. Having identified
4 particular safety risks in the trial aids us in collecting appropriate data, assessing and reporting
5 these harms, as recommended by SPIRIT. [1, 2] We do not use these to define stopping
6
7 180 criteria however, which is left at the discretion of the Data Monitoring Committee.
8
9

10 **Participant timeline**

11
12 Please refer to Fig. 1 for details of the visit schedule and participant timeline.
13
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15 **Sample size and recruitment**

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17 185 Estimates of effect size are difficult for several reasons. Foremost, there are large
18 discrepancies between outcome rates quoted in the literature. Moreover, the impact of recent
19 improvements in techniques on outcomes cannot yet be quantified accurately and, finally the
20 effect size depends on the improvement due to the trial intervention, which, in turn, depends
21 on anatomy, post-repair management and other complex factors. Taking a random effects
22 model of the data from large recent publications for open [10, 28–30] and endovascular repair
23 [31–33] one finds an estimated incidence of 18% (95% prediction interval 15% to 23%) for
24 open repair and a very uncertain 24% (2 to 79)% for endovascular repair. The prediction
25 interval as opposed to the confidence interval provides the correct bounds for what can be
26 190 expected in the trial.[34] The resources and time available to the study allow for the
27 recruitment of 500 patients. Assuming success rates of 80% in the control arm and 90% in the
28 intervention arm and using a group-sequential design [35] with two interim analyses, this then
29 implies a power of just over 87%.[36] The definitions of the primary endpoint and the full
30 analysis set imply that only very few dropouts are to be expected for this analysis and that
31 compliance will not be a problem. The severity of the therapy and recovery times mean that
32 loss to follow-up is not expected to be a major factor.
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45 The planned recruitment is between 8 and 9 patients per site per year. This is roughly half the
46 number of patients that meet the inclusion criteria. However, slow recruitment plagues many
47 trials and mitigation strategies have already been developed. A list of interested recruitment
48 sites ($n > 10$) is being collected to expand the consortium. Statistical monitoring will be used
49 to identify reasons for screened patients not being included in the trial so that minor and
50 clinically justified amendments to the trial protocol can address these issues, e.g. through
51 adjustments to the inclusion and exclusion criteria. Finally, a newsletter including recruitment
52 205 by site will be distributed at regular intervals to spawn healthy competition among the team
53 members.
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3 **210 Randomization**
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5 Patients will be randomized in a 1:1 ratio to the intervention and control arms with a random
6 number generator. Randomization will be performed online at the recruitment centres with a
7 tool prepared and hosted by the Clinical Trial Centre Leipzig
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11 Some of the centres are expected to recruit a very small number of patients, meaning that
12
13 **215** block randomization stratified by centre is unfeasible. Although minimization schemes could
14 be used to attain roughly balanced allocation of patients, even at the centre level, there is
15 controversy about the methods needed to analyse such trials. To avoid potential complexities
16 in analysis, we have thus opted for a very simple randomization scheme, knowing that small
17 imbalances in the number of patients per arm are to be expected.
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22 **220 Selected data collection methods**
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24 Neurological examinations will be performed by board certified neurologists whenever
25 possible. If such an examination is made upon discharge and no signs of impairment are
26 found, then verification that this holds at 30 days is only required by telephone. Any signs of
27 impairment necessitate a full examination at 30 days however.
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32 **225** If the assessment of Crawford classification or successful treatment carried out by the
33 radiological unit in Copenhagen should disagree with the treating physician's opinion, the
34 blinded independent Endpoint Committee will make the final decision. The definition of
35 success does not necessarily require that the MRI/CT be made within six months of
36 randomization. Later verification of success is acceptable.
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41 **230 Data management**
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43 The EDC tool SecuTrial®, developed and distributed by interActive Systems GmbH, is used
44 for creation of the study database. Data entry uses eCRF data entry masks and data changes
45 are tracked automatically including date, time and person who entered/changed information
46 (audit trail). Major corrections or major missing data have to be explained.
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51 **235** The information entered into the eCRF by the investigator or an authorised member of the
52 study team is systematically checked for completeness, consistency and plausibility by
53 routines implemented in the database, such that discrepancies can be dealt with at data entry.
54 Errors and warnings are listed in a validation report and can be resolved at any time during
55 the data entry process. On completion of data entry, the site staff flags the eCRF-pages as
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60 **240** 'data entry completed'.

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3 Throughout the study, a backup of all data is made daily. Unauthorised access to patient data
4 is prevented by the access concept of the study database, which is based on strict file system
5 permission.
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9 At the end of the study, once the database is complete and accurate, the database will be
10
11 245 locked. Subsequent changes to the database are possible only by joint written agreement
12 between co-ordinating investigator, trial statistician and data manager.
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15 **Statistical methods**

16 *Analysis Sets*

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19 If patients retract informed consent before any procedure is performed (repair or SA
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21 250 occlusion), they will be excluded from the primary analysis, since we expect some control
22 arm patients to be dissatisfied with their assigned treatment, retract consent, and seek
23 MIS²ACE outside of the trial. Including them would be anti-conservative. The full analysis
24 set (FAS) includes all randomized patients that have had a session for occluding segmental
25 arteries (intervention arm) or have had a repair procedure (conventional arm). Randomized
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27 255 patients whose aneurysm ruptures or who die from any cause will be included in the FAS,
28 irrespective of the above stipulations.
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34 If a sufficiently large number of patients violate the trial protocol, particularly regarding the
35 trial intervention, then a per protocol analysis will be performed using the set of patients that
36 conformed to the major terms in the protocol. A precise definition of the per protocol set will
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38 260 be provided in the statistical analysis plan.
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41 Patients are generally analysed regarding safety according to treatment received. In our case,
42 an undue delay between randomization and treatment is a risk factor, meaning that such
43 patients will be included in the safety analyses even if they have not yet received treatment.
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47 *Statistical Analysis*

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49 265 The primary analysis is an intention to treat (ITT) analysis based on the FAS and makes use
50 of a generalized linear mixed model with the logit link function. The success/failure of
51 treatment will be the dependent variable. The assigned randomization arm, mode of repair
52 (open or endovascular repair), the Crawford type and the euroSCORE II are fixed effects and
53 the centre will be treated as a random effect. The euroSCORE II already takes age, sex and
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55 270 other relevant factors into account. The interaction term between the randomization arm and
56 the other fixed effects will only be included if evidence for a strong interaction effect are seen,
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3 since this would otherwise lead to a substantial loss of power.[37, 38] As a supplementary
4 analysis, an analogous mixed model will be performed with a unity link function to provide
5 estimates and confidence intervals for absolute risk differences.
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9 275 The definitions of the full analysis set and the primary endpoint are chosen so that almost no
10 missing data are expected. If success cannot be ascertained with certainty, the patient will be
11 treated as a failure. Sensitivity analyses will be used to gauge the effect of missing data on the
12 estimates and conclusions drawn.
13
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16 Interim analyses are planned 30 days after 50% of patients (n=250) and 75% (n=375) have
17
18 280 been treated for the aneurysm. The primary endpoint will be analysed and randomization can
19 be terminated for efficacy if a p-value of 0.0030 (first interim analysis) or 0.018 (second
20 interim analysis) is reached. The p-value for demonstrating efficacy in the final analysis is
21 0.044.
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26 Analysis of binary secondary outcomes will be treated on the same footing as the primary
27
28 285 analysis. Mortality at 30 days will be treated as binary as opposed to time-to-event, since
29 prolonging life in the post-operative phase for a matter of days is not considered clinically
30 relevant. Subgroup analyses of the two Crawford types and of the two modes of repair will be
31 presented in the form of contingency tables. Mixed model Cox regression with covariates
32 euroSCOREII, Crawford type and mode of repair will be used for one-year mortality with
33 randomization arm as the independent variable of interest and centre as a random effect. If the
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35 290 assumption of proportional hazards is violated substantially, a logistic regression will be used.
36 Kaplan-Meier curves will be used to represent the data.
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43 In explorative analyses, the number of patent segmental arteries and the number occluded will
44 be taken into account with respect to SCI and mortality. The anatomical position of the
45
46 295 segmental arteries may also be used.
47

48 ICU-time and ICMU-time will be analysed with a linear mixed effects model with the same
49 fixed and random effects as in the primary analysis and may be log transformed if warranted.
50 Re-operation for bleeding and type II endoleaks will be presented for the subgroups of
51 patients treated with open or endovascular repair, respectively.
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55 300 Descriptive statistics will be used for further safety outcomes along with odds ratios
56 according to treatment received, as appropriate.
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59 Total mean cost per patient over one year will be estimated by multiplying healthcare
60 resource use collected in the trial by unit costs from the country health system.[39] QALYs

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3 will be calculated in each treatment group using the EQ-5D-5L value set.[40] The ICER will
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5 305 be calculated, and will inform whether MIS²ACE is cost-effective on average for patients with
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7 TAAA Crawford type II or III. Bootstrap methods will be used to characterize
8
9 uncertainty.[26]

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11 Further details will be provided in a statistical analysis plan.

12 13 **Statistical monitoring**

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15 310 The trial conduct will be closely supervised by means of central and statistical monitoring.
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17 The objectives are a) to detect safety relevant signals as soon as possible, b) to detect non-
18
19 compliance and relevant protocol violations and to prevent their future occurrence by prompt
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21 reaction, c) to prevent missing visits or measurements by prompt reminders and d) to explore
22
23 means of improving on the MIS²ACE procedure.

24
25 315 Statistical and central monitoring will start immediately after inclusion of the first patient. The
26
27 relevant reports and descriptive statistics will be updated and discussed at the regular
28
29 meetings of the Leipzig study team. Problems and abnormalities will be presented at regular
30
31 intervals to the co-ordinating investigator.

32 33 **On-site monitoring**

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35 320 A risk-based monitoring strategy will be implemented as required by ICH E6 (Chapter 5.0)
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37 According to the risk analysis, treatment delivery parameters, adverse events, follow-up
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39 information, data transmission and protection and informed consent documents comprise risk-
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41 bearing trial aspects and will be monitored.

42
43 Prior to recruitment, each participating centre will receive a site initiation visit, during which
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45 325 the trial protocol (if necessary) and the eCRFs will be reviewed with centre staff and any
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47 necessary training will be provided. During the study, trial monitors will maintain regular
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49 contact with trial centre staff (by telephone/fax/email/post) to track the progress of the trial,
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51 respond to any problems, and provide general assistance and support.

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53 330 The first regular monitoring visit at a site will take place after the randomization of the site's
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55 first patient to check protocol compliance and to prevent further systematic errors due to
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57 misunderstandings. Trial site visits will take place on a regular basis. The frequency of
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59 monitoring visits will depend on the trial site's recruitment rate as well as on potential
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61 problems detected during previous on-site visits or by central monitoring.

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3 Prior to every scheduled on-site visit, the monitor will receive summaries of the site's patient
4 data already documented in the database, and if applicable with data indicating possible
5 335 data already documented in the database, and if applicable with data indicating possible
6 protocol deviations or inconsistencies. During the visits, the monitor will a) check informed
7 consent forms of all patients enrolled, b) perform source data verification of key data in a
8 random sample of at least 20% of the site's patients, c) perform targeted source data
9 verification for patients with possible deviations, d) discuss open queries raised by data
10 management or drug safety personnel, e) check essential parts of the investigator site file, f)
11 340 check source data for AEs or SAEs, which have not been properly reported in the CRF/eCRF
12 and g) check for major GCP-breaches and/or protocol violations.
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19 **Harms**

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21 Safety endpoints related directly to MIS²ACE include kidney failure, respiratory failure and
22 embolic events (also from debris). These endpoints will be listed according to treatment
23 345 received with a breakdown according to the number of MIS²ACE sessions. In addition, data
24 on radiation exposure will be collected and presented descriptively.
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29 **Patient and Public Involvement**

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31 The trial protocol was developed in part by physicians with years of experience in treating
32 TAAA patients. Their experience indicated that paraplegia is the greatest concern that patients
33 350 have when deliberating on whether or not to be treated, and was thus chosen along with
34 mortality for the primary outcome. A qualitative study will recruit about 30 patients after
35 surgical wound healing for one-on-one in-depth interviews in different sites of the trial.
36 Purposive sampling will be used to select information-rich cases to be interviewed, according
37 to criteria of clinical outcome, age, gender and other patient social variables as social class or
38 ethnicity. The finalization of the data collection process will be determined following the
39 principle of theoretical saturation. Interviews will take place with an experienced qualitative
40 researcher in the patient's own language in a mutually convenient, private comfortable place.
41 A literature review will be conducted to broadly inform the interview guide, though patients
42 355 will be encouraged to speak freely. The goal is for the patient to express in his or her own words
43 the impact on their life of diagnosis and treatment, and look at changes that occur in quality of
44 life, family, work, lifestyle and social environment from an ethnographic standpoint. The
45 interviews will be recorded and transcribed literally. Summative content analysis will be
46 performed using NVivoTM software (QSR International, Melbourne, Australia). Patients and
47 the public have not yet been involved directly in the trial.
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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 MIS²ACE 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

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3 the project to the public and specific dissemination to four target communities. One objective
4 of the dissemination plan will be to support the project partners with the clinical recruitment.
5
6 The other objective will be to reach out to wide audiences outside the project consortium at
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8 400 national, European and international levels (medical and health professionals, academics,
9
10 medical and biomedical industries, policy makers, EU regulators (e.g. the European
11
12 Medicines Agency), patients groups, health NGOs, civil societies, scientific and lay media.
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14 The dissemination vehicles will be seminars, medical conferences and publications, project
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16 partners' individual communication streams. Dissemination material may include a project
17 405 leaflet, newsletter, press releases and a trial website.
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For peer review only

Authors' contributions

515 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
520 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

530 The authors have no competing interests related to this trial.

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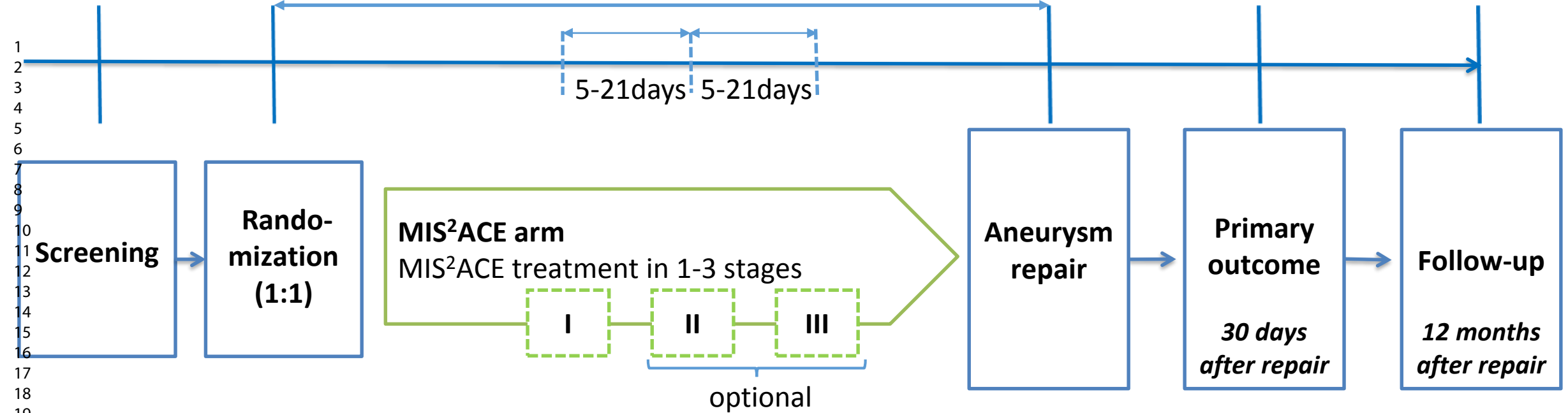
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3 545 Author wishes to make the Work available on an Open Access basis (and intends to pay the
4 relevant APC), the terms of reuse of such Open Access shall be governed by a Creative
5 Commons licence – details of these licences and which Creative Commons licence will apply
6 to this Work are set out in our licence referred to above.
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13 550 **Figure Legends**

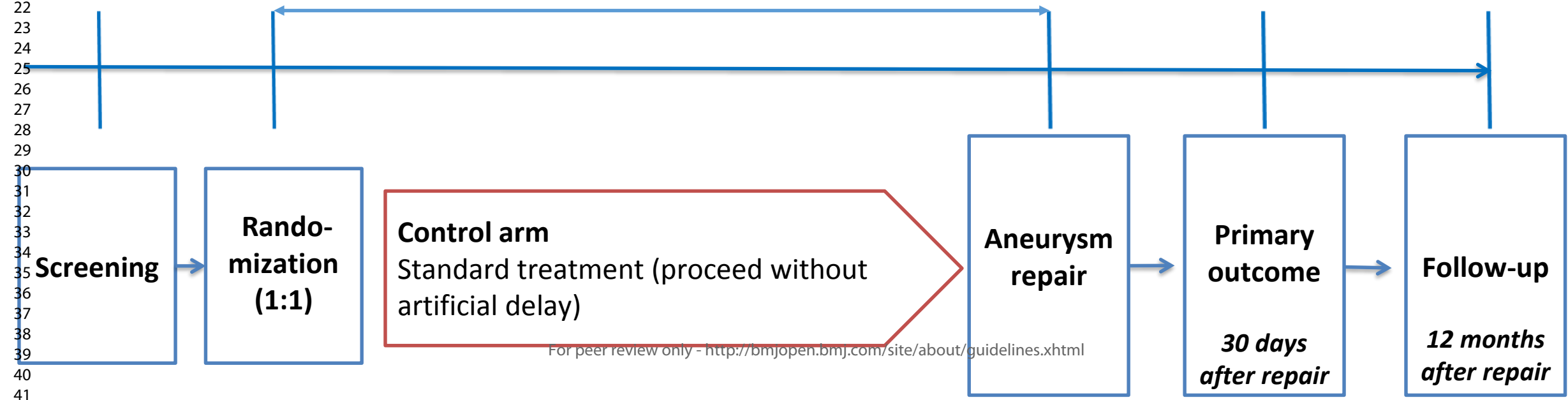
14
15
16 **Figure 1:** Schematic portrayal of the participant timeline and visit schedule for the PAPAartis
17 trial.
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max. 6 months

BMJ Open



max. 6 months





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 <i>Title page</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <i>End of Abstract</i>
	2b	All items from the World Health Organization Trial Registration Data Set <i>Available through the clinicaltrials.gov website and in the full trial protocol</i>
Protocol version	3	Date and version identifier <i>Not applicable</i>
Funding	4	Sources and types of financial, material, and other support <i>Lines 508-510</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <i>Lines 496-506</i>
	5b	Name and contact information for the trial sponsor <i>Not applicable (there is no legal "sponsor" function, but the coordinating investigator was named)</i>
	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 <i>Not applicable</i>

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- 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)

Described throughout paper

10
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Introduction

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- 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

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Line 32-44

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- 6b Explanation for choice of comparators

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Lines 116-119

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- Objectives 7 Specific objectives or hypotheses

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Lines 45-47

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- 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)

33
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Lines 49-51

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Methods: Participants, interventions, and outcomes

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- 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

42
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Lines 54-64

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- 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)

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Lines 66-89

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- Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

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Lines 91-118

1			
2		11b	Criteria for discontinuing or modifying allocated interventions for a
3			given trial participant (eg, drug dose change in response to harms,
4			participant request, or improving/worsening disease)
5			
6			<i>Lines 119-121</i>
7			
8		11c	Strategies to improve adherence to intervention protocols, and any
9			procedures for monitoring adherence (eg, drug tablet return,
10			laboratory tests)
11			
12			<i>Lines 309-317</i>
13			
14		11d	Relevant concomitant care and interventions that are permitted or
15			prohibited during the trial
16			
17			<i>Not applicable</i>
18			
19			
20			
21	Outcomes	12	Primary, secondary, and other outcomes, including the specific
22			measurement variable (eg, systolic blood pressure), analysis metric
23			(eg, change from baseline, final value, time to event), method of
24			aggregation (eg, median, proportion), and time point for each
25			outcome. Explanation of the clinical relevance of chosen efficacy and
26			harm outcomes is strongly recommended
27			
28			<i>Lines 124-176</i>
29			
30			
31			
32	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
33	timeline		washouts), assessments, and visits for participants. A schematic
34			diagram is highly recommended (see Figure)
35			
36			<i>Figure 1</i>
37			
38			
39	Sample size	14	Estimated number of participants needed to achieve study objectives
40			and how it was determined, including clinical and statistical
41			assumptions supporting any sample size calculations
42			
43			<i>Lines 184-198</i>
44			
45			
46	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
47			target sample size
48			
49			<i>Lines 199-207</i>
50			

Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
8			
9			
10			<i>Lines 209-211</i>
11			
12	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
13	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
14	mechanism		describing any steps to conceal the sequence until interventions are
15			assigned
16			
17			
18			<i>Lines 213-214</i>
19			
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
21			and who will assign participants to interventions
22			
23			
24			<i>Line 211</i>
25			
26	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
27	(masking)		participants, care providers, outcome assessors, data analysts), and
28			how
29			
30			
31			<i>Not applicable (discussed as limitation)</i>
32			
33		17b	If blinded, circumstances under which unblinding is permissible, and
34			procedure for revealing a participant's allocated intervention during
35			the trial
36			
37			
38			<i>Not applicable</i>
39			
40	Methods: Data collection, management, and analysis		
41			
42	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
43	methods		trial data, including any related processes to promote data quality (eg,
44			duplicate measurements, training of assessors) and a description of
45			study instruments (eg, questionnaires, laboratory tests) along with
46			their reliability and validity, if known. Reference to where data
47			collection forms can be found, if not in the protocol
48			
49			
50			
51			<i>Lines 142, 219-227</i>
52			
53		18b	Plans to promote participant retention and complete follow-up,
54			including list of any outcome data to be collected for participants who
55			discontinue or deviate from intervention protocols
56			
57			
58			<i>Not applicable (since intervention always well documented and short-</i>
59			<i>term and mortality data are expected to be very complete)</i>
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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
- 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
- Lines 263-276*
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)
- 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)
- 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
- 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
- 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
- Lines 172-179, 342-345*

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2	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
3			whether the process will be independent from investigators and the
4			sponsor
5			
6			
7			<i>Lines 318-340, 365-380</i>
8			
9	Ethics and dissemination		
10			
11	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board
12			(REC/IRB) approval
13			
14			
15			<i>Lines 357-361</i>
16			
17	Protocol amendments	25	Plans for communicating important protocol modifications (eg,
18			changes to eligibility criteria, outcomes, analyses) to relevant parties
19			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
20			regulators)
21			
22			
23			<i>Line 362.</i>
24			
25	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
26			participants or authorised surrogates, and how (see Item 32)
27			
28			
29			<i>Not applicable (part of trial protocol and delegation lists, but too</i>
30			<i>technical for manuscript)</i>
31			
32		26b	Additional consent provisions for collection and use of participant data
33			and biological specimens in ancillary studies, if applicable
34			
35			<i>Not applicable</i>
36			
37	Confidentiality	27	How personal information about potential and enrolled participants will
38			be collected, shared, and maintained in order to protect confidentiality
39			before, during, and after the trial
40			
41			
42			<i>Not applicable (part of full protocol, but too technical and detailed for</i>
43			<i>this manuscript).</i>
44			
45	Declaration of interests	28	Financial and other competing interests for principal investigators for
46			the overall trial and each study site
47			
48			
49			<i>Not applicable (site contracts are confidential).</i>
50			
51	Access to data	29	Statement of who will have access to the final trial dataset, and
52			disclosure of contractual agreements that limit such access for
53			investigators
54			
55			
56			<i>Not applicable (not regulated contractually).</i>
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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5			<i>Not applicable (insurance provided for all patients however).</i>
6			
7	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
8	policy		participants, healthcare professionals, the public, and other relevant
9			groups (eg, via publication, reporting in results databases, or other
10			data sharing arrangements), including any publication restrictions
11			
12			<i>Lines 382-394</i>
13			
14			
15		31b	Authorship eligibility guidelines and any intended use of professional
16			writers
17			
18			<i>Not applicable (will be decided within consortium at later date).</i>
19			
20			
21		31c	Plans, if any, for granting public access to the full protocol, participant-
22			level dataset, and statistical code
23			
24			<i>Not applicable (will be decided within consortium at later date).</i>
25			
26			
27	Appendices		
28			
29	Informed consent	32	Model consent form and other related documentation given to
30	materials		participants and authorised surrogates
31			
32			<i>Not applicable (part of full protocol, but too technical and detailed for</i>
33			<i>this manuscript).</i>
34			
35			
36	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
37	specimens		specimens for genetic or molecular analysis in the current trial and for
38			future use in ancillary studies, if applicable
39			
40			<i>Not applicable (part of full protocol, but too technical and detailed for</i>
41			<i>this manuscript).</i>
42			
43			

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025488.R3
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Neurology
Keywords:	Thoracoabdominal aortic aneurysms, TAAA, spinal cord injury, SCI, segmental artery coil embolization, MISACE

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Manuscripts

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3 **Paraplegia Prevention in Aortic Aneurysm Repair by Thoracoabdominal**
4 **Staging with ‘Minimally-Invasive Staged Segmental Artery Coil-**
5 **Embolization’ (MIS²ACE): Trial protocol for a Randomized Controlled**
6 **Multicentre Trial**
7
8
9
10

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56 **Word count:** 3956

57
58 **Keywords:** Thoracoabdominal aortic aneurysms, TAAA, spinal cord injury, SCI, segmental
59 artery coil embolization, MIS²ACE
60

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 (MIS²ACE) 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 MIS²ACE 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

1
2
3 paraparesis, but it remains high with an incidence of up to 20% for Crawford type II
4
5 30 aneurysms.[10]
6

7 **Rationale**

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9 Members of the study team have found that the deliberate staged occlusion of segmental
10
11 arteries leading to the paraspinous collateral network and finally supplying the spinal cord can
12
13 trigger arterial collateralization, thus stabilizing blood supply to the spinal cord from alternate
14
15 35 inflow sources and potentially preventing ischaemia.[11–16] This approach was devised after
16
17 years of research that included recognition of the body's ability to tolerate segmental artery
18
19 sacrifice[17] given haemodynamic stability[18, 19] along with the identification of the
20
21 paraspinous arterial collateral network itself.[12, 16] One means of occluding arteries in the
22
23 clinical setting has been termed 'minimally invasive staged segmental artery coil
24
25 40 embolization' (MIS²ACE), which was proved feasible in 2015.[20] A consecutive case series
26
27 of over 50 patients lends credence to its safety.[21] This is thus the ideal time to carry out
28
29 such a trial – where the need to test efficacy, effectiveness and safety are paramount, but
30
31 before it has gained acceptance despite lack of evidence.

32 **Objectives**

33
34 45 The primary objective of the PAPAartis trial is to test the hypothesis that MIS²ACE can
35
36 greatly reduce the incidence of ischaemic SCI and mortality compared to standard open
37
38 surgical or endovascular thoracoabdominal aneurysm repair alone.

39 **Trial Design**

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41 PAPAartis is a multi-national, open label, randomized controlled trial. It has two parallel
42
43 50 groups with equal allocation and the primary endpoint is to be tested in a superiority
44
45 framework.
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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)

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3 9. severe contrast agent allergy, severe reduction in glomerular filtration rate
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6 The first two exclusion criteria were chosen since patients should not be subjected to
7 85 additional risk as a result of the waiting time in the MIS²ACE arm before TAAA repair can be
8 performed. The third exclusion criterion was chosen since these patients have considerable
9 risk unrelated to the focus of the trial. Exclusion criterion 4 was chosen, since sufficient blood
10 supply after MIS²ACE cannot be guaranteed on the one hand, and the prior occlusion implies
11 that no additional treatment options are available in this anatomic region.
12
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16 90 **Intervention**
17

18 An overview of the trial is provided in Fig. 1. The treating physicians choose the mode of
19 repair, after which the patient is randomized to the interventional or the control arm.
20
21

22 In the interventional arm (MIS²ACE), segmental arteries (SAs) will be occluded in one to
23 three sessions some weeks before the aneurysm repair. Target SAs for coil/plug deployment
24 will be identified considering the extent of the planned repair and individual SA anatomy. The
25 95 occlusion of up to 7 SAs will be performed in a single session and conducted through a
26 peripheral artery access (e.g. the common femoral artery) in local anaesthesia. Local
27 anaesthesia is important so that patients can provide immediate feedback regarding potential
28 neurological symptoms. Selected SAs will be catheterized (e.g. with a 5F catheter or 2.7F
29 microcatheter). Microcoils or vascular plugs will be used for the occlusion itself, not however
30 100 particles, which could cause unwanted microembolisms to the spinal cord directly. This will
31 be performed in the proximal SA to ensure that the collateral network itself is not affected.
32 The procedure may be done without spinal fluid drainage but this is left at the discretion of
33 the centre. The length of the procedure, the amount of contrast dye and the dose of radiation
34 105 will be documented exactly. The recommended interval between sessions is 21 days, with a
35 strict safety minimum of 5 days.[11] Experts in endovascular catheterization in small vessels
36 (e.g. cardiovascular surgeons, interventionalists, endovascular surgeons, interventional
37 radiologists, paediatric cardiologists) will perform MIS²ACE. It is essential to maintain blood
38 pressure above 140 mmHg, but for hypertensive patients, it is imperative that the post-
39 110 operative pressure should not fall below their individual pre-operative systolic blood pressure
40 during and after the procedure (invasive monitoring), ideally for at least 2 days. Anti-
41 hypertensive drugs have to be adjusted accordingly. Therefore, the patient should stay in the
42 IMCU for at least 48 hours, preferably longer. Reduction or even interruption of oral anti-
43 hypertensive medication and use of low-dose vasopressors may be utilized and are preferable
44 115 to volume therapy, which increases central venous pressure and thereby also CSF pressure.
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3 In the control arm, treatment will be according to the optimal state-of-the art procedures at the
4 local site. This ensures a real-world comparison in which the control arm is as strong as
5 possible.
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9 As the trial proceeds, statistical monitoring and concomitant projects may identify need for
10
11 120 revisions to the intervention. These alterations will then be adopted with protocol
12 amendments to optimize patient safety.
13

14 **Endpoints**

15 *Primary endpoint*

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19 The primary endpoint is successful treatment of the aneurysm. We define “success” as (a) the
20
21 125 patient is alive and without substantial SCI 30 days after treatment, and (b) the aneurysm did
22 not rupture and was excluded within six months of randomization.
23

24
25 Patients, who have not been treated within six months of randomization will be treated as
26 failures to ensure that success/failure is defined for all randomized patients. This facilitates
27 the intention to treat analysis (see below) and reduces the amount of missing data. During
28
29 recruitment, the Trial Steering Committee will ensure that time lapse alone leads only very
30
31 130 rarely to failure, otherwise this criterion will be reworked. The definition of success
32 pertaining to mortality and SCI will be assessed 30 days after TAAA repair and “substantial
33 SCI” means that the patient is unable to stand without assistance and is defined using the
34 modified Tarlov scale[22] (see below) and assessed by a board certified neurologist whenever
35 possible:
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41 0 – No lower extremity movement

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43 1 – Lower extremity motion without gravity

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45 2 – Lower extremity motion against gravity

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47 3 – Able to stand with assistance

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49 4 – Able to walk with assistance

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51 140 5 – Normal
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55 A training video describing this scale is provided for study personnel.

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58 Treatment success for open repair is defined by complete resection and graft replacement in
59 the absence of major related complications.
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3 145 *Secondary endpoints*
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5 For secondary endpoints, treatment success will be assessed and based on follow-up CT/MR
6 images. Treatment success for endovascular repair is defined based on the position paper of
7 the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of
8 Cardiology (ESC), in collaboration with the European Association of Percutaneous
9 Cardiovascular Interventions (EAPCI)[23] and takes into account upcoming guideline papers.
10 Failure is defined as substantial progression of the aneurysm sac (> 3 mm) or the presence of
11 major related complications (e.g. type I/III endoleaks). Completion angiography and/or
12 follow-up MRI/CT from patients with endovascular repair will be conducted as part of
13 clinical routine and will be sent to Copenhagen for assessment.
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22 155 Note: The point in time “one year” refers to one year after TAAA repair. If patients retained
23 in the full analysis set have not had a repair, then “30 days after TAAA repair” and “at one
24 year” will be treated as 30 days and one year after randomization.
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- 27 1. Substantial SCI at 30 days after TAAA repair and at one year
- 28 2. SCI according to the modified Tarlov scale from TAAA repair treatment to one year
- 29 3. All-cause mortality at 30 days and one year after TAAA repair
- 30 4. Length of stay in intensive care unit and intermediate care unit after TAAA repair
- 31 5. Sub-group analyses for open repair and endovascular repair separately
- 32 6. Re-operation for bleeding and drainage volumes in the first 24 h and use of blood
33 products (only for open repair)
- 34 7. Cross-clamping times during open surgery
- 35 8. Residual aneurysm sac perfusion, i.e. type II endoleaks (only for endovascular repair)
- 36 9. Health-related quality of life will be collected using the WHOQOL-BREF[24] and the
37 EuroQoL EQ-5D-5L instruments.[25] Hospital and other healthcare resource use will
38 be collected. Healthcare costs, quality-adjusted life years (QALYs) and the
39 incremental cost-effectiveness ratio (ICER) over one year will be calculated.[26]
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49 *Safety endpoints*
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51 Beyond AE/SAE reporting and descriptive statistics on radiation exposure, the following
52 issues will receive special attention: acute kidney injury (AKI), respiratory failure and
53 embolic events (also from debris). AKI is defined using the MAKE criteria [27], comparing
54 baseline to the time-point of the primary outcome, where we note that the nature of the trial
55 and logistics of the visits preclude the use of MAKE at precisely 90 days (MAKE90). We also
56 record new dialysis separately and deterioration in chronic kidney disease (CKD) stage by at
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3 least two stages. Acute and chronic kidney disease will be distinguished. Having identified
4 particular safety risks in the trial aids us in collecting appropriate data, assessing and reporting
5 these harms, as recommended by SPIRIT. [1, 2] We do not use these to define stopping
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7 180 criteria however, which is left at the discretion of the Data Monitoring Committee.
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10 **Participant timeline**

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12 Please refer to Fig. 1 for details of the visit schedule and participant timeline.
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15 **Sample size and recruitment**

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17 185 Estimates of effect size are difficult for several reasons. Foremost, there are large
18 discrepancies between outcome rates quoted in the literature. Moreover, the impact of recent
19 improvements in techniques on outcomes cannot yet be quantified accurately and, finally the
20 effect size depends on the improvement due to the trial intervention, which, in turn, depends
21 on anatomy, post-repair management and other complex factors. Taking a random effects
22 model of the data from large recent publications for open [10, 28–30] and endovascular repair
23 [31–33] one finds an estimated incidence of 18% (95% prediction interval 15% to 23%) for
24 open repair and a very uncertain 24% (2 to 79)% for endovascular repair. The prediction
25 interval as opposed to the confidence interval provides the correct bounds for what can be
26 190 expected in the trial.[34] The resources and time available to the study allow for the
27 recruitment of 500 patients. Assuming success rates of 80% in the control arm and 90% in the
28 intervention arm and using a group-sequential design [35] with two interim analyses, this then
29 implies a power of just over 87%.[36] The definitions of the primary endpoint and the full
30 analysis set imply that only very few dropouts are to be expected for this analysis and that
31 compliance will not be a problem. The severity of the therapy and recovery times mean that
32 loss to follow-up is not expected to be a major factor.
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45 The planned recruitment is between 8 and 9 patients per site per year. This is roughly half the
46 number of patients that meet the inclusion criteria. However, slow recruitment plagues many
47 trials and mitigation strategies have already been developed. A list of interested recruitment
48 sites ($n > 10$) is being collected to expand the consortium. Statistical monitoring will be used
49 to identify reasons for screened patients not being included in the trial so that minor and
50 clinically justified amendments to the trial protocol can address these issues, e.g. through
51 adjustments to the inclusion and exclusion criteria. Finally, a newsletter including recruitment
52 205 by site will be distributed at regular intervals to spawn healthy competition among the team
53 members.
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3 **210 Randomization**
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5 Patients will be randomized in a 1:1 ratio to the intervention and control arms with a random
6 number generator. Randomization will be performed online at the recruitment centres with a
7 tool prepared and hosted by the Clinical Trial Centre Leipzig
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11 Some of the centres are expected to recruit a very small number of patients, meaning that
12
13 **215** block randomization stratified by centre is unfeasible. Although minimization schemes could
14 be used to attain roughly balanced allocation of patients, even at the centre level, there is
15 controversy about the methods needed to analyse such trials. To avoid potential complexities
16 in analysis, we have thus opted for a very simple randomization scheme, knowing that small
17 imbalances in the number of patients per arm are to be expected.
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22 **220 Selected data collection methods**
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24 Neurological examinations will be performed by board certified neurologists whenever
25 possible. If such an examination is made upon discharge and no signs of impairment are
26 found, then verification that this holds at 30 days is only required by telephone. Any signs of
27 impairment necessitate a full examination at 30 days however.
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32 **225** If the assessment of Crawford classification or successful treatment carried out by the
33 radiological unit in Copenhagen should disagree with the treating physician's opinion, the
34 blinded independent Endpoint Committee will make the final decision. The definition of
35 success does not necessarily require that the MRI/CT be made within six months of
36 randomization. Later verification of success is acceptable.
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41 **230 Data management**
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43 The EDC tool SecuTrial®, developed and distributed by interActive Systems GmbH, is used
44 for creation of the study database. Data entry uses eCRF data entry masks and data changes
45 are tracked automatically including date, time and person who entered/changed information
46 (audit trail). Major corrections or major missing data have to be explained.
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51 **235** The information entered into the eCRF by the investigator or an authorised member of the
52 study team is systematically checked for completeness, consistency and plausibility by
53 routines implemented in the database, such that discrepancies can be dealt with at data entry.
54 Errors and warnings are listed in a validation report and can be resolved at any time during
55 the data entry process. On completion of data entry, the site staff flags the eCRF-pages as
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60 **240** 'data entry completed'.

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3 Throughout the study, a backup of all data is made daily. Unauthorised access to patient data
4 is prevented by the access concept of the study database, which is based on strict file system
5 permission.
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9 At the end of the study, once the database is complete and accurate, the database will be
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11 245 locked. Subsequent changes to the database are possible only by joint written agreement
12 between co-ordinating investigator, trial statistician and data manager.
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15 **Statistical methods**

16 *Analysis Sets*

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19 If patients retract informed consent before any procedure is performed (repair or SA
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21 250 occlusion), they will be excluded from the primary analysis, since we expect some control
22 arm patients to be dissatisfied with their assigned treatment, retract consent, and seek
23 MIS²ACE outside of the trial. Including them would be anti-conservative. The full analysis
24 set (FAS) includes all randomized patients that have had a session for occluding segmental
25 arteries (intervention arm) or have had a repair procedure (conventional arm). Randomized
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27 255 patients whose aneurysm ruptures or who die from any cause will be included in the FAS,
28 irrespective of the above stipulations.
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34 If a sufficiently large number of patients violate the trial protocol, particularly regarding the
35 trial intervention, then a per protocol analysis will be performed using the set of patients that
36 conformed to the major terms in the protocol. A precise definition of the per protocol set will
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38 260 be provided in the statistical analysis plan.
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41 Patients are generally analysed regarding safety according to treatment received. In our case,
42 an undue delay between randomization and treatment is a risk factor, meaning that such
43 patients will be included in the safety analyses even if they have not yet received treatment.
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47 *Statistical Analysis*

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50 265 The primary analysis is an intention to treat (ITT) analysis based on the FAS and makes use
51 of a generalized linear mixed model with the logit link function. The success/failure of
52 treatment will be the dependent variable. The assigned randomization arm, mode of repair
53 (open or endovascular repair), the Crawford type and the euroSCORE II are fixed effects and
54 the centre will be treated as a random effect. The euroSCORE II already takes age, sex and
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56 270 other relevant factors into account. The interaction term between the randomization arm and
57 the other fixed effects will only be included if evidence for a strong interaction effect are seen,
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3 since this would otherwise lead to a substantial loss of power.[37, 38] As a supplementary
4 analysis, an analogous mixed model will be performed with a unity link function to provide
5 estimates and confidence intervals for absolute risk differences.
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9 275 The definitions of the full analysis set and the primary endpoint are chosen so that almost no
10 missing data are expected. If success cannot be ascertained with certainty, the patient will be
11 treated as a failure. Sensitivity analyses will be used to gauge the effect of missing data on the
12 estimates and conclusions drawn.
13
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16 Interim analyses are planned 30 days after 50% of patients (n=250) and 75% (n=375) have
17
18 280 been treated for the aneurysm. The primary endpoint will be analysed and randomization can
19 be terminated for efficacy if a p-value of 0.0030 (first interim analysis) or 0.018 (second
20 interim analysis) is reached. The p-value for demonstrating efficacy in the final analysis is
21 0.044.
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26 Analysis of binary secondary outcomes will be treated on the same footing as the primary
27
28 285 analysis. Mortality at 30 days will be treated as binary as opposed to time-to-event, since
29 prolonging life in the post-operative phase for a matter of days is not considered clinically
30 relevant. Subgroup analyses of the two Crawford types and of the two modes of repair will be
31 presented in the form of contingency tables. Mixed model Cox regression with covariates
32 euroSCOREII, Crawford type and mode of repair will be used for one-year mortality with
33 randomization arm as the independent variable of interest and centre as a random effect. If the
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35 290 assumption of proportional hazards is violated substantially, a logistic regression will be used.
36 Kaplan-Meier curves will be used to represent the data.
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43 In explorative analyses, the number of patent segmental arteries and the number occluded will
44 be taken into account with respect to SCI and mortality. The anatomical position of the
45
46 295 segmental arteries may also be used.
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48 ICU-time and ICMU-time will be analysed with a linear mixed effects model with the same
49 fixed and random effects as in the primary analysis and may be log transformed if warranted.
50 Re-operation for bleeding and type II endoleaks will be presented for the subgroups of
51 patients treated with open or endovascular repair, respectively.
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55 300 Descriptive statistics will be used for further safety outcomes along with odds ratios
56 according to treatment received, as appropriate.
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59 Total mean cost per patient over one year will be estimated by multiplying healthcare
60 resource use collected in the trial by unit costs from the country health system.[39] QALYs

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3 will be calculated in each treatment group using the EQ-5D-5L value set.[40] The ICER will
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5 305 be calculated, and will inform whether MIS²ACE is cost-effective on average for patients with
6 TAAA Crawford type II or III. Bootstrap methods will be used to characterize
7
8 uncertainty.[26]
9

10 Further details will be provided in a statistical analysis plan.
11
12

13 **Statistical monitoring**

14
15 310 The trial conduct will be closely supervised by means of central and statistical monitoring.
16 The objectives are a) to detect safety relevant signals as soon as possible, b) to detect non-
17 compliance and relevant protocol violations and to prevent their future occurrence by prompt
18 reaction, c) to prevent missing visits or measurements by prompt reminders and d) to explore
19 means of improving on the MIS²ACE procedure.
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25 315 Statistical and central monitoring will start immediately after inclusion of the first patient. The
26 relevant reports and descriptive statistics will be updated and discussed at the regular
27 meetings of the Leipzig study team. Problems and abnormalities will be presented at regular
28 intervals to the co-ordinating investigator.
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32 **On-site monitoring**

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35 320 A risk-based monitoring strategy will be implemented as required by ICH E6 (Chapter 5.0)
36 According to the risk analysis, treatment delivery parameters, adverse events, follow-up
37 information, data transmission and protection and informed consent documents comprise risk-
38 bearing trial aspects and will be monitored.
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44 325 Prior to recruitment, each participating centre will receive a site initiation visit, during which
45 the trial protocol (if necessary) and the eCRFs will be reviewed with centre staff and any
46 necessary training will be provided. During the study, trial monitors will maintain regular
47 contact with trial centre staff (by telephone/fax/email/post) to track the progress of the trial,
48 respond to any problems, and provide general assistance and support.
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53 330 The first regular monitoring visit at a site will take place after the randomization of the site's
54 first patient to check protocol compliance and to prevent further systematic errors due to
55 misunderstandings. Trial site visits will take place on a regular basis. The frequency of
56 monitoring visits will depend on the trial site's recruitment rate as well as on potential
57 problems detected during previous on-site visits or by central monitoring.
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3 Prior to every scheduled on-site visit, the monitor will receive summaries of the site's patient
4 data already documented in the database, and if applicable with data indicating possible
5 335 data already documented in the database, and if applicable with data indicating possible
6 protocol deviations or inconsistencies. During the visits, the monitor will a) check informed
7 consent forms of all patients enrolled, b) perform source data verification of key data in a
8 random sample of at least 20% of the site's patients, c) perform targeted source data
9 verification for patients with possible deviations, d) discuss open queries raised by data
10 management or drug safety personnel, e) check essential parts of the investigator site file, f)
11 340 check source data for AEs or SAEs, which have not been properly reported in the CRF/eCRF
12 and g) check for major GCP-breaches and/or protocol violations.
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19 **Harms**

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21 Safety endpoints related directly to MIS²ACE include kidney failure, respiratory failure and
22 embolic events (also from debris). These endpoints will be listed according to treatment
23 345 received with a breakdown according to the number of MIS²ACE sessions. In addition, data
24 on radiation exposure will be collected and presented descriptively.
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29 **Patient and Public Involvement**

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31 The trial protocol was developed in part by physicians with years of experience in treating
32 TAAA patients. Their experience indicated that paraplegia is the greatest concern that patients
33 350 have when deliberating on whether or not to be treated, and was thus chosen along with
34 mortality for the primary outcome. A qualitative study will recruit about 30 patients after
35 surgical wound healing for one-on-one in-depth interviews in different sites of the trial.
36 Purposive sampling will be used to select information-rich cases to be interviewed, according
37 to criteria of clinical outcome, age, gender and other patient social variables as social class or
38 ethnicity. The finalization of the data collection process will be determined following the
39 principle of theoretical saturation. Interviews will take place with an experienced qualitative
40 researcher in the patient's own language in a mutually convenient, private comfortable place.
41 A literature review will be conducted to broadly inform the interview guide, though patients
42 355 will be encouraged to speak freely. The goal is for the patient to express in his or her own words
43 the impact on their life of diagnosis and treatment, and look at changes that occur in quality of
44 life, family, work, lifestyle and social environment from an ethnographic standpoint. The
45 interviews will be recorded and transcribed literally. Summative content analysis will be
46 performed using NVivoTM software (QSR International, Melbourne, Australia). Patients and
47 the public have not yet been involved directly in the trial.
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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 MIS²ACE 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

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3 the project to the public and specific dissemination to four target communities. One objective
4 of the dissemination plan will be to support the project partners with the clinical recruitment.
5 The other objective will be to reach out to wide audiences outside the project consortium at
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8 400 national, European and international levels (medical and health professionals, academics,
9 medical and biomedical industries, policy makers, EU regulators (e.g. the European
10 Medicines Agency), patients groups, health NGOs, civil societies, scientific and lay media.
11 The dissemination vehicles will be seminars, medical conferences and publications, project
12 partners' individual communication streams. Dissemination material may include a project
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17 405 leaflet, newsletter, press releases and a trial website.

19 **Data Sharing Statement**

21 We are committed to transparent research and are aware of the International Committee of
22 Medical Journal Editors (ICMJE) recommendations on data sharing. After publication of the
23 major results and upon reasonable request from researchers performing an individual patient
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27 410 data meta-analysis, individual patient data that underlie published results will be shared after
28 de-identification. This requires approval by the local Institutional Review Board (IRB) of the
29 researcher requesting the data along with public registration of the meta-analysis. Summary
30 statistics that go beyond the scope of published material will be made available to researchers
31 for meta-analysis upon reasonable request and if the necessary data analysis is not unduly
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36 415 time-consuming. Together with publication of the main results, the trial protocol in full will
37 be made publically available as well as the statistical analysis plan.
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525 **Authors' contributions**

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

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27 innovation programme under grant agreement 733203 and from the German Research
28 Foundation under grant number ET 127/2-1.
29
30

31 **Competing interests statement**

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34 The authors have no competing interests related to this trial.
35

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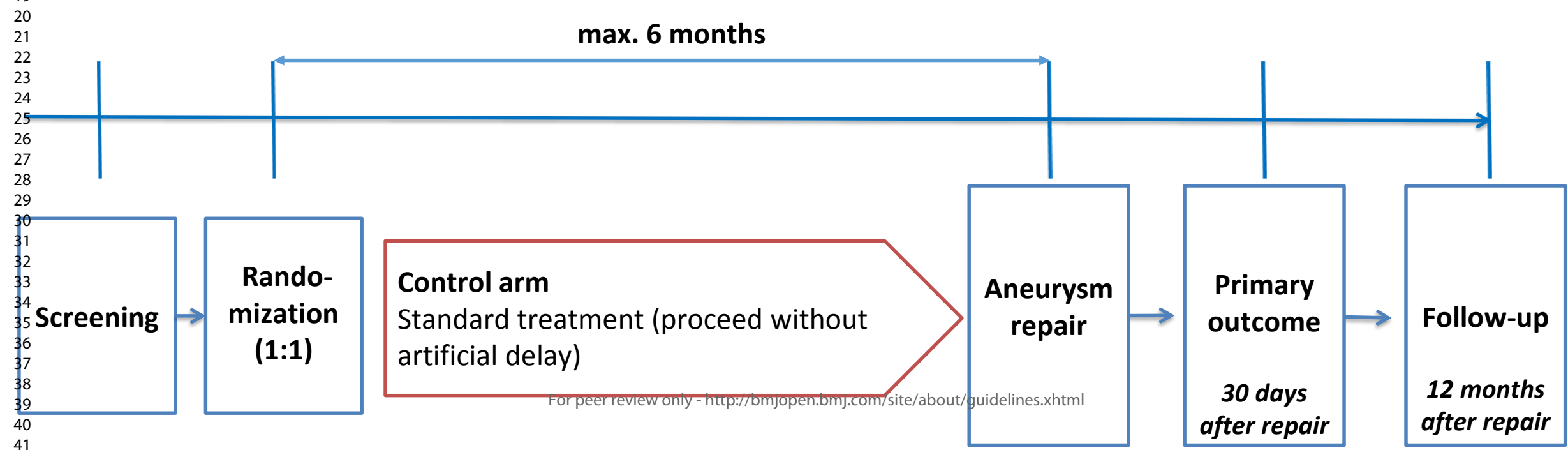
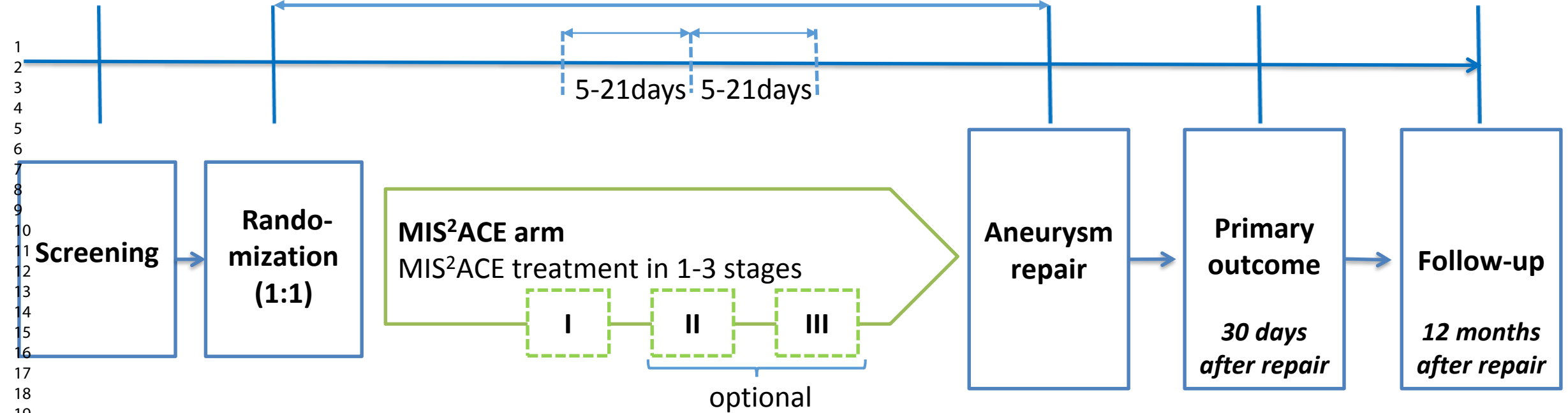
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13 **Figure Legends**

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16 **Figure 1:** Schematic portrayal of the participant timeline and visit schedule for the PAPAartis
17 trial.
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max. 6 months BMJ Open





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 <i>Title page</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <i>End of Abstract</i>
	2b	All items from the World Health Organization Trial Registration Data Set <i>Available through the clinicaltrials.gov website and in the full trial protocol</i>
Protocol version	3	Date and version identifier <i>Not applicable</i>
Funding	4	Sources and types of financial, material, and other support <i>Lines 508-510</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <i>Lines 496-506</i>
	5b	Name and contact information for the trial sponsor <i>Not applicable (there is no legal "sponsor" function, but the coordinating investigator was named)</i>
	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 <i>Not applicable</i>

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- 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)

Described throughout paper

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Introduction

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- 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

Line 32-44

- 6b Explanation for choice of comparators

Lines 116-119

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- Objectives 7 Specific objectives or hypotheses

Lines 45-47

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- 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)

Lines 49-51

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Methods: Participants, interventions, and outcomes

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- 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

Lines 54-64

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- 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)

Lines 66-89

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- Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

Lines 91-118

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2		11b	Criteria for discontinuing or modifying allocated interventions for a
3			given trial participant (eg, drug dose change in response to harms,
4			participant request, or improving/worsening disease)
5			
6			<i>Lines 119-121</i>
7			
8		11c	Strategies to improve adherence to intervention protocols, and any
9			procedures for monitoring adherence (eg, drug tablet return,
10			laboratory tests)
11			
12			<i>Lines 309-317</i>
13			
14		11d	Relevant concomitant care and interventions that are permitted or
15			prohibited during the trial
16			
17			<i>Not applicable</i>
18			
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20			
21	Outcomes	12	Primary, secondary, and other outcomes, including the specific
22			measurement variable (eg, systolic blood pressure), analysis metric
23			(eg, change from baseline, final value, time to event), method of
24			aggregation (eg, median, proportion), and time point for each
25			outcome. Explanation of the clinical relevance of chosen efficacy and
26			harm outcomes is strongly recommended
27			
28			<i>Lines 124-176</i>
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32	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
33	timeline		washouts), assessments, and visits for participants. A schematic
34			diagram is highly recommended (see Figure)
35			
36			<i>Figure 1</i>
37			
38			
39	Sample size	14	Estimated number of participants needed to achieve study objectives
40			and how it was determined, including clinical and statistical
41			assumptions supporting any sample size calculations
42			
43			<i>Lines 184-198</i>
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46	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
47			target sample size
48			
49			<i>Lines 199-207</i>
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Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
8			
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10			<i>Lines 209-211</i>
11			
12	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
13	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
14	mechanism		describing any steps to conceal the sequence until interventions are
15			assigned
16			
17			
18			<i>Lines 213-214</i>
19			
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
21			and who will assign participants to interventions
22			
23			
24			<i>Line 211</i>
25			
26	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
27	(masking)		participants, care providers, outcome assessors, data analysts), and
28			how
29			
30			
31			<i>Not applicable (discussed as limitation)</i>
32			
33		17b	If blinded, circumstances under which unblinding is permissible, and
34			procedure for revealing a participant's allocated intervention during
35			the trial
36			
37			
38			<i>Not applicable</i>
39			
40	Methods: Data collection, management, and analysis		
41			
42	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
43	methods		trial data, including any related processes to promote data quality (eg,
44			duplicate measurements, training of assessors) and a description of
45			study instruments (eg, questionnaires, laboratory tests) along with
46			their reliability and validity, if known. Reference to where data
47			collection forms can be found, if not in the protocol
48			
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51			<i>Lines 142, 219-227</i>
52			
53		18b	Plans to promote participant retention and complete follow-up,
54			including list of any outcome data to be collected for participants who
55			discontinue or deviate from intervention protocols
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57			
58			<i>Not applicable (since intervention always well documented and short-</i>
59			<i>term and mortality data are expected to be very complete)</i>
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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
- 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
- Lines 263-276*
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)
- 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)
- 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
- 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
- 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
- Lines 172-179, 342-345*

1
2 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
3 whether the process will be independent from investigators and the
4 sponsor
5

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7 *Lines 318-340, 365-380*
8

9 **Ethics and dissemination**

10
11 Research ethics 24 Plans for seeking research ethics committee/institutional review board
12 approval (REC/IRB) approval
13

14
15 *Lines 357-361*
16

17 Protocol amendments 25 Plans for communicating important protocol modifications (eg,
18 changes to eligibility criteria, outcomes, analyses) to relevant parties
19 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
20 regulators)
21

22
23 *Line 362.*
24

25 Consent or assent 26a Who will obtain informed consent or assent from potential trial
26 participants or authorised surrogates, and how (see Item 32)
27

28
29 *Not applicable (part of trial protocol and delegation lists, but too
30 technical for manuscript)*
31

32 26b Additional consent provisions for collection and use of participant data
33 and biological specimens in ancillary studies, if applicable
34

35
36 *Not applicable*
37

38 Confidentiality 27 How personal information about potential and enrolled participants will
39 be collected, shared, and maintained in order to protect confidentiality
40 before, during, and after the trial
41

42
43 *Not applicable (part of full protocol, but too technical and detailed for
44 this manuscript).*
45

46 Declaration of interests 28 Financial and other competing interests for principal investigators for
47 the overall trial and each study site
48

49
50 *Not applicable (site contracts are confidential).*
51

52 Access to data 29 Statement of who will have access to the final trial dataset, and
53 disclosure of contractual agreements that limit such access for
54 investigators
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57 *Not applicable (not regulated contractually).*
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1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5			<i>Not applicable (insurance provided for all patients however).</i>
6			
7	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
8	policy		participants, healthcare professionals, the public, and other relevant
9			groups (eg, via publication, reporting in results databases, or other
10			data sharing arrangements), including any publication restrictions
11			
12			<i>Lines 382-394</i>
13			
14		31b	Authorship eligibility guidelines and any intended use of professional
15			writers
16			<i>Not applicable (will be decided within consortium at later date).</i>
17			
18		31c	Plans, if any, for granting public access to the full protocol, participant-
19			level dataset, and statistical code
20			<i>Not applicable (will be decided within consortium at later date).</i>
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27	Appendices		
28			
29	Informed consent	32	Model consent form and other related documentation given to
30	materials		participants and authorised surrogates
31			
32			<i>Not applicable (part of full protocol, but too technical and detailed for</i>
33			<i>this manuscript).</i>
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36	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
37	specimens		specimens for genetic or molecular analysis in the current trial and for
38			future use in ancillary studies, if applicable
39			
40			<i>Not applicable (part of full protocol, but too technical and detailed for</i>
41			<i>this manuscript).</i>
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