



SUNDAY TRIAL

Scandinavian trial of Uncomplicated
Aortic Dissection Therapy

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ABBREVIATIONS

ADSORB: Acute Dissection: Stent graft OR Best medical therapy
AE: Adverse event
CE: Conformité Européenne
CVA: Cerebrovascular accidents
DCC: Data coordinating center
DMC: Data monitoring committee
DRG: Diagnosis related group
HADS: Hospital and Anxiety Depression Score
HRQoL: Health related quality of life
INSTEAD: Investigaton of Stent Grafts in Aortic Dissection
INSTEAD-XL: Investigaton of Stent Grafts in Aortic Dissection extended
ISO: International Organization for Standardization
QOL: Quality of life
RCT: Randomized controlled trial
REDCap: Reseach Electronic Data Capture
SF-12: Short-Form Health Survey
SMT: Standard medical therapy
TBAD: Type B aortic dissection
TEVAR: Thoracic endovascular aortic repair
TSC: Trial steering committee
uTBAD: uncomplicated type B aortic dissection

1. Introduction

This randomized, open-label, observer-blinded, two-armed controlled study addresses the question of whether thoracic endovascular aortic repair (TEVAR) impacts five-year survival among patients with an uncomplicated Stanford type-B aortic dissection (uTBAD). It is investigator-driven, and patients will be randomized to either standard medical therapy (SMT) alone or SMT + subacute TEVAR. The primary outcome is five-year survival, while secondary outcomes include aortic-related mortality, neurological events, quality of life, costs, reinterventions and readmissions. In addition, subgroup analyses based on the extent of aortic treatment will be investigated.

Primary Hypothesis

The null hypothesis for this trial states that the five-year survival results for subjects treated with either SMT or SMT + TEVAR are equivalent.

Purpose of the Study Protocol

This document serves to describe the background, rationale, and procedural details, as well as practical and ethical considerations, for the proposed clinical trial.

2. Background

The incidence of a Stanford type-B thoracic aortic dissection (TBAD) is estimated at 3.9 – 6.0 per 100,000 person years, although this may be an underestimate.¹⁻³ These account for approximately 30-40% of all types of aortic dissection.⁴ The diagnosis of TBAD is further classified with respect to timing: acute, ≤ 14 days, subacute, 15-90 days, and chronic, > 90 days. Approximately 40-50% of TBADs are considered complicated and defined by the presence of one or more of the following: rupture and/or hypotension/shock, organ malperfusion, rapid aortic expansion, paraplegia/paraparesis, peri-aortic haematoma, or intractable pain or hypertension.^{2,5} The definition of intractable is somewhat vague in the literature, yet the guidelines from the American Society for Vascular Surgery suggest a duration of > 12 hours despite medical therapy.⁶ In the absence of these complications, the dissection is considered uncomplicated. In-hospital survival for these patients has been reported as approximately 90%.⁷

Open surgery has previously played a role in the treatment of TBAD patients, but its dismal outcomes, particularly when compared to medical treatment, have led to changes in strategy.⁸⁻¹⁰ Contemporary TBAD management is dependent upon the above-mentioned factors, i.e., complicated or uncomplicated, acute or chronic, as well as accompanying comorbidities. An underlying and universal component for all these patients is standard medical therapy, which includes antihypertensive therapy, typically β -blockers, in order to mitigate aortic wall stress and false lumen pressures, as well as pain relief.¹¹ Furthermore, lifestyle improvements and cardiovascular risk profile modification are recommended.

The introduction of thoracic endovascular aortic repair (TEVAR) in 1994 radically changed the treatment of TBAD, and TEVAR is now the recommended therapy for complicated TBADs, thoracic aortic aneurysms, and traumatic thoracic transections, among others.^{12,13} To

date, the use of TEVAR in the treatment of uncomplicated TBAD is uncertain, if not controversial. Several analyses have found that TEVAR confers improved aortic remodeling and possibly survival, albeit with the implied and inherent procedural risks of intervention, including paraplegia, retrograde dissection, and death.^{14,15}

There are two relevant randomized clinical trials (RCTs), addressing the issue of early TEVAR among TBAD patients. The Acute Dissection: Stent graft OR Best medical therapy (ADSORB) trial, notably underpowered, randomized a total of 61 patients from 17 European centers with acute uTBAD.¹⁶ There were no aortic ruptures at 1-year in either arm of the trial, while TEVAR was associated with improved thrombosis of the false lumen and reduction of its lumen. The Investigation of Stent Grafts in Aortic Dissection (INSTEAD) trial included 140 patients in the subacute phase.¹⁷ The overall survival at two years was statistically equivalent, 95.6% in the SMT group and 88.9% in the TEVAR plus SMT group. The long-term results from the extended INSTEAD-XL found a non-significant absolute reduction in all-cause mortality of 8.2% at five years for those patients who underwent TEVAR.¹⁸ The authors performed an additional Landmark analysis, thus focusing only on outcomes from years two to five, and identified an absolute mortality reduction of 16.9%.

The conclusions from the retrospective and above-mentioned RCTs have not been persuasive enough for the European Society of Vascular Surgery to render a higher recommendation than “TEVAR may be selectively considered” for those patients presenting with uncomplicated type B aortic dissections.² This is furthermore echoed by a recent international survey regarding preferred treatment of uTBAD, in which 54.8% of respondents answered that they do not routinely use TEVAR, as opposed to 37.4% who prefer this strategy. More importantly, 88.6% of respondents agreed that equipoise was present and that an RCT was needed.¹⁹

Notwithstanding the clinical implications of various treatment algorithms, there are two further relevant aspects regarding the treatment of uTBAD patients that must be considered. First, the economic ramifications of potential interventions, readmissions, reinterventions, and rehabilitation are complex. A recent Canadian study demonstrated that the median and total yearly costs of treating aortic dissection have increased beyond the rate of inflation, while rehabilitation constitutes a significant portion of these costs.²⁰ Second, and somewhat coupled to the first, is the quality of life of these patients. Although evidence is limited, patients surviving a dissection have reported poorer levels of mental health and sexual function.²¹ These two issues must be accounted for in any future societal appraisals of the evidence and evaluations of the costs and benefits.

3. Research Objectives

Primary Objective

To compare the overall survival at five years between subjects treated with SMT or SMT + subacute TEVAR.

Secondary Objectives

To compare the risk of aortic-related mortality.

To compare the risk of neurological injury, including stroke or paraplegia.

To compare the proportion and indication of subjects who underwent an aortic intervention within 5 years due to development of an aortic complication.

To compare the number of disease-related readmissions during follow-up.

To compare, based on subgroup analyses, whether extent of TEVAR is associated with either improved survival or neurological injury.

To compare the associated risk of reinterventions, including those subjects who were initially randomized to SMT and subsequently required an aortic intervention.

To compare the associated changes in quality-of-life.

To compare the 10-year overall survival and aortic-related mortality.

To compare the costs.

Endpoint Definitions

These endpoints will be collected from the electronic database and correlated, where relevant, with the individual national board of health registries. These definitions are in accordance with the guidelines from the European Society of Vascular Surgery and the reporting standards document from the American Society for Vascular Surgery.^{2,6}

Primary endpoint: All-cause mortality.

Secondary endpoints:

Aortic-related mortality: Death as a result from aortic rupture or organ malperfusion, or death due to aortic intervention.

Aortic intervention: Any open surgical or endovascular intervention performed in any anatomical location, performed for the following indications, which are related to the aortic pathology: aneurysmal degeneration, visceral ischemia, lower extremity ischemia, rupture, or any of the criteria listed above under the definition of a complicated TBAD.^{2,22} Both the timing and indication for the aortic intervention should be recorded. Importantly, the decision for intervention is at the discretion of the treating physician and medical team.

Neurological injury: These are divided into two categories: cerebrovascular accidents (CVA) and spinal cord ischemia (SCI). CVAs are defined according to the Society for Vascular Surgery reporting standards and classified as any central neurological complication, ischemic and hemorrhagic. For this project, the modified Rankin scale will be used for classifying stroke severity (Table 1).²³ Spinal cord ischemia is defined as either ischemic or hemorrhagic

resulting in paraparesis or paraplegia. The modified Tarlov scoring scale will be used for the grading of any spinal cord injuries (Table 2)²⁴ It is recommended, but not mandatory, that an independent neurologist be consulted for this purpose.

The scale runs from 0-6, running from perfect health without symptoms to death.	
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Table 1: Modified Rankin scale for stroke severity.²³

Scale	Motor Function	Deficit
0	No lower extremity movement	Paraplegia
1	Lower extremity motion without gravity	Paraplegia
2	Lower extremity motion against gravity	Paraplegia
3	Able to stand with assistance	Paraparesis
4	Able to walk with assistance	Paraparesis
5	Normal	Normal

Table 2: Modified Tarlov scoring scale for spinal cord injury.²⁴

Reintervention: Any open or endovascular intervention after the original TEVAR procedure that was related to the dissection. These should be categorized as either planned reintervention, e.g., a staged procedure, or unplanned, which indicates a complication from the original procedure, a failure of the device, or progression of disease.

Quality of life: The quality of life will be assessed with the three following self-assessment forms:

1)The EuroQOL-5D-5L instrument from the EuroQol Group, comprised of five dimensions with five levels of scoring that can be combined into a five-digit number of description. ²⁵

2)The Hospital and Anxiety Depression Score (HADS)²⁶

3)The 12-Item Short-Form (12-SF) Health Survey.²⁷

Economic evaluation

The economic evaluation will be performed from a payer/healthcare point of view, including resource use associated with healthcare, intervention and medication, whereas broader potential consequences for society, i.e., effects on productivity, will not be included. During the course of the trial, the accumulated costs will be measured per treatment arm from the participating hospital's administrative/controlling/billing systems. As far as possible, the following resource use items will be included and captured as accumulated costs from the hospital's cost-per-subject system on all outpatient and inpatient visits:

- costs for healthcare staff
- subject-specific costs for primary and secondary endovascular and surgical procedures postoperative care unit costs
- costs of drugs during surgery and postoperative care
- costs of anaesthetic procedures and blood transfusions
- additional diagnostic procedures from the radiology and clinical physiology departments and from clinical chemistry.

The costs for healthcare staff will comprise the full wage costs, including costs for social security. Costs for each endovascular and surgical procedure will be retrieved individually, and, as far as possible, be based on the price per minute according to the hospital's cost-per-subject systems.

Changes in health status will be assessed in terms of quality-adjusted life-years (QALYs), which combine the time spent in a specific health state with the corresponding self-assessed health-related quality of life (HRQoL), as derived from the EuroQOL EQ-5D-5L questionnaire. Time is measured in years and the HRQoL is measured on an index scale ranging from 0 (equivalent to being dead) to 1 (best possible health state). The total number of QALYs will be calculated by multiplying the HRQoL index score (QALY weight) by the time spent in each health state. Group differences in total costs will be calculated and divided by the difference in QALYs in the interval from baseline until end of study, and the incremental cost-effectiveness ratio will be calculated as follows:

$$(\text{CostTEVAR} - \text{CostSMT}) / (\text{QALYsTEVAR} - \text{QALYsSMT}) = \Delta\text{Cost} / \Delta\text{QALY}.$$

Rationale for objectives and endpoint selection

Despite evidence from retrospective and descriptive studies suggesting long-term benefits for early TEVAR intervention among uTBAD subjects, the underlying unanswered question is whether TEVAR confers a benefit of survival. The two previous RCTs, mentioned above, were underpowered to address this issue. Despite potential theoretical and procedural advantages of various composite endpoints, it was determined that a trial based on a clearly expressed question with a binary outcome will have the most clinical impact. Similarly, focus on the albeit interesting, but not essential, endpoint of aortic morphological changes and imaging findings, would complicate the pragmatic design of this trial.

4. Therapeutic Agents and their Definitions

Standard Medical Therapy (SMT)

Contemporary standard medical therapy for TBAD consists of antihypertensive agents and pain relief. The choice of the specific agents will be left to the discretion of the individual treatment sites/surgical team, based on the individual subject's prior and current therapy and tolerance to various medical regimens. While the goal is to reduce the systolic blood pressure to between 100 - 120 mm Hg and the pulse rate below 60 beats/minute in the acute phase, the advocated first-line therapy consists of intravenous β -blockade, with calcium channel antagonists and/or renin-angiotensin inhibitors as alternatives. Pain relief is furthermore critical in order to mitigate activation of the sympathetic nervous system and resultant tachycardia and blood pressure elevation. Anxiolytic medication may also be used in this role.

Long-term SMT is essential and, although not evaluated in any clinical trials, the target blood pressure is 120/80 mmHg.²⁸ All subjects will be equipped with a home blood pressure apparatus in order to measure and record their values. As detailed below, these measurements will be recorded in the electronic database for all subjects at follow-up consultations.

Clearly, medical therapy for aortic dissection is a complex and unresolved research topic in and of itself, and individual-specific therapy can only be supported by guidelines from the European Society of Vascular Surgery and the European Society of Cardiology. Consideration in the trial was given to the connotations of "best" or "optimal" medical therapy, as well as kindred RCT protocols, e.g. Asymptomatic Carotid Surgery Trial-1 (ACST-1)²⁹, and the ramifications of these definitions vis-à-vis endpoint determination. Because of the recognized local differences in medical therapy and the interest in maintaining the pragmatic nature of this trial, it was determined that the terminology of "standard medical therapy" is most appropriate.

To that end, all sites, investigators, and subjects will be informed of the blood pressure target oriented nature of this treatment and the following recommendations from the European Society of Vascular Surgery: Initial therapy consists of β -blockers. In subjects who do not respond to β -blockers or who do not tolerate the drug, calcium channel antagonists and/or renin-angiotensin inhibitors can be used as alternatives.² In addition to these recommendations for hypertension, efforts should be made to alter and improve lifestyle and cardiovascular risk profiles, including smoking cessation, weight control, and potential treatment of other comorbidities such as diabetes mellitus and ischemic heart disease.

Thoracic Endovascular Aortic Repair (TEVAR)

Subjects randomized to TEVAR therapy will undergo placement of an endovascular stentgraft in the descending thoracic aorta. The selection of the stent graft is left to the discretion of the treating physicians. While the implicit goal of TEVAR in dissection treatment is to treat the primary tear, certain adjunct proximal and/or distal procedures are often

required, e.g., coverage of the left subclavian artery with or without a supplementary left subclavian artery revascularization, e.g., left carotid artery-to-left subclavian artery bypass/transposition or fenestration to left subclavian artery. Any or all adjunct procedures deemed necessary or beneficial by the treating physicians and subjects are allowable under the allocation to the TEVAR subject cohort, as this reflects real-world considerations and the question at hand based on analysis of an intention-to-treat. This includes distal or proximal aortic sealing, as well as Provisional Extension To Induce Complete Attachment (PETTICOAT) or Stent-Assisted Balloon-Induced Intimal Disruption and Relamination in Aortic Dissection Repair (STABILISE).^{30,31}

5. Adverse Events

An adverse event (AE) is defined by the third edition of the Clinical investigation of medical devices for human subjects-Good clinical practice from the International Organization for Standardization (ISO) as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Whilst the use of TEVAR is not new and is moreover CE-marked for aortic dissections, any AE related to its use must be noted in the allocated space in the electronic data capture system. Reported AEs will be assessed by the Data and Safety Monitoring Committee (DSMC) and assessed in conjunction with the Trial Steering Committee for any primary suspected relationship to the TEVAR procedure, planned or unplanned. The following categorization will be used in the electronic data capture system:

Adverse events	Non-device-related	Device- or Procedure-related	
Non-serious	Adverse event	Adverse device effect	
Serious	Serious adverse event	Serious adverse device effect	
		Anticipated	Unanticipated
		Anticipated serious adverse device effect	Unanticipated serious device effect

Device- or Procedure-related Adverse Event Classification

Any AE assessed to be device- or procedure-related will be classified as Serious or Non-Serious, and furthermore as anticipated or unanticipated:

Serious Adverse Event (ISO 14155:2020 Definition)

A Serious Adverse Event is an Adverse Event that

- Led to death
- Led to serious deterioration in the health of the Subject that either resulted in
 - A life-threatening illness or injury, or
 - A permanent impairment of a body structure or body function, or
 - Inpatient or prolonged hospitalization, or
 - Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the Site medical consultants, without serious deterioration in health, is not considered a Serious Adverse Event.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

Non-Serious Adverse Event (ISO 14155:2020 Definition)

A Non-Serious Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons.

Anticipated or unanticipated Serious Adverse Event (ISO 14155:2020 Definition)

The characterization of anticipated or unanticipated serious adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment (See Section 11 for further definitions), and iterated here:

- Death
- Retrograde type A aortic dissection
- Neurological injury
- Organ malperfusion
- Foreign body retainment
- Infection
- Myocardial infarction
- Aortic rupture

Device or Procedure-related Adverse Event Reporting

Each of the five countries carry legal obligations for any healthcare professional to report serious adverse events in relation to interventional devices to their respective ministries of health. These authorities follow the guidelines on medical device vigilance system (MEDDEV 2.12/1) from the EU-commission for manufacturers and competent authorities.

Specific details and adverse event reporting forms for each country are provided below and, moreover, provided in the manual at each participating Site:

Denmark

Reports of adverse events is sent to both the Danish Medicines Agency and the Danish Patient Safety Authority. These authorities are responsible for sharing this information with other European working parties. No provisions are given in regards to the timing of the adverse event and the date of report. Links to both of these forms are found on the following link: <https://laegemiddelstyrelsen.dk/en/devices/incident-reporting/>

Sweden

All serious adverse events must be reported immediately after the causal link has been established or, if such, a causal link could reasonably exist. The regulatory framework stipulates that reporting must take place at the very latest after the manufacturer has become aware of the incident. Furthermore, reports must be made within two days in the case of a serious threat to public health, within 10 days in the case of death or serious deterioration in a person's health, and within 30 days in the case of other serious adverse events. The reporting form is found on the following link:

<https://www.lakemedelsverket.se/en/medical-devices/post-market-surveillance-of-medical-devices/reporting>

Finland

Serious adverse events shall be reported within 10 days of the user or manufacturer first becoming aware of the incident. The cases of a near incident should be reported within 30 days. In addition to the following link, reports may be made by contacting +35 8295223341:

<https://www.fimea.fi/web/en/medical-devices/incident-reporting>

Norway

Serious adverse events are reported using the following link:

<https://legemiddelverket.no/english/medical-devices/reporting-of-adverse-incidents-involving-medical-devices#legal-requirements-for-the-obligation-to-report-adverse-incidents>

Iceland

Serious adverse events are reported using the following link:

https://www.ima.is/medical_devices/incident_report/nr/3713

The reporting of adverse events begins after enrollment in order to ensure that all events are captured. For purposes of the study, events after five years will not be included in the analysis, but they must nonetheless be reported to the authorities as given above.

Adverse events will be reported both in the electronic database as well as in the subject's permanent medical record. The following information, as a minimum, on each reported AE must be recorded:

- Adverse Event Name
- Adverse Event Onset Date
- Relationship
- Classification [Serious/Non-Serious]
- Treatment
- Outcome
- Resolution Date

Adverse Event reporting guidelines:

- Event reporting begins once the subject is enrolled in the study. All Adverse Events should be reported from enrollment through study completion / discontinuation.
- Provide a diagnosis if possible. If unable to provide a diagnosis, report the symptoms as separate events. Adverse Events should be reported using the full name without abbreviations or narratives.

Adverse Events with an outcome status of “Ongoing” should be assessed at each follow-up evaluation to determine if the event has resolved. Adverse Events ongoing at study completion / discontinuation should be left as “Ongoing” on the AE case report form.

6. Study Design

Summary

The trial is a randomized, open label, clinical trial with parallel assignment of subjects in multiple clinical centers (referred to as “Sites” in the remainder of this document) in Denmark, Sweden, Norway, Iceland, and Finland. Recruited subjects will be randomized to either SMT exclusively or TEVAR + SMT, as schematically represented in Figure 1.

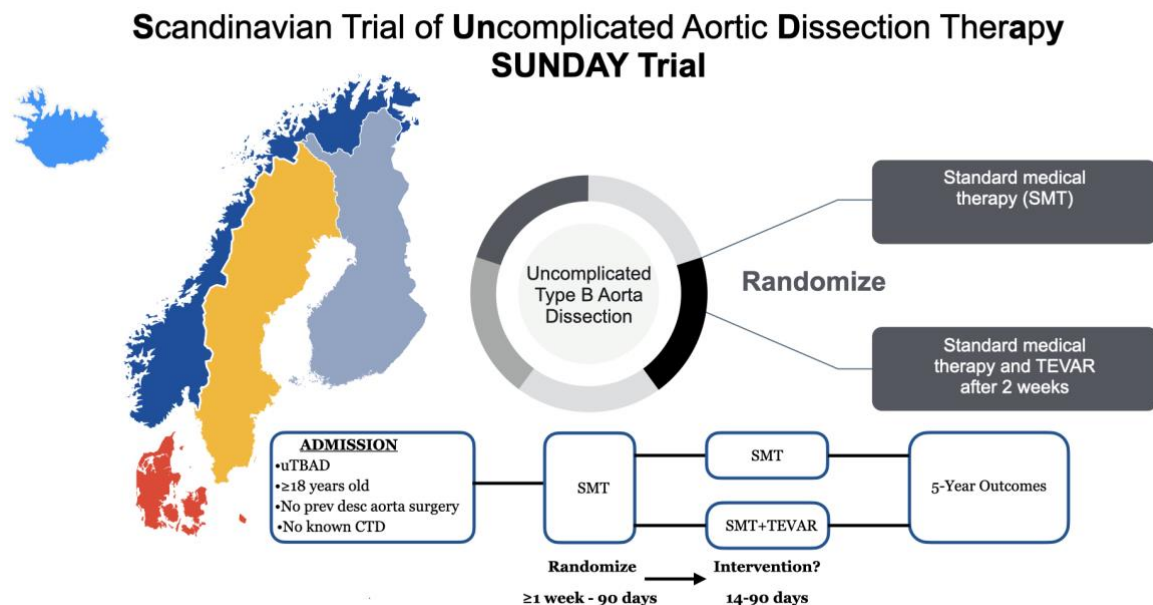


Figure 1: Schematic summary of study design.

Description of the population

Any subject with a type B aortic dissection is eligible for screening for participation in the study. Only subjects who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be recruited and enrolled.

For the purposes of this trial, day zero is considered the day of onset of symptoms.

Screening

The screening of potentially eligible subjects begins once any admitted or referred subject has undergone diagnostic imaging, and the diagnosis of a TBAD has been determined. It is at this point that data should be recorded in the electronic screening log (more below). For this trial, the distinction between a complicated and uncomplicated TBAD can only be made clinically, with the exception of aortic rupture. That is, for example, an occluded visceral vessel should not be considered a complication without ascertainment of clinical signs. Clinical evaluation is therefore mandatory for subsequent consideration of recruitment. This process should be undertaken, although not be limited by, consultation with those specialists who would potentially perform the TEVAR procedure. It is anticipated that subjects with TBAD are treated by several and multiple medical specialties, including the departments of internal medicine, cardiology, vascular medicine, vascular surgery, interventional radiology, and cardiothoracic surgery.

The following data from the screening process will be recorded in the electronic database:

- Age
- Sex
- Eligible for recruitment?
- Reason for ineligibility

Following this screening process of diagnostic imaging, clinical evaluation, and consideration of the inclusion and exclusion criteria, a subject may then be deemed eligible for recruitment and randomization.

The premise of this trial is based on both pragmatism and on an intention to treat. Any screened subject with an uTBAD should therefore be considered for recruitment. It is important to underscore, however, that discretion for recruitment is relegated to the Site and investigators, as they must consider the clinical ramifications and the safety of the subject. All efforts should be made to maintain equipoise in the trial and randomize eligible and willing subjects once the screening process has been completed. This is an important point, as once subjects are enrolled and randomized, clinical aspects may change, while subjects will still primarily be evaluated based on the intention to treat and the arm of treatment to which they were originally assigned.

Eligibility criteria

Inclusion criteria

All subjects, aged 18 or greater at the time of informed consent signature, admitted or referred to the participating cardiovascular Sites with an uTBAD of less than 90 days duration.

Exclusion criteria

- Subjects with no signed informed consent.

- Subjects presenting with a *complicated* type B aortic dissection according to the above definition.
- Subjects previously treated in their descending aorta, either open surgery or TEVAR.
- Subjects with pre-existing thoracoabdominal aortic aneurysm.
- Subjects with other aortic pathology with an indication for intervention that requires TEVAR.
- Subjects with traumatic aortic dissections.
- Subjects with an established connective tissue disease at the time of randomization, including but not limited to Marfans and Loeys-Dietz syndrome.
- Subjects with a clinically estimated life expectancy < 2 years.
- Subjects with dementia.
- Pregnant or nursing subjects.
- Subjects with current sepsis.
- Subjects currently participating in other clinical interventional trials.

Recruitment, consent, randomization, and withdrawal

Recruitment

Subjects deemed eligible following the screening process and fulfillment of the inclusion and exclusion criteria will be informed by investigators from the participating Sites of the clinical trial regarding eligibility for participation. This process should be performed in an undisturbed location, and both verbal and written information should be provided. Any member of the medical team may offer information regarding the trial, but each site has a specifically appointed investigator who is responsible for the proper process of information and informed consent, as detailed below.

Consent

Subjects recruited for this study can and should not be limited by their sex, ethnic origin, or age, with the exception of children, i.e., under the age of 18, as stated in the exclusion criteria. Consideration should be given to willingness or hesitation to participate and, under no circumstances, should coercion play a role in study enrolment. Subjects should be informed that unwillingness to participate will have no impact on future decisions regarding their standard of care.

Consent procedures will follow local and national regulatory guidelines. A written form of consent should be thoroughly reviewed, and subjects should be informed of their right to take time for consideration and to use relatives, general practitioners, or any member of their social network during this process. The informed consent will be signed in a confidential manner. A copy of the informed consent document will be given to the subject for their records. More details are provided below (Section 11) regarding the information provided to the subject and issues regarding data protection.

Randomization

The process of randomization will be carried out by the same third-party electronic dataset system, Research Electronic Data Capture (REDCap) with 24-hour access (see below). Because

of the multi-site nature of the trial, randomization will be stratified by the number of clinical sites.

As noted above, day zero is the day of onset of symptoms. Subjects may be randomized as early as one week but not later than 90 days. If randomized to the SMT+TEVAR arm, subjects must undergo TEVAR treatment within 90 days from the onset of symptoms. This window of randomization is selected with pragmatism in mind, as some subjects may already be discharged or transferred to another hospital after one week, which would thus hinder the process of informed consent.

Withdrawal of participants

Subjects should be informed at the time of consent that they have the right, at any time, to withdraw from the study. Clarification must be obtained regarding the use of previously collected data, as subjects maintain the right to either partially or completely withdraw from any or all aspects of the trial.

Withdrawal process

As per participant’s decision

Any participant wishing to withdraw may either contact the specialist team at the original site of enrollment or the principal investigators using the contact details provided on the consent form.

7. Subject, Procedural, and Follow-Up Data

The following Table 3 provides an overview of the planned data collection. These data will be collected in addition, and should supplement, any unplanned follow-up for readmission or reintervention. Finally, 5- and 10-year data will be captured and cross-checked from applications to the national registries.

Observation	Baseline	Discharge	Procedure	3-month	1-year	3-year	5-year
Imaging	X		X	*	*	*	*
Informed Consent	X						
Medical History	X						X
Physical Exam	X		X				
EQ-5D-5L, HADS, SF-12	X			X	X	X	X
Blood Pressure	X	X	X	X	X	X	X
Medication List	X	X	X	X	X	X	X

Procedural Data			X				
Adverse Event Evaluation		X	X	X	X	X	X

Table 3: Planned subject-data collection upon admission and during follow-up.

*Imaging is not mandatory, but data entry is possible at these follow-up dates.

Baseline

At the time of admission and enrolment, the following data will be recorded:

Subject data

- Date of birth
- Sex
- Comorbidities and previous medical/surgical history
- Smoking status
- Medications
- Height and weight
- Blood pressure
- Heart rate

Anamnesis

- Description of symptoms
- Debut and duration of symptoms

Paraclinical data

- Hemoglobin (g/dL) or (g/L)
- Serum creatinine (micromoles/L)
- Estimated glomerular filtration rate (ml/min/1,73 m²)
- Serum cholesterol and LDL-cholesterol

Diagnostic imaging

- Modality of imaging
- Stanford and DeBakey classification of dissection
- Essential aortic findings, including diameter (true, false, and total lumens), entry tear diameter, and entry location (inner or outer aortic curve) from imaging with specific description according to the Society for Vascular Surgery and Society of Thoracic Surgery Reporting Standards for Type B Aortic Dissections (Figure 2).⁶

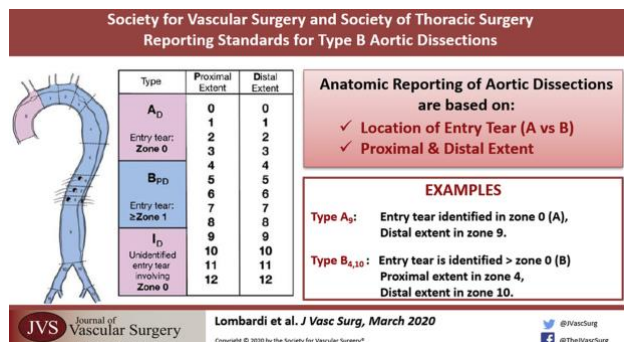


Figure 2: Reporting standards for Type B Aortic Dissections.⁶

Procedural and peri-procedural data

Data relevant to the interventional arm of TEVAR treatment. Peri-procedural is defined in relation to the in-hospital period of treatment.

- Access, e.g. groin, brachial
- Type of TEVAR stent graft (Company name) used
- Number of stent grafts placed
- Diameter and length of stent grafts placed
- Adjunctive procedures, including left subclavian artery revascularization, distal bare-metal stenting, false lumen occlusion, mesenteric or iliac artery revascularization, femoro-femoral bypass operations, femoral artery thrombendarterectomy, or fasciotomy. These will be noted to be either planned or ad hoc.
- Technical success, as defined by coverage of primary entry and no type Ia endoleak
- Complications, including death, stroke (according to modified Rankin scale), myocardial infarction, acute kidney injury, spinal cord ischemia (according to modified Tarlov score, bowel ischemia, or rupture.
- Proximal and distal landing zones.
- Use and type of closure devices

Follow-up

As given in Table 3, information garnered from the physical exam, medication list review, and adverse event reporting will be used, in addition to any details from the latest, or five-year, imaging. Medication lists and self-reported blood pressures will be obtained either from telephone consultation or ambulatory visits. Each subject, in both arms of the trial, will be provided with a home blood pressure apparatus in order to provide this information.

8. Statistical Considerations and Analysis Plan

Sample size and power

The literature supports an overall estimated 5-year survival for TBAD subjects of approximately 80%, i.e., a 5-year mortality of 20%.³² The above-mentioned INSTEAD-XL clinical trial identified a reduction in 5-year mortality from 19.3% to 11.1% for those who

were randomized to TEVAR, corresponding to a hazard ratio of 0.52.¹⁸ The estimate was not statistically significant, possibly due to a low sample size.

The primary analysis will be based on the intention to treat principle using the full analysis set and all-cause mortality events as confirmed by the local investigator. The primary objective of the study is to determine the superiority of TEVAR versus SMT in reducing the incidence of all-cause mortality. Assuming a true hazard ratio of 0.52 between TEVAR and SMT, using a two-sided alpha of 5%, 80 subjects with primary endpoint events will provide a statistical power of 80% for the test of all-cause mortality between treatment arms, based on an overall 1:1 allocation between TEVAR and SMT and analysed with a log-rank test. All Scandinavian countries have registries of vital statistics with a high reliability and almost complete follow-up. Consequently, loss-to-follow-up is expected to be negligible, except for migration, and thus a conservative estimate of loss-to-follow-up is given as 3%.

The study is event-driven. With an estimated annual event rate of 4% for the primary endpoint in the control group and a withdrawal probability of 3%, approximately 550 subjects are estimated to provide the required number of primary events.

In summary, the parameters used for the power calculation are as follows:

Log-rank test for comparison of two groups

Two-sided significance level (alpha) = 0.05 (5%)

Power (1-Beta) = 0.80 (80%)

Hazard ratio = 0.52

Withdrawal probability = 0.03 (3%)

Inflation factor due to single interim analysis (See below) = 1.0071

Estimated number of events, i.e. deaths = 80

Estimated total sample size = $550 \times 1.0071 = 554$

Estimated number in each arm = $225 \times 1.0071 = 277$

Study oversight

Blinded event rate data checks will be performed to re-assess the event rate assumptions, and a re-estimation of sample size will be allowed if actual event rates during the study are lower than estimated. The DSMC will furthermore evaluate safety of the study treatment periodically according to a specifically developed charter.

Analysis plan

Once the number of events has been reached as confirmed by both all local Investigators and the DSMC, further enrolment will be halted. Further data acquisition regarding adverse events, reinterventions, or death will be continued and reported.

Given the long duration of the study and the potential for achieving sufficient evidence prior to the end of follow-up, as well as the potential for safety issues, a single interim analysis is planned. The interim analysis will be undertaken when approximately half of the total events have occurred, i.e., 40 events. This will use the O'Brien-Fleming boundary with a two-sided significance level of .0052 in conjunction with the log-rank test. This virtually preserves the

overall type I error rate (4.8% vs. 5.0%), and thus the final analysis at the end of follow-up will be conducted with the conventional significance level of .05.³³

Both an intention-to-treat and a per-protocol analysis will be performed. As mentioned, in the primary analysis, survival rates will be compared using the log-rank test. To explore treatment effect heterogeneity in sub-groups, Cox Proportional Hazards (Cox PH) regression will be used. Before analysis, log-log-survival versus time plots will be used to visually assess the assumption of proportional hazards supported by statistical tests based on inclusion of a time-varying covariate for the treatment effect. In case of crossing survival curves, the overall log-rank test will be reported together with effect estimates in-between crossings. If repeated crossings occur, this will in itself suggest that the intervention does not result in superior outcomes for the subjects, which will then be reported.

9. Trial Registration, Masterfile, and Protocol Modifications

Study registration

The trial has been posted on clinicaltrials.gov, NCT05215587.

Source Data and Masterfile

Source data are defined as all information or data that are necessary for the reconstruction and evaluation of the trial. The investigators will keep all study records and source data available for inspection and audit from the DSMC, as well as the respective national ethical committees and regulatory authorities.

All source data will be transferred and kept in a Masterfile. Current Good Clinical Practice guidelines recommend an archival period of five years following closure of the trial. The EU Clinical Trials Regulation Nr. 536/2014, Article 58, which is set to replace the Clinical Trials Directive, now requires a minimum period of 25 years following closure, which will be followed in this trial.

Protocol Deviations

A Protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol. Investigators are responsible for promptly recording and reporting Protocol Deviations to the Trial Steering Committee and the reviewing national ethical committees in accordance with their policies. The Trial Steering Committee will determine the effect of the protocol deviation on the scientific soundness of the study and subject safety and determine if additional reports or actions are required. Additional action may include Site retraining or Site termination.

Protocol Amendments

The investigators will not implement any changes to the protocol without first obtaining written agreement and approval from the individual national ethical committees, except in the event of an immediate hazard(s) to a subject. The Investigator will report the Protocol Deviation in accordance with the applicable regulations.

Study Discontinuation or Suspension

In compliance with the EU regulation of the European Parliament and of the Council of 5 April 2017 on medical devices, the end of the trial is deemed to coincide with the last visit of the last subject. The Trial Steering Committee will notify each Site within 15 days of the end of the trial. If the Trial Steering Committee requires a temporary suspension of the trial, each site must be informed with justification within 24 hours. Irrespective of the outcome of the trial, within one year of the trial or within three months of early termination or temporary suspension, the Trial Steering Committee will submit a report to each of the Sites.

Study discontinuation or suspension may be a result of statistically based stopping rules, lack of funding, poor recruitment, safety concerns, or new information regarding the benefit-risk balance from breaking research. Decisions regarding discontinuation or suspension will be made in consultation with the Safety Monitoring Committee individual national health authorities.

10. Data Collection and Safety Monitoring

Data collection

Data will be collected and administered using the online Research Electronic Data Capture (REDCap) dataset system, <https://projectredcap.org>. Access to data input will be allocated to one member from each participating Site, as well as the DSMC (see below). Importantly, all data entry and revisions will be logged, and all investigators, as well as members of the Trials Steering Committee, will be blinded from data within the electronic database.

As iterated above, data will be recorded at the screening stage, that is, once the diagnosis of TBAD has been made. Data at this point, will be limited to age and sex. If, for whatever reason, the subject is not recruited into the trial, no further data will be collected or recorded, with the exception of why the subject was not recruited into the trial.

Data and Safety Monitoring

The Data and Safety Monitoring Committee (DSMC) is composed of a trained and accredited data coordinating center (DCC) from Uppsala University, Uppsala, Sweden, three clinical experts, and one independent statistician.

As explicit in their separate charter, the DSMC has the responsibility of safeguarding the welfare of study participants, maintaining the integrity of the trial, and promoting the timely delivery of credible results.

The DCC will carry out data entry validation and site progress reports biannually via direct contact with individual sites. Safety monitoring reports will be created annually in conjunction with the statistician for review with the three clinical experts.

An independent statistician is also part of the DSMC in an advisory role, with no voting mandate regarding recommendations to the Trial Steering Committee. The DSMC will meet annually in order to review performance reports of blinded data of all the primary and relevant secondary endpoints, as well as any serious adverse events. A report from these meetings will be submitted and shared with the Trial Steering Committee for discussion and storage in the Master File.

Study Completion, Discontinuation or Suspension

In compliance with the EU regulation of the European Parliament and of the Council of 5 April 2017 on medical devices, the end of the trial is deemed to coincide with the last visit of the last subject. The Trial Steering Committee will notify each Site within 15 days of the end of the trial. If the Trial Steering Committee requires a temporary suspension of the trial, each site must be informed with justification within 24 hours. Irrespective of the outcome of the trial, within one year of the trial or within three months of early termination or temporary suspension, the Trial Steering Committee will submit a report to each of the Sites.

Study discontinuation or suspension may be a result of statistically based stopping rules, lack of funding, poor recruitment, safety concerns, or new information regarding the benefit-risk balance from breaking research. Decisions regarding discontinuation or suspension will be made in consultation between the TSC and DSMC or the individual national health authorities

11. Ethics, Risk Assessment, and Benefit-Risk Rationale

Statement of Compliance

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.³⁴ It will furthermore be conducted in compliance with the International Organization for Standardization Good Clinical Practice for clinical investigation of medical devices for human subjects, ISO 14155:2020 and any other national or regional applicable regulatory requirements.

Compliance Responsibilities

The Trial Steering Committee and site investigators will conduct the study in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing national ethical committees and governing regulatory agencies. The Trial Steering Committee will verify that approvals from all countries are obtained prior to enrollment, maintained throughout the course of the study, and that all reporting requirements are met. The Trial Steering Committee is responsible for protecting the rights, safety, and welfare of subjects under the Investigators' care and for the control of devices under investigation. The Trial Steering Committee is also ultimately responsible for ensuring that informed consent is properly obtained.

Independent Ethical Review

The Investigator will submit the protocol, informed consent forms, and other information to be provided to subjects to the respective national ethical committees for written approval.

The investigators shall not enroll any subjects prior to obtaining approval for the study from the properly constituted independent national ethical committee.

Ethical applications of approval will uphold the following three following values of ethical conduct into consideration:

1. **Autonomy:** Given that the subject has the understanding and intentionality of the clinical trial, as provided in the informed consent process, this principle obliges the investigators to respect the self-determination of the subject to participate or withdraw from the trial at any time and as they see fit.
2. **Beneficence:** This principle respects the benefit of others and the removal of conditions that may cause harm. The risk analysis of this project and the conclusions from the benefit-risk analysis must be vigilantly upheld in conjunction with respect to the safety reporting from the DSMC.
3. **Justice:** The distribution of benefits, risks, costs, and resources of SMT or TEVAR + SMT are balanced, given the benefits or risks of either arm of the trial.

Risk Assessment

The risk assessment of any intervention includes the combination of the probability of occurrence of harm and the severity of that harm, both in their immediate and residual forms. An adverse event can be attributed either to intervention with the planned device/delivery system or to a combination of the device and the underlying pathology. Estimates of incidences vary in the literature, and this is, in part, due to the heterogeneity of the subjects, the indication for treatment, and the timing of the procedure. The incidences reported below were reported by the above-mentioned INSTEAD trial and represent those events most clinically relevant and conventionally reported in the literature.¹⁷ A more exhaustive list of potential yet albeit rare events, e.g., changes in mental status, and tissue necrosis are included in the instructions for use for all devices used in this trial. These will, moreover, be included in every Site manual.

- **Death:** the risk of peri-procedural death with TEVAR procedures among uTBAD subjects is approximately 2%. This is most often a result of one of the below-listed adverse events, in particular, rupture and organ malperfusion. Mitigation of this event is best achieved by appropriate preoperative clinical evaluation for risk reduction and compliance with instructions for use. Death is the primary outcome of this trial, and all deaths will be recorded, regardless of cause. The residual risk of death specifically related to an adverse event from the device is not known.

- Retrograde type A aortic dissection: The incidence of this event is 1%, most often perioperatively, although residual risk is not entirely insignificant. This event almost necessarily requires further intervention, most often open surgical aortic repair. Clinical and imaging follow-up are mandatory and important elements in the screening and recruitment of subjects in the trial in order to monitor the residual risk.
- Neurological injury: This adverse event was described above under study endpoints. The incidence of spinal cord ischemia is approximately 2%. Adjunct procedures, including central spinal fluid drainage, left subclavian artery revascularization, staged pre-procedural lumbar artery embolization, and procedural staging are known strategies to prevent this event. Notably, all of these preventive strategies are allowable under the present protocol and left to the discretion of the treating Site and physicians. The risk of cerebrovascular injury is also estimated at 1% and is dependent on many underlying factors, including the age and comorbidities of the subject, as well as device manipulation during the procedure. Again, appropriate risk assessment is required prior to the procedure, and consideration must be given to ancillary procedures, such as left subclavian artery revascularization, carotid artery treatment, and possible additional medical therapy.
- Organ malperfusion: This adverse event typically relates to malperfusion of the gastrointestinal system, one or both kidneys, and the lower extremities. Clinical consequences include extended lengths-of-stay, further clinical work-up, temporary or permanent dialysis, and colonic surgery. It is important to stress that the preexistence of any of these clinical states should disqualify subject enrollment in the trial, as the dissection should be characterized as “complicated”. Proper screening during recruitment is paramount in order to reduce the risk of this adverse event, while various measures are available in order to mitigate its clinical consequences, including further stent grafting, open surgery, and aggressive medical therapy. All of these additional measures will be recorded and, as noted above in the definition of endpoints, will be noted as either planned or unplanned.
- Foreign body retainment: The risk of retainment of some part of the device or delivery system is minimal but is recognized and documented. Its occurrence may be benign but may also lead to vascular thrombosis, bleeding, or infection, thus requiring further intervention, either endovascular or open surgery.

- Infection: The risk of infection must be considered in any intervention. Other factors often play a role in the immediate and residual risk of infection, particularly age, underlying comorbidities, and the acuity of the procedure. Screening prior to recruitment should exclude subjects with ongoing infection, just as preoperative prophylactic antibiotic therapy should be administered for this elective procedure. Treatment of infection mandates further antibiotic therapy, and sometimes additional procedures are required, including open aortic surgery in order to remove the foreign body.
- Myocardial infarction: This risk may be disease- or procedure-related, yet no myocardial infarctions were reported in the INSTEAD trial.¹⁷ Treatment during the subacute phase and appropriate medical management should furthermore mitigate this risk.
- Aortic rupture: While aortic interventions is one of the secondary endpoints, including for rupture, the risk for a procedure-related aortic rupture should be anticipated and recorded.

Benefit-Risk Rationale

The benefits of TEVAR treatment for a subject with an uTBAD are based on the previously discussed RCTS above, the ADSORB and INSTEAD-XL trials, in addition to several retrospective studies.^{16,17} There are two main benefits: first, it is well-documented that TEVAR treatment improves aortic remodeling and delays the progression of disease. While SMT may be sufficient to maintain early overall survival, the transformation of an acute/sub-acute dissection to a chronic dissection entails a new pathological entity, i.e., a thoracoabdominal aorta aneurysm, which is technically more challenging to treat with increased associated risks. TEVAR intervention, on the other hand, delays this process, thus reducing the yearly risk of rupture, which increases to approximately 12.5-18.8% once the aortic diameter reaches a diameter of 6.0 cm.³⁵

The second benefit is overall survival. The INSTEAD-XL trial demonstrated this, using their prespecified use of a Landmark analysis for mortality. Between two and five years, the survival for TEVAR subjects was 100% versus 83.1% for the SMT cohort.¹⁸ Their test for interaction between treatment effect and time was moreover significant, suggesting a late survival benefit for TEVAR. The use of the Landmark statistical analysis has had limited impact in altering international guidelines regarding treatment of uTBADs, hence the need for the present proposed trial.

The risk of TEVAR intervention is implicit in the very analysis performed in the INSTEAD-XL trial, revealed when the Landmark analysis is replaced by the standard Kaplan-Meier analysis, i.e., the starting point is moved back to day zero. When this analysis is performed, the overall survival still appears to benefit TEVAR patients, but the statistical p-value was nonsignificant. In other words, there were “up-front” risks of death within the first year, although none of these events were documented as periprocedural. Within one year, there were five deaths (7.5%) in the TEVAR cohort and two deaths (3.0%) in the SMT cohort,

p=0.44. In addition to the risk of death, there were three cases of neurological injury documented (1 paraplegia, 1 major stroke, and 1 transient paraparesis).

These risks must also be considered for those subjects initially treated with SMT who ultimately cross over to TEVAR (26.5% within five years). Indeed, the risk of rupture, or aorta-specific mortality, is significantly greater for those individuals on SMT, and any potential indication for aortic intervention may be associated with increased risks, particularly in cases of acuity.

It is in this light that the benefit-risk rationale supports the probable benefit of preemptive TEVAR treatment. This rationale has furthermore been provided to each of the national ethical committees and will be aligned with the recruitment of subjects and the process of obtaining informed and written consent.

Equipoise

As iterated above in the benefit-risk rationale, subjects may potentially benefit from participation in the trial but, more importantly, the literature to date supports the notion that participation will not expose subjects to unnecessary or significant risks. This is furthermore reflected in the introductory background remarks (Section 2.4.b) highlighting the equivocal positions of clinicians as to whether uTBAD subjects should undergo early TEVAR treatment or not.

Benefit

For those subjects participating in the trial, some may benefit from participation in the important outcomes of long-term survival and avoidance of complex surgery, and possibly even improved quality of life. As noted in the introduction, observational studies and underpowered RCTs have suggested this.

For those subjects not participating in the trial, i.e., future uTBAD patients, the successful completion of this RCT can and should provide an array of answers of how to best treat them. Presumed subanalyses should also help clarify and improve potential questions of appropriate patient selection. Moreover, the economic assessment of this trial should also help guide healthcare organizations in any deliberation of healthcare financial allocations.

12. Data protection policy, Informed Consent, and Confidentiality

Data Protection

All subject personal health data will be regarded as confidential and processed according to the General Data Protection Regulation (GDPR), Chapter 2, Article 6, 1a, in that processing shall be lawful when the data subject has given consent to the processing of his or her personal data for one or more specific purposes.

Informed Consent

All subjects will receive an approved subject participation and information brochure regarding the trial and their rights as a participant. In addition to a clinical evaluation and thorough discussion, a formal consent document will also be provided.

The formal consent of a subject, using the approved consent form each country in their respective native language, must be obtained by the Investigators before that subject undergoes any study-related procedure. The consent form will be signed and personally dated by the subject and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the subject's records. A copy of the informed consent document will be given to the subject for his or her records. Any significant, new information which emerges while the study is in progress that may influence a subject's willingness to continue to take part in the study will be provided to the subject.

The investigator shall verify that documentation of the acquisition of informed consent is recorded in each subject's records in accordance with applicable regulations.

Confidentiality

All subject records will be kept confidential to the extent provided by applicable laws and regulations. Such records may also be reviewed by the DSMC, the individual national ethical committees, and other regulatory authorities. The investigator will inform any subject that their records will be reviewed.

Signed consent is mandatory for all enrolled subjects in both arms of the clinical trial. Only pre-specified research investigators will have access to the REDCap database to ensure data confidentiality. Participants will be assigned a unique identification number that will be used for all database forms. REDCap is a secure web application, supported and recommended by most academic centers for managing databases online. More specific and non-trial related subject data will otherwise remain on the individual hospital and national healthcare electronic journal systems. Any hard copy information related to the trial will be kept in a locked office at the respective participating Sites.

13. Organizational Structure

Trial Steering Committee

A Trial Steering Committee (TSC) has been formed with representatives from each of the five countries involved, in addition to two laypersons and a statistician. The TSC maintains the overall responsibility and conduct of the trial in consultation with the independent DSMC. In addition to annual reporting on updates regarding recruitment, they will monitor the recording of data and any violations of protocol. They will, moreover, act in accordance with concerns or criticisms from the DSMC regarding serious adverse events, safety, and study viability.

Data and Safety Monitoring Committee

As mentioned above, the DSMC is formed as an independent body under a formed charter according to the Data Monitoring Committee Charter (DAMOCLES)³⁶. Specifics regarding interim data reviews, communication with the TSC, and decisions regarding conduct of the trial are specified in the charter.

Funding

Funding for the trial will be sought from the public and private sector, as soon as the protocol is accepted and approved by members from all of the five countries involved.

Timetable

The tentative timetable provided below in Figure 3 will be updated accordingly.



Figure 3: Tentative project timetable.

14. Publication Policy

A writing committee will be established early in the project planning stages composed of both the primary investigators and several invited colleagues from the participating Sites. Following analysis of data, a manuscript will be prepared for publication in a peer-reviewed journal. Authorship will be shared and reported as a writing committee under the name *Scandinavian Aortic Collaboration*.

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