Research protocol

PROTOCOL TITLE: ACTION-1: ACT guided heparinization during open abdominal aortic aneurysm repair, a randomised trial.

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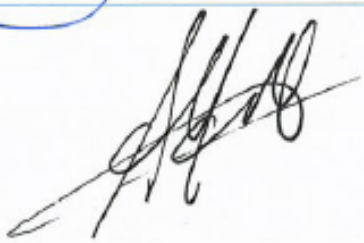
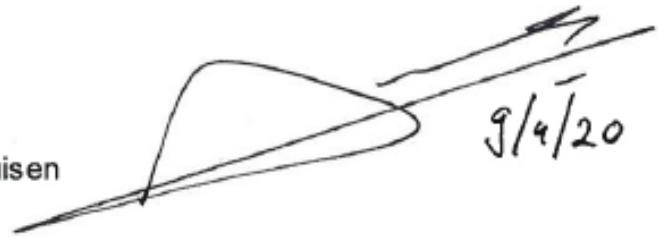
Head of Department: Drs. A.L.A. van IJsseldijk, traumachirurg Afdeling chirurgie Dijklander ziekenhuis T: 0229 257 257 E: a.vanijssedijk@westfriesgasthuis.nl Postbus 600, 1620 AR Hoorn		10/4/20
[Coordinating Investigator/Project leader/ Principal Investigator]: Dr. A.M. Wiersema, vaatchirurg T: 06 53444515 E: arno@wiersema.nu Afdeling (Vaat)chirurgie Dijklander ziekenhuis en Amsterdam UMC, loc. VUmc Afdeling (Vaat)chirurgie Maelsonstraat 3, 1624 NP Hoorn		9/4/20

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AAA	Abdominal Aortic Aneurysm
ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
ACT	Activated Clotting Time
AE	Adverse Event
AR	Adverse Reaction
ASA	Acetylsalicylic acid
ASA	American Society of Anaesthesiologists
ATN	Acute Tubular Necrosis
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CEA	Cost Effectiveness Analysis
CPI	Consumer Price Indices
CRB	Clinical Research Bureau
CRO	Clinical Research Organisation
CRF	Case Record Form
CV	Curriculum Vitae
CVA	Cerebrovascular accident
DOAC	Direct Oral Anticoagulant
DSAA	Dutch Surgical Aneurysm Audit
DSAA class C aneurysm	Abdominal aortic aneurysm distal from superior mesenteric artery (including infrarenal, juxtarenal and suprarenal aortic aneurysms)
DSMB	Data Safety Monitoring Board
E-CABG	Classification for bleeding complications: class 1 or higher if any of the following: transfusion of platelets, fresh frozen plasma, or 2 or more units of red blood cells, or reoperation for bleeding
ECG	Electrocardiography
eCRF	electronic Case Report Form
EGFR	Estimated Glomerular Filtration Rate
EPF	Electronic patient file
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
HIT	Heparin Induced Thrombocytopenia
HMS	Hemostasis Management System
HR-ACT	High Range-Activated Clotting Time
IB	Investigator's Brochure
IC	Informed Consent
ICAC	Independent Central Adjudication Committee
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IMCQ	iMTA Medical Consumption Questionnaire
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product Dossier
IPCQ	iMTA Productivity Cost Questionnaire
IQR	Inter-Quartile Ranges
IRB	Institutional Review Board
ISF	Investigator Site File
IU	International Unit
LMWH	Low-Molecular-Weight Heparin
MANCO	Measuring the ACT during Non-Cardiac prOcedures
METC	Medical research Ethics Committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie (METC)
MI	Myocardial Infarction
MRA	Magnetic Resonance Angiography
MREC	Medical Research Ethics Committee
NCAP	Non-Cardiac Arterial Procedures
QALY	Quality-Adjusted Life Year
RBC	Red Blood Cell
RCT	Randomised Controlled Trial
RIFLE	Risk, Injury, Failure, Loss, End stage renal disease. Criteria for classifying the severity of acute kidney injury
(S)AE	(Serious) Adverse Event
SD	Standard Deviation
SDV	Source Data Verification
SMA	Superior Mesenteric Artery
SOP	Standard Operation Procedures
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
SPONSOR	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party
SPSS	Statistical Package for Social Sciences
TAI	Thrombocyte Aggregation Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEC	Thrombo-Embolic Complications. TEC are any complication as caused by thrombus or embolus perioperatively, including but not exclusively: myocardial infarction, leg ischemia, deep venous thrombosis, colon ischemia, TIA/stroke, graft thrombosis, peroperative thrombus requiring embolectomy or redo of an anastomosis, thrombus or embolus in organs or lower limbs and other peripheral thrombosis
TMF	Trial Master File
UK	United Kingdom
USA	United States of America
VKA	Vitamin K antagonists
WBP	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMA	World Medical Association
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch Wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Heparin is used during open abdominal aortic aneurysm (AAA) surgery to reduce thrombo-embolic complications (TEC): such as myocardial infarction, stroke, peripheral embolic events and the related mortality. On the other hand, heparin may increase blood loss, causing harm for the patient.
Heparin has an unpredictable effect in the individual patient. The effect of heparin can be measured by using the Activated Clotting Time (ACT). ACT measurement in open AAA repair could be introduced to ensure the individual patient of safe, tailor-made anticoagulation with a goal ACT of 200-220 seconds. A randomized controlled trial (RCT) has to prove that ACT guided heparinization would result in fewer TEC and lower mortality than a standardized bolus of heparin of 5 000 IU, the current gold standard. ACT guided heparinization results in higher doses of heparin during operation and this should not result in significantly more bleeding complications of importance. The above-described objectives were tested in a pilot study: Measuring the ACT during non-cardiac procedures (MANCO). The pilot study had the same study protocol as the current study.

Objective: To determine whether ACT guided heparinization decreases TEC and mortality after elective open AAA surgery, without causing more bleeding complications.

Study design: International multi-centre single blind RCT. Patients will be randomized using a computerized program (CASTOR EDC) with a random block size of 2, 4, 6. The randomization will be stratified by participating centre. Separate evaluation of results and if complications can be labelled as TEC, will be performed by an Independent Central Adjudication Committee. The 3 members of this Committee will be blinded with regard to if the patient was randomized for ACT guided heparinization or standard bolus of 5 000 IU without ACT measurements.

Study population: Patients older than 18 years scheduled for elective, open repair of an iliac or abdominal aortic aneurysm distal to the superior mesenteric artery (SMA).

Intervention:
Investigational use:
Heparin is given to reach an ACT of 200-220 seconds. At the start of the procedure, before any heparin is given, a baseline ACT measurement is performed. 3-5 minutes before clamping of the aorta 100 IU/kg bodyweight of heparin is administrated intravenously, with a maximum of 15.000IU of heparin. 5 minutes after administration of heparin, ACT measurement is performed.
- If the ACT is below 180 seconds, an additional dose of heparin of 60 IU/kg is administered.
- If the ACT is between 180 and 200 seconds, an additional dose of heparin of 30 IU/kg is administered.
- If the ACT is 200 seconds or longer, no extra heparin is given.

Five minutes after every administration of heparin the ACT is measured. If the ACT is 200 seconds or longer, the next ACT measurement is performed every 30 minutes, until the end of the procedure or until new heparin administration is required (because of ACT < 200 seconds). After

each new dose of heparin, an ACT measurement is performed after 5 minutes and the above-described protocol of ACT measurements will be repeated. In case of near completion of the final anastomosis and re-establishment of arterial flow the attending vascular surgeon can decide not to give extra heparin despite an ACT below 200. After re-establishing blood flow and removing all clamps, the ACT is measured. Depending on that ACT value near the end of surgery, protamine is given to neutralize the effect of heparin.
If the ACT at closure is between 200 and 250 seconds, 25 mg protamine should be administered. If the ACT is higher than 250 seconds, 50 mg protamine should be administered. If the ACT is between 180 and 200 seconds, 10 mg protamine should be administered. Five minutes after the administration of protamine, the ACT is measured. The ACT should preferably be below 180 seconds. If the ACT is still more than 200 seconds, protamine should be administered again. When an additional dose of protamine is required, according to the above depicted protocol, ACT measurement is performed 5 minutes after that administration.

Comparative use:
A single dose of 5 000 IU of heparin is given 3-5 minutes before clamping of the aorta. No ACT measurements are performed. Only on clarified indications extra doses of heparin or protamine are permitted, at the discretion of the attending vascular surgeon. Indications could be clot formation intravascular or in a prosthesis, excessive bleeding or prolonged operation duration. Deviations from protocol should be clearly stated with reasoning in the operative report. Patients with additional doses of heparin or protamine outside protocol will not be excluded from the trial. Evaluation will be performed according to intention-to-treat analysis but also a per-protocol analysis will be performed and, if indicated, a sensitivity analysis.

Main study parameters/endpoints:
Primary endpoints: 30-day mortality and in-hospital mortality during the same admission. Incidence of all thrombo-embolic complications, including myocardial infarction, leg ischemia, deep venous thrombosis, colon ischemia, stroke, graft thrombosis, thrombo-embolic complications in kidney or spleen and other peripheral thrombosis. Also, peroperative thrombosis requiring additional actions peroperatively (i.e. embolectomy, atherectomy or re-do of an anastomosis because of thrombus). Incidence of bleeding complications according to E-CABG classification, grade 1 and higher (Brascia et al. and Biancari et al.).

Secondary endpoints: serious complications as depicted in the Suggested Standards for Reports on Aneurysmal disease: all complications requiring re-operation, longer hospital stay, all complications. Peroperative blood loss, blood transfusions either autologous or homologous, other blood products administration, total operative time, clamping time, use of adjunctive haemostatic products, length of hospital (including ICU) stay. Health status as measured with the EQ-5D-5L questionnaire. Economic evaluation, see separate chapter.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
In this trial the extra burden for the included patients is only present in the group with the ACT guided heparinization. They will undergo extra blood sampling. Maximal quantity will, in general, be 48 ml. of blood, which is not harmful for the patient. The blood samples are taken out of

an intra-arterial line, which is inserted in all patients during open AAA surgery, whether they are participating in this trial or not, as this is standard of care during this type of surgery. The

participating patients will be asked to visit the outpatient clinic at 6 weeks. This will be a short visit with a limited time burden: 10 minutes. This visit is also standard of care, so no extra visits because of participation in the ACTION-1 trial. No extra blood sampling or other tests will be performed. Also, the patients at baseline before surgery fill in a short questionnaire of 5 questions, 1 week, 4 weeks, 13 and 26 weeks postoperatively. At the 23 and 26 weeks, 1 and 2 other questionnaires on economic evaluation will be asked to fill in. This will take approximately 30 minutes maximally.
If the above stated hypothesis is proven, the group with ACT guided heparinization will suffer less thrombo-embolic complications and related mortality. No further extra burden, risks or benefits are expected.

1. INTRODUCTION AND RATIONALE

Vascular disease, both occlusive and dilating, is a major contributor to mortality and morbidity, also in The Netherlands. Techniques in both open surgery and endovascular treatments have been refined over the past decades, but at present they are still associated with mortality and high complication rates.[1-8] Since more than 70 years unfractionated heparin is used by all vascular surgeons worldwide during open and endovascular non-cardiac arterial procedures (NCAP).[9,10] Heparin is used as a periprocedural prophylactic antithrombotic to reduce the clotting of blood and thereby preventing arterial thrombo-embolic complications, such as myocardial infarction, stroke, bowel-ischemia and peripheral emboli.[11] The use of heparin also has a major clinical disadvantage: the prolonged clotting time of blood may increase blood loss, lengthens time needed for adequate haemostasis and may cause an increase in bleeding complications. The severity of bleeding complications can be mild such as a hematoma or pain but may sometimes require blood transfusions or even surgical (re-)exploration in case of extensive and even life-threatening bleeding. Because of the fine line between thrombosis and bleeding, vascular interventions require precise technique and an accurate level of coagulation. Another major disadvantage of the use of heparin as a periprocedural prophylactic antithrombotic, is the fact that heparin has an unpredictable effect in individual patients.[12] The molecular structure of heparin causes a variety of its effect, creating not only a difference in efficacy between different brands, but even between batches of the same brand.[13] The above described characteristics of heparin result in an unpredictable effect as an antithrombotic in the individual patient, possibly being harmful.

In many countries heparin is administered as a standardized bolus in every patient undergoing NCAP. The most often used dosage is 5 000 IU, irrespective of sex, bodyweight, type of procedure or duration of procedure.[9,10]

In all cardiac interventions worldwide, open or endovascular and using cardio-pulmonary bypass or not, the effect of heparin is measured routinely. Many studies have shown that the activated clotting time (ACT) is the preferred test to measure the effect of heparin and that using this test increases safety of these cardiac interventions.[14,15] This results in better patient related outcomes. Surprisingly vascular surgeons have not adopted this measurement of the ACT during NCAP.

The Consensus on Arterial Peri-Procedural Anticoagulation (CAPPA) study group, was formed in the Netherlands to reach consensus on periprocedural anticoagulation during non-cardiac procedures.[9,10] After surveys and two published systematic reviews, CAPPA concluded that ACT measurement in NCAP is to be preferred and should be introduced in daily practice.

This ACT measurement could ensure the individual patient of safe, tailor-made periprocedural anticoagulation.[16-23] This should lead to better results of procedures, with improved patient-related outcomes and less harm for the patient. In a consortium of 4 large university and teaching hospitals we initiated a study to evaluate the feasibility and safety of measuring the ACT during NCAP (MANCO, NTR nr. 6973, ClinicalTrials.gov M016-045). The infrastructure of research in these 4 hospitals proved to be effective.

All ACT measurements were performed according to a standardized protocol using the same device: Hemostasis Management System (HMS) by Medtronic®, with high-range ACT cartridges (HR-ACT). The percentage of successful measurements was 99% and results were reproducible and comparable between the different hospitals. The validation and standardization of the HMS for ACT measurements are extensively proven in the literature during cardiac interventions.[24,25] Similar studies were performed with other cartridges (low-range ACT) for the HMS and other

brands of ACT measurement systems. Results (on file) show that the HMS and the HR-ACT guarantee the most stable, reproducible and comparable results during NCAP. Results of these studies for comparing these different machines and cartridges will be submitted to peer-reviewed journals. Results of the MANCO study, in more than 500 patients, show that ACT measurements can be introduced safely and adequately in daily routine in the operation room and angio-suite, both during open and endovascular procedures. Evaluation of these data resulted in a safe and adequate protocol to ensure the patient of optimal, ACT guided heparinization during NCAP. A goal ACT of 200-220 seconds is considered to be optimal. We conducted a systematic review in which we found 4 studies that investigated the relation between ACT values and clinical outcomes.[35] Two studies[19,23] did not find a relationship between ACT value and bleeding complications. Saw et al.[21] found that an ACT > 300 seconds was associated with increased combined event rate (death, stroke or MI) in carotid artery stenting. Kasapis et al.[16] found increased bleeding in peripheral endovascular interventions when the ACT was > 250 seconds. In those 500+ patients the individual baseline ACT value was: 132 sec (+/- 16, mean). Results of our pilot study with the ACTION protocol in 46 patients with open AAA repair resulted in a decrease of TEC from 22% in the 5 000 IU group to 7% in the ACT guided group. No increase in bleeding complications or mortality was detected (no mortality in both groups, E-CABG class 1 bleeding[26,27] in 39% in 5000 IU group versus 36% in ACT guided group). In the ACT guided group the use of protamine at the end of surgery was also described in a protocol.[28,29] Because of the limited number of included patients, no statistical significance was reached. This underlines the importance of performing a RCT. Next step will be to conduct a large international multicentre trial to provide level 1 evidence that ACT guided heparinization will result in less thrombo-embolic complications, without more bleeding complications than unmonitored heparinization with the use of a standardized bolus. This will be evaluated during open abdominal aortic aneurysm (AAA) surgery DSAA[30] classification C: aneurysm originating below the Superior Mesenteric Artery). DSAA being the Dutch Surgical Aneurysm Audit, a Dutch registration that is mandatory for all Dutch vascular surgeons who treat patients with an AAA. In this registry details are stored regarding indication, techniques and periprocedural care. The reason to choose open AAA repair for this RCT, is that this procedure is subject to standardized care in all hospitals around Europe, also by following the 2019 European Society of Vascular Surgery Guidelines on Management of Patients with an AAA.[31] The hiatus of sound evidence on periprocedural anticoagulation and heparinization during NCAP, has also been prioritized by the Dutch Board of Surgery, the Board of Vascular Surgery, and by the Federation of Medical Specialists. These boards have granted their full cooperation, also to expand the already existing infrastructure of this research. The intended study will be used to create an infrastructure and consortium of 20, or more, major vascular surgical centres in the Netherlands for research. Supported by the Dutch Board of Vascular Surgery and initiated by the already existing collaboration between the mentioned 4 large hospitals, this will secure implementation of major clinical trials in the near future. Part of the grant will be used for the founding and securing of this infrastructure.

2. OBJECTIVES

Primary Objective: To establish that ACT guided heparinization results in safe and optimal anticoagulation during open AAA repair. We hypothesize that ACT guided heparinization will result in a decrease of thrombo-embolic complications, without a significant increase in bleeding complications when compared to the use of a non-ACT guided standardized bolus of 5 000 IU. The decrease in thrombo-embolic complications will lead to less mortality and morbidity, lower number of re-operations or better patency, all substantially improving patient's quality of health, efficiency of medical care and quality of vascular medical care. Results will be implemented in guidelines in the Netherlands and Europe for vascular surgeons and promoted worldwide.

Secondary Objective(s): NA

3. STUDY DESIGN

International multi-centre RCT, reported according to CONSORT 2010 statement. Patients will be blinded for the allocated treatment. Patients will be randomized using a computerized program (CASTOR EDC) with a random block size of 2, 4, 6. The randomization will be stratified by participating centre. Analysis will be performed by intention to treat principle. A separate analysis per protocol will also be performed as a sensitivity analysis. Separate evaluation of results and if complications can be labelled as TEC, will be performed by an Independent Central Adjudication Committee. The 3 members of this Committee will be blinded to the allocated treatment.

4. STUDY POPULATION

4.1 Population (base)

Patients eligible for inclusion will be patients with an AAA seen in daily vascular surgery practice. Patients will receive all regular examinations, ultrasound, Computed Tomography Angiography, Magnetic Resonance Angiography, and blood sampling. All patients will be discussed in a mandatory, multidisciplinary consultation with vascular surgeons and interventional radiologists. If the proposed treatment will be open repair of the AAA originating from below the SMA, the patient is eligible for participation in this trial.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Able to speak and read in local language of trial hospital.
- Patients older than 18 years scheduled for elective, open repair of an iliac or abdominal aortic aneurysm distal of the SMA (DSAA segment C).
- Implantation of a tube or bifurcation prosthesis.
- Trans-abdominal or retroperitoneal surgical approach of aneurysm.
- Able and willing to provide written informed consent.

4.3 Exclusion criteria

A subject who meets any of the following criteria will be excluded from participation in this study:

- Not able to provide written informed consent.
- Previous open or endovascular intervention on the abdominal aorta (previous surgery on other parts of the aorta or iliac arteries is not an exclusion criterion).
- History of coagulation disorders, heparin induced thrombocytopenia (HIT), allergy for heparin or thrombocyte pathology.
- Impaired renal function with EGFR below 30 ml/min.
- Acute open AAA surgery.
- Hybrid interventions.
- Connective tissue disorders.
- Dual anti-platelet therapy, which cannot be discontinued.
- Life expectancy less than 2 years.
- Inflammatory, mycotic or infected aneurysms.
- Allergy for protamine or fish protein

4.4 Sample size calculation

In the DSAA (2014 to 2016) the rate of serious complications was 29% for all patients. According to the Society for Vascular Surgery AAA 2018 guidelines the incidence of thrombo-embolic complications (TEC) is between 15 and 36%. In our preliminary MANCO trial the incidence of TEC was 14%. For our power calculation the incidence of TEC is set at 14%. The vast majority of mortality after open AAA repair stems from thrombo-embolic complications. A mortality rate of 5% after open AAA repair is derived from DSAA. Hypothesis is that decrease of TEC will result in a lower mortality of 3%. Bleeding complications derived from the literature and from our MANCO trial and ACTION pilot study: 18-39% (Scored according to E-CABG classification). Derived from data from our pilot study (depicted in 1. Page 18) and from literature, we hypothesize

that ACT guided heparinization will lower the rate of TEC to 8%. The expected incidence for the combined endpoint of TEC and mortality is therefore set at 19% for the 5000 IU group and 11% for the ACT guided group. Using a continuity corrected chi-square test with a two-sided alpha of 5%, 337 patients are needed in each group to achieve a power of 80%. Including a drop out of 10%, a total of 750 patients are needed for the combined primary end-points of TEC and mortality.
In our pilot study no increase in bleeding complications was found for open AAA repair (E-CABG class 1 bleeding was 39 versus 36%). Nevertheless we deem it important that excessive bleeding does not occur in the intervention group. Therefore a non-inferiority calculation was performed. Bleeding complications and TEC are different and have a different impact on patients. Bleeding complications Grade 1 E-CABG have less impact on mortality and quality of life than TEC. As we expect an improvement in combined TEC and mortality of 8%, we think it is justified to set the non-inferiority for bleeding complications at 11%.
Expecting 32% bleeding complications in the standard group and 33% in the intervention group and a non-inferiority limit of 43% (11% limit difference) with a power of 80% and a one-sided alpha of 5%, 272 patients required in each group. Therefore the 750 patients included are sufficient to also evaluate the non-inferiority for bleeding complications.

In summary, based on literature search and results of pilot study:
For a decrease of the combined endpoint of TEC and mortality from 19% to 11% for the ACT guided group, with an alpha of 5% and power of 80% and dropout of 10%, 750 patients are needed (375 per group).
This number of patients is also sufficient to cover the non-inferiority hypothesis for bleeding complications of max 11% (272 per group).

Between 2014 and 2016, 1703 patients had elective open AAA repair in the Netherlands. Using our consortium, which will be extended to at least 20 major vascular centres in the Netherlands we expect to complete inclusion within 42 months. This is confirmed by the letters of intention with a precautious estimation of expected numbers of inclusion per centre. The estimated number of inclusions has been scaled down to achieve a realistic prediction of inclusions.

5. TREATMENT OF SUBJECTS

5.1 Intervention:

Investigational use:

Heparin is given to reach an ACT of 200-220 seconds. At the start of the procedure, before any heparin is given, a baseline ACT measurement is performed. 3-5 minutes before clamping of the aorta 100 IU/kg bodyweight of heparin is administrated intravenously. If patients weighing more than 150 kg, a maximum heparin dose of 15.000 IU heparin is administered to prevent overdose. 5 minutes after administration of heparin, ACT measurement is performed.

- If the ACT is below 180 seconds, an additional dose of heparin of 60 IU/kg is administered.
- If the ACT is between 180 and 200 seconds, an additional dose of heparin of 30 IU/kg is administered.
- If the ACT is 200 seconds or longer, no extra heparin is given.

Five minutes after every administration of heparin the ACT is measured. If the ACT is 200 seconds or longer, the next ACT measurement is performed every 30 minutes, until the end of the procedure or until new heparin administration is required (because of ACT < 200 seconds). After each new dose of heparin, an ACT measurement is performed after 5 minutes and the above-described protocol of ACT measurements will be repeated. In case of near completion of the final anastomosis and re-establishment of arterial flow the attending vascular surgeon can decide not to give extra heparin despite an ACT below 200. After re-establishing blood flow and removing all clamps, the ACT is measured. Depending on that ACT value near the end of surgery, protamine is given to neutralize the effect of heparin.

If the ACT at closure is between 200 and 250 seconds, 25 mg protamine should be administered. If the ACT is higher than 250 seconds, 50 mg protamine should be administered. If the ACT is between 180 and 200 seconds, 10 mg protamine should be administered. Five minutes after the administration of protamine, the ACT is measured. The ACT should preferably be below 180 seconds. If the ACT is still more than 200 seconds, protamine should be administered again. When an additional dose of protamine is required, ACT measurement is performed 5 minutes after that administration.

Comparative use:

A single dose of 5 000 IU of heparin is given 3-5 minutes before clamping of the aorta. No ACT measurements are performed. Only on clarified indications extra doses of heparin or protamine are permitted, at the discretion of the attending vascular surgeon. Indications could be clot formation intravascular or in a prosthesis, excessive bleeding or prolonged operation duration. Deviations from protocol should be clearly stated with reasoning in the operative report. Patients with additional doses of heparin or protamine outside protocol will not be excluded from the trial. Evaluation will be performed according to intention-to-treat analysis but also a per-protocol analysis will be performed and, if indicated, a sensitivity analysis.

5.2 Use of co-intervention: NA

5.3 Escape medication: NA

6. INVESTIGATIONAL PRODUCT 1: HEPARIN

6.1 Name and description of investigational product(s)

Heparine LEO 5000 I.E./ml, suspension for injection, 5 ml per capsule. LEO PHARMA BV; RVG: 01372; ATC/ARC: B01AB01

6.2 Summary of findings from non-clinical studies

Unfractionated heparin has been used in humans during vascular surgery and endovascular interventions for more than 70 years.[11]

6.3 Summary of findings from clinical studies

Unfractionated heparin is used worldwide in humans during surgery and endovascular interventions for more than 70 years.[11]

6.4 Summary of known and potential risks and benefits

Unfractionated heparin is used worldwide in humans during surgery and endovascular interventions for more than 70 years.[11] See Summary (page 8) and Introduction (page 11).

6.5 Description and justification of route of administration and dosage

Unfractionated heparin is used worldwide in humans during surgery and endovascular interventions for more than 70 years.[11] See Summary (page 8) and Introduction (page 11). Intravenously, 3-5 minutes before cross clamping of abdominal aorta. 5000 IU of heparin or 100 IU/kg and adjunctive doses according to study protocol of 60 IU/kg and/or 30 IU/kg.

6.6 Dosages, dosage modifications and method of administration

Intravenously, 1 ml of 5000 IU/ml heparin or 100 IU/kg and additional dosages of 60 IU/kg and/or 30 IU/kg.

6.7 Preparation and labelling of Investigational Medicinal Product

NA, regular use in all hospitals worldwide.

6.8 Drug accountability

See 5.1

6. Investigational product 2: PROTAMINE

6.9 Name and description of investigational product(s)
Protaminehydrochloride MPH 1000 IE/ml, suspension for injection, 5 ml per capsule.

6.10 Summary of findings from non-clinical studies
Protamine has been used in humans during vascular surgery and endovascular interventions for more than 70 years (J Biol Chem, 122 (1937–1938), pp. 153-167).

6.11 Summary of findings from clinical studies
Protamine has been used in humans during vascular surgery and endovascular interventions for more than 70 years.

6.12 Summary of known and potential risks and benefits
A benefit of protamine is that it can reverse the effect of heparin. A potential risk is an allergy for protamine, which can cause an anaphylactic shock. People with fish protein allergy, or men after vasectomy have a higher risk of this. Another potential risk is that overdosing of protamine may contribute to bleeding, as the anticoagulant properties are particularly exerted in the absence of heparin (Br J Anaesth. 2018 May;120(5):914-927).

6.13 Description and justification of route of administration and dosage
Protamine should be used intravenously. Protamine has been used intravenously in humans during vascular surgery and endovascular interventions for more than 70 years.

6.14 Dosages, dosage modifications and method of administration
Depending on the ACT value near the end of surgery, protamine is given to neutralize the effect of heparin. If the ACT at closure is between 200 and 250 seconds, 25 mg protamine should be administered. If the ACT is higher than 250 seconds, 50 mg protamine should be administered. If the ACT is between 180 and 200 seconds, 10 mg protamine should be administered. Five minutes after the administration of protamine, the ACT is measured. The ACT should preferably be below 180 seconds. If the ACT is still more than 200 seconds, protamine should be administered again. When an additional dose of protamine is required, according to the above depicted protocol, ACT measurement is performed 5 minutes after that administration.

6.15 Preparation and labelling of Investigational Medicinal Product
NA, regular use in all hospitals worldwide.

6.16 Drug accountability
See 5.1.

7. NON-INVESTIGATIONAL PRODUCT:

Not Applicable

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Combined incidence of all thrombo-embolic complications (TEC) and all-cause mortality within 30 days or during the same admission in hospital. TEC are any complication as caused by thrombus or embolus perioperatively, including but not exclusively: myocardial infarction, leg ischemia, deep venous thrombosis, colon ischemia, TIA/stroke, graft thrombosis, peroperative thrombus requiring embolectomy or redo of an anastomosis, thrombus or embolus in organs or lower limbs and other peripheral thrombosis. All definitions of TEC are based on the international definitions provided by Chaikof et al.: Reporting standards for endovascular aortic aneurysm repair, and Johnston et al.: Suggested standards for reporting on arterial aneurysms. Also the above mentioned mandatory Dutch Surgical Aneurysm Audit guidelines and definitions for TEC/complications will be followed.[30] The definitions of TEC based on these three publications are implemented in the CRF.

Incidence of bleeding complications according to E-CABG classification.[26, 27] The E-CABG classification is a validated classification for excess bleeding or bleeding complications in coronary artery bypass grafting, predicting postoperative mortality. Grade 1 and higher: per- or postoperative transfusion of 2 or more units of red blood cells, transfusion of platelets, transfusion of fresh frozen plasma or reoperation for bleeding during hospital stay.

8.1.2 Secondary study parameters/endpoints

Secondary endpoints: complications (non-TEC), within 30 days postoperative or in the same admission, as defined by DSAA and suggested standards for reports on aneurysmal disease: all complications requiring re-operation, longer hospital stay, all other complications. Incidence of kidney injury as defined by RIFLE criteria: rise of serum creatinine > 100% or decrease of eGFR with 50%.[32] Allergic reactions. ACT values (in intervention group), total heparin administration, protamine administration. Peroperative blood loss, blood transfusions either autologous or homologous, other blood products administration, total operative time, aortic clamping time, use of adjunctive haemostatic products, length of hospital (including ICU) stay. Health status as measured with the EQ-5D-5L. Economic and healthcare costs evaluation by IMCQ and IPCQ and addition of out-of-pocket expenses.

8.1.3 Other study parameters

Preoperative parameters

Patient demographics: sex, smoking history, body length and weight and body mass index, medical history (general, cardiac, pulmonary, diabetes, surgical), medication, all previous vascular interventions. Blood pressure and pulse at outpatient visit, ECG reports. Diameter and anatomical classification of abdominal or iliac aneurysms. Preoperative laboratory results: Hb, leucocytes, sodium, potassium, creatinine, eGFR, platelets. Presence of impaired renal function (eGFR < 60 ml/min).

Peroperative parameters

Epidural analgesia. Surgical approach. Clamping sites at arteries.

8.2 Randomization, blinding and treatment allocation

International multi-centre RCT, reported according to CONSORT 2010 statement. Patients will be blinded for the allocated treatment. Patients will be randomized using an online computerized program (CASTOR EDC) with a random block size of 2, 4, 6. The randomization will be stratified by participating centre. Randomization will be performed by the treating vascular surgeon using the online computerized program CASTOR, during induction of general anesthesia. The patient will be blinded for the intervention. Treating physicians will not be blinded.

An Independent Central Adjudication Committee will evaluate all complications and decide whether or not complications are considered to be TEC. The 3 members of this Committee will be blinded to the intervention (standard heparin or ACT guided).

8.3 Study procedures

Patients are subjected to all regular and usual pre-operative tests, according to the recent European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms. Informed consent is to be obtained at the outpatient clinic according to ICH-GCP Guidelines E6 (R2). EQ-5D questionnaire is handed out to the patient preoperatively after receiving informed consent. The patient returns the form by post to the investigators, or bring the form when admitted for surgery, for baseline values. Furthermore EQ-5D questionnaires are recorded at baseline, 1 week, 4 weeks, 13 and 26 weeks postoperatively. If the patient wants to fill in de questionnaires online, the patient will receive a reminder per mail to fill in the questionnaire in week 1, 4, 13
and 26. An extra informed consent for contact per email will be signed. The email-address of the patient will be entered in CASTOR EDC by the site staff. This email address will be encrypted. Only the site staff can see this email address. The iMCQ (week 23 and 26) and the iPCQ (26 weeks) will be handled in the same manner.

Perioperative antithrombotic medication

Anticoagulation preoperatively according to Dutch national guideline: antithrombotisch beleid, richtlijnendatabase.

Thrombocyte aggregation inhibitors (TAI)

- Monotherapy with thrombocyte aggregation inhibitors like acetylsalicylic acid (ASA) may be continued. Other TAI like clopidogrel or ticagrelor should be discontinued 5 to 7 days preoperatively and ASA 80 or 100mg then started. After removal of epidural catheter postoperatively, clopidogrel or ticagrelor can be restarted if preferred by the treating physician.

Vitamin K antagonists

- Vitamin K antagonists (VKA): acenocoumarol: stop 3 days before surgery. Fenprocoumon: stop 7 days before surgery. Control INR preoperatively.
- Patients with a high risk of thrombo-embolic complications should receive bridging therapy with LMWH.

Direct oral anticoagulations

- DOACs should be discontinued 48 hours before surgery and started 48 hours after surgery, depending on renal function.

Thrombosis prophylaxis should be applied according to local protocols.

Operative procedure
Surgery is performed according to standard operative technique according to local protocols using a trans- or retroperitoneal exposure. Operative report according to local protocol with SOP ACTION added. A red blood cell-saver or equivalent should preferably be used during surgery. Local haemostatic agent may be used if considered necessary. Usage of local haemostatic agents should be depicted in the operative report and in the CRF.

Heparin protocol
See 5.1 for details.

ACT measurements
In all patients an arterial catheter is placed inside the radial artery for blood pressure measurements and blood sampling. Trial patients will not receive any invasive procedures other than all normal perioperative care. The only extra measurements will be drawing of blood samples from the arterial catheter during surgery. In general, maximally 48 cc of blood: before performing the ACT measurements, 5 cc of blood is withdrawn from catheter to ensure that no contamination with heparin from the arterial line can occur. This could influence the ACT. The ACT measurement itself is done in a special syringe containing 3 cc. of blood. All ACT measurements are performed using the ACT-plus (HMS) machine from Medtronic and standard HR-cartridges for this machine. Immediately after measurement, the blood sample will be destroyed. SOP is present for these measurements.

Blood transfusions
Red blood cell perfusion is performed according to local protocol. Preferably, red blood cells collected by RBC-saver should be re-infused peroperatively. If despite reinfusion of RBC the haemoglobin is below 5 mmol/L RBC should be transfused to reach haemoglobin > 5 mmol/L. In patients ASA IV haemoglobin should be > 6 mmol/L.

Postoperative
Postoperative treatment according to local protocols. Serum haemoglobin measurement at least directly postoperative and on first, second and third day post-surgery. Creatinine and estimated GFR measurements at least on postoperative day one and three and before discharge. At 30 days post-operative SOP will be filled in to evaluate all possible complications. This will be performed on day 30 by telephone. Outpatient clinic control at 2 weeks post discharge and at 6 weeks post- operatively. SOP is present for this visit, as is SOP for no show of patient at this appointment.
All study parameters (see enclosed CRF) are standard care and can be reproduced from EPFs. CRFs are web-based and data gathering is done by researchers or vascular surgeons, preferably present at surgical procedures. Extensive SOPs are present to secure that data is properly scored from eCRF.
A temporarily CRF, in paper form, is allowed to be created. These forms will be kept in the local hospital, according to ICH-GCP Guidelines E6 (R2). All data on outpatient visits after surgery are also standard of care, depicted in CRF and prescribed in SOP.

An Independent Central Adjudication Committee (ICAC) is instituted to decide whether complications are rightfully labelled as TEC in the CRF. Two vascular surgeons and 1 registered Intensive-Care

specialist will form this committee, none of them being a member of the ACTION project group. This committee will gather 30 days after 100, 200, 500 inclusions and 6 weeks after the last inclusion. They are blinded for the intervention and will judge the CRFs of all included patients. This CRF will not include the group to which the patient is randomized. A separate field will be included for this ICAC scoring. In case of disagreement within this committee, the majority will be decisive.

In case this committee decides that they need further clarification on a specific complication, this will be provided by the project group with data from the original EPF of the patient. Members of this ICAC are: prof. G.J. de Borst, MD, PhD, vascular surgeon, department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands; J.A. Vos, MD, PhD, interventional radiologist, department of radiology, St Antonius Hospital Nieuwegein, The Netherlands; F.H. Bosch, intensive care and internal medicine specialist, MD, PhD, department of intensive care, Rijnstate Hospital, Arnhem, the Netherlands.

Protocol deviations:

- HMS malfunction: in the ACT group (no ACT measurements possible): treat as randomised; 100 IU/kg bolus, no ACT measurements, no extra heparin doses. Eventual heparin or protamine doses at the discretion of the attending surgeon. Event and reasons registered in eCRF.
- ACT < 200 sec. after 5 minutes and attending surgeon decides not to apply another heparin dose. After 30 minutes, next ACT measurement is performed and protocol is rightly applied. Event and reasons registered in eCRF.
- If patient is randomised in the 5 000 IU group and the attending surgeon decides to administer another dose of heparin. Event and reasons registered in eCRF.
- If ACT is higher than 180 sec. at end of surgery and no protamine is administered. Event and reasons registered in eCRF.
- Any other deviation in the amount of protamine administered other than protocol instructs. Event and reasons registered in eCRF.
- ICF not dated by subject/site.
- Incorrect version PIF signed.
- Procedures performed by individuals not included in the Delegation of Responsibilities Logs, without completing appropriate project specific training.
- Survey not completed by subject after reminder.
- Other: any other protocol deviation labelled as such by ACTION-1 PI and co-PI (AW and VJ). Event and reasons registered in eCRF.

Protocol violations:

- No heparin at all administered. (Event en reasons registered in eCRF).
- AAA appears to be mycotic or inflammatory during surgery. (Event registered in eCRF).
- During surgery an aorto-caval fistula or an aorto-enteric fistula appears to be present. (Event registered in eCRF)
- ICF not signed before the first procedure (first ICF to be signed by subject); Missing ICF from file
- Signed ICF not in site file/lost
- Failure to report SAE (either late or not at all)

All protocol deviations and violations will be separately registered in eCRF. All these violations or deviations can be shown in separate reports for evaluation.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason. If they wish to do so this will be without any consequences. The attending vascular surgeon or any other member of the medical staff in the local hospital can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal: NA

8.5 Replacement of individual subjects after withdrawal:

Patients who have signed the informed consent form but (are) withdraw(n) from the study before randomization will be replaced in order to include the number of patients required for analysis as depicted in the power calculations. Replacement is independent of the reason for withdrawal. Patients who withdraw after randomization will not be replaced.

8.6 Follow-up of subjects withdrawn from treatment

Subjects will receive all regular follow-up care, not different from standard care.

8.7 Premature termination of the study

Premature termination of study will be decided by the DSMB, see separate chapter. This will be based amongst others on interim-analysis and safety reporting (see separate chapters).

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. All adverse events, within 30 days postoperative or in the same admission, reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

All non-serious AEs of particular interest will be reviewed and recorded in the CRF. All other non-serious AEs will not be collected as part of this study.

AEs of particular interest in this trial are:

- All TEC or non-TEC, not leading to dead, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or, in the view of the investigator, is no life-threatening event.
- Bleeding complications according to E-CABG classification grade 1 and higher
- Incidence of kidney injury as defined by RIFFLE criteria: rise of serum creatinine > 100% or decrease of eGFR with 50%.
- Allergic reactions to heparin.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.
- an elective hospital admission will not be considered as a serious adverse event.

For the purpose of this trial all:

- combined incidence of all thrombo-embolic complications (TEC) within 30 days postoperative or in the same admission
- bleeding complications according to E-CABG classification, grade 1 and higher leading to dead, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity or, in the view of the investigator, is a life-threatening event will be considered SAE's.

TEC are any complication as caused by thrombus or embolus per-operatively, including but not exclusively: myocardial infarction, leg ischemia, deep venous thrombosis, colon ischemia, TIA/stroke, graft thrombosis, per-operative thrombus requiring embolectomy or redo of an anastomosis, thrombus or embolus in organs or lower limbs and other peripheral thrombosis.

All non-TEC complications, within 30 days postoperative or in the same admission, as defined by DSAA and suggested standards for reports on aneurysmal disease, requiring re-operation, longer hospital stay, all other complications are to be expected considering the composition of the study population. The sponsor will register all the above mentioned SAEs (caused by TEC, non-TEC, bleeding complications or all other causes) in a line listing, which will be reported once every six months to the METC.

Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulation for reporting an SAE, the study site must formally notify the Sponsor as soon as possible, within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

All Serious Events that occur within 30 days postoperatively or in the same admission must be reported to the Sponsor as soon as possible, within 24 hours of the study site staff becoming aware of the event.

1. A report must be submitted by mail to the sponsor regardless of the following:
   - the severity of the SAE; and
   - the relationship to the intervention

2. All Serious Events that occur within 30 days postoperatively or in the same admission must be registered in the eCRF.

The mail address is provided in the SOP reporting AEs / SAEs

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.
  The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
  The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as

indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Due to the fact that this study is labelled as moderate risk, a full DSMB will be installed, and will be in compliance with all legal demands.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

Descriptive statistics of continuous variables will be presented as means with standard deviations (SD) or medians with inter-quartile ranges (IQR) depending on the distribution of the data. Categorical data will be presented as proportions and numbers. The statistical efficacy analysis will be conducted according to the intention-to-treat principle with a chi-square test for proportions. A separate per protocol analysis will be performed additionally as a sensitivity analysis. All analyses will be performed with the latest version of the Statistical Package for Social Sciences (SPSS, SPSS Inc., Armonk, NY, USA).
For the bleeding complications a non-inferiority test will be used. If the confidence interval for the bleeding complications does not include the non-inferiority limit in the per-protocol analysis and the intention-to-treat analysis non-inferiority for bleeding complications is established.

10.1 Primary study parameter(s)

The primary endpoint is the composite of the incidence of all thrombo-embolic complications, including myocardial infarction, leg ischemia, deep venous thrombosis, colon ischemia, stroke, graft thrombosis, thrombo-embolic complications in kidney or spleen and other peripheral thrombosis and all-cause mortality within 30 days after surgery or during the same admission. Also, peroperative thrombosis requiring additional actions peroperatively (i.e. embolectomy, atherectomy or re-do of an anastomosis because of thrombus). Incidence of bleeding complications according to E-CABG classification, grade 1 and higher.
Differences in the incidence of this composite endpoint between the intervention and control group will be expressed as the absolute risk difference with 95% confidence interval.

10.2 Secondary study parameter(s)

Secondary endpoints include all complications as defined by DSAA and suggested standards for reports on aneurysmal disease. Health status measured with the EQ-5D-5L questionnaire. Differences in categorical outcomes between the intervention and control group will be expressed as the absolute risk difference with 95% confidence interval. Differences in continuous outcomes will be tested with the student's t-test in case of a normal distribution or the Mann-Whitney U-test in case the data do not follow the normal distribution. The level of significance is set at a two-sided p-value < 0.05.

10.3 Other study parameters

Peroperative blood loss, blood transfusions either autologous or homologous, other blood products administration, total operative time, clamping time, use of adjunctive haemostatic products, length of hospital (including ICU) stay and health status. ACT values measured. Amount of heparin and protamine used.

ECONOMIC EVALUATION:
COST EFFECTIVENESS ANALYSIS (CEA)

General considerations: We hypothesize that ACT guided heparinization could lower the rate of TEC and TEC related mortality to in total 11% and that the quality of life can be increased from 73% to 76%. The economic evaluation of ACT guided heparinization against standard care with a standardized bolus of heparin will be performed as cost-utility analyses and a cost effectiveness

analysis from a societal perspective with the costs per quality adjusted life year (QALY) and the costs per prevented complication as the primary economic outcomes. The cost-utility analysis can be used for policy making and composition of a guideline. The cost-effectiveness analysis (CEA) relates to the clinical outcome parameter and may be used for prioritization or bench marking of strategies that enhance surgical patient safety. The CEA and CUA will be based on a time horizon of 6 months. All related complications are within the time horizon of 6 months and patients will be recovered from the surgery. For on-going complications such as leg amputations, colostomy, permanent neurological deficits, dialysis a CEA and CUA with a lifelong time horizon will be made using extrapolation and model based techniques. For this time horizon discounting of effects and costs will be performed as stated in the most recent guidelines for cost analysis.[33] To account for uncertainties in the lifelong time horizon, a probabilistic sensitivity analysis will be performed. Incremental cost-effectiveness ratios will be calculated as the difference in costs per QALY gained and as the difference in costs prevented complications. Sampling variability will be accounted for by bias-corrected and accelerated non-parametric bootstrapping. Results will be reported along with their 95% confidence intervals and displayed graphically with cost-effectiveness planes and with cost- effectiveness acceptability curves. One-way and multi-way sensitivity analyses will be done for the unit costs of the most common complications. Some missing data can be expected, if missing data is at random, this will be handled through multiple imputations with predictive mean matching.

Cost analysis

Medical costs, patient costs and productivity losses will be included in the evaluation. The medical costs cover the costs of surgery and related complications, anaesthesia, theatre, peri- operative materials, inpatient stay at the ICU and the wards and medications. The patient costs include out-of-the pocket expenses like over-the-counter medication and health care related travel costs. Productivity losses are costs resulting from being absent and decreased productivity during work. Hospital health care utilization will be retrieved from CRFs and hospital information systems. Data on out-of-hospital health care will be gathered with the iMTA Medical Consumption Questionnaire (iMCQ) adjusted to the study setting. The productivity losses will be documented with the iMTA Productivity Cost Questionnaire (iPCQ). Questions on out-of-pocket expenses will be added to these patient questionnaires. Costs will be price indexed based on consumer price indices(CPI). Costs will be calculated for individual patients as the product sum of the resource use and the respective unit costs. The iMCQ questionnaire will be send 13 and 26 weeks after surgery, the iPCQ only 26 weeks after surgery.

Patient outcome analysis

Patients will be asked to complete the EQ-5D-5L health status questionnaire at baseline, 1 week, 4 weeks, 13 and 26 weeks after surgery. These forms can be completed online or at home by the patients and send to the investigators by post. These questionnaires will be included in the CRFs. The EQ-5D-5L scoring profiles can be converted into a health utility score based on general population based Dutch tariffs.[34] QALYs will be calculated for each patient using linear interpolation between the successive health utility assessments over time.

10.4 DSMB and Interim analysis

A safety review will be performed by an independent statistician (T. van der Ploeg, PhD) and reviewed by the data safety monitoring committee after the results are available for 100, 200 and 500 patients.
This is a safety review, which looks at the combination several outcomes as opposed to a traditional interim analysis with specified stopping rules.
In case of strong concerns about safety, the safety monitoring committee can advise to stop the study. Furthermore, SAEs will be reported to the data and safety monitoring committee: the expected SAEs (as described in paragraph 8.2.2) will be reported every 6 months and all other SAEs per 5 cases.

A total of three blinded interim analyses are planned:

- A first interim analysis is planned when approximately 100 subjects have been enrolled. This will provide data sample size calculations, and safety assessments.
- A second interim analysis is planned when approximately 200 subjects have been enrolled. This will provide data sample size calculations, and safety assessments.
- A third interim analysis is planned when approximately 500 subjects have been enrolled. This will provide data sample size calculations, and safety assessments.

Additional ad-hoc interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.
Independent personnel who are not directly involved in conducting the study will perform the interim analyses and review of the unblinded outputs.

The following formal stopping rules are applicable:
Statistically significant absolute risk differences:

- a difference in absolute risk of 10% in the combined endpoint of TEC and mortality between intervention and control group.
- a difference in absolute risk of 10% in all cause mortality between the groups
- a difference in absolute risk of 20% in bleeding according E-CABG classification class 1.

No further dissemination of interim results should occur, in particular not with individuals involved in treating the study's subjects or assessing clinical data.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO). Also all applicable legal demands will be met in all participating countries according to Medical Ethics Committees demands.

11.2 Recruitment and consent

Patients scheduled to undergo open AAA repair, will be informed about the study by their attending vascular surgeon in outpatient clinic of participating hospitals about the study and the informed consent procedure will be explained. Patient information letter and Dutch legal documentation will be provided. First questions can be answered. Emphasis will be made that not participating will have no consequences for the patient regarding his/hers treatment. Time for consideration of 1 week or longer will be mentioned. If patient wants to use this consideration-time, an appointment will be made with investigator, research nurse/physician assistant or another vascular surgeon than the surgeon who put the patient on the operation list, depending on local participating hospital. Than informed consent will possibly be obtained and forms will be signed after all possible questions of the patient will be discussed and answered.

11.3 Objection by minors or incapacitated subjects: NA

11.4 Benefits and risks assessment, group relatedness

For more than 70 years heparin has been used during (non-)cardiac vascular procedures, including open AAA repair. Heparin is used to minimize thrombo-embolic complications (TEC). A large percentage of mortality of these interventions is related to these TEC. Contrary to cardiac procedures, the effect of heparin is not routinely measured during open AAA repair. This effect is measured by the activated clotting time (ACT). During these NCAP and thus also in open AAA repair, a standard bolus of 5 000 IU of heparin is administered in all patients, regardless of sex, bodyweight and duration of procedure. From literature it is known that heparin has complex and individually variable kinetics. This results in inaccurate prediction of the effect of heparin in the individual patient. Hypothesis of the current trial is that measurement of the ACT during open AAA repair and establishing an ACT of 200-220 seconds will reduce thrombo-embolic complications without increase in bleeding complications. An initial bolus of 100 IU/kg will be used and additional dosages of heparin will be administered to stabilize the ACT to 200-220 seconds. After the procedure protamine should be used to diminish the effect of heparin to reach an ACT of < 180 seconds. This use of protamine is derived from abundant literature and is considered safe and effective. Benefits for the patient by participating in this study, are that there could be a reduction in TEC and TEC-related mortality when heparin is dosed by ACT guidance. Risks could be that this ACT guided heparinization could lead to more bleeding complications. The ACT of 200-220 seconds and the use of protamine are proven to be safe. In a pilot study on 46 patients, the intervention (ACT guided heparinization aimed at ACT 200 < x < 220 seconds) did not lead to increased bleeding complications compared to a standard dose of 5 000 IU heparin (E-CABG classification grade 1 or higher: 38.9% versus 35.7%, P= 0.83).

11.5 Compensation for injury

The sponsor/investigator has liability insurance, which is in accordance with article 7 of the WMO. The sponsor (also) has insurance, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives: NA

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Complete Data Management Plan ZonMw which is created using DMPonline. Handling of personal data complies with the current EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (Uitvoeringswet AVG). DMP attached as appendix 4. Data collection will be carried out using the electronic database Castor EDC (see appendices for safety guarantees). Each participating center will maintain a key list. This key list stays in the local hospital and will not be shared. After completion of the study, all study documents will be stored on site for 25 years. This will be strictly monitored in collaboration with ZonMw and Julius Clinical.

12.2 Monitoring and Quality Assurance

Monitoring plan and quality assurance plan attached as appendix 5 and 6.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial;
- The scientific value of the trial;
- The conduct or management of the trial; or
- The quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The start and end date of the study will be provided to the METc VUmc. The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

Sponsor and coordinating investigator will handle data and results confirming to the statement on publication policy from the CCMO. Study design will be registered and published in a manuscript. Results will be submitted for publication in appropriate peer-reviewed journals. All other (legal) demands from ZonMw will be met according to grant application rules.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues ofconcern

Heparin, as depicted in 6, has been registered for more than 70 years for the current subject of use in the ACTION-1 trial. Heparin has been used extensively in randomized clinical trials in that 70 years period. In the described trial ACTION-1, heparin is used in a regular way. All the described protocols are already in use in hospitals around the world. The used dosages are far less than in cardiac interventions. No extra risks are existent for patients in the proposed trial.
Heparin will not be used in combination with any other product.

13.2 Synthesis

For the ACTION-1 Trial all possible safety measures are implemented. Monitoring and DMSB are installed at the highest possible level.

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APPENDIX 4: DATA MONITORING PLAN

ACTION: ACT guided heparinization during open abdominal aortic aneurysm repair, a randomised trial. - Data management ZonMw (English version)

1. General features of the project and data collection
1.1 Project leader contact details
A.M. Wiersema, MD, PhD
Vascular surgeon
Dijklander Ziekenhuis
Maelsonstraat 3
1624 NP Hoorn, the Netherlands
Email: Bij voorkeur: arno@wiersema.nu of a.wiersema@westfriesgasthuis.nl
Tel.: +31 (0)653444515 of +31 (0)229208260

1.2 I have composed my DMP with the assistance of a data management expert. List his or her name, function, organisation/department, phone number and email address.
The expert is not connected to my department or institution
Dr. S. van Dieren
Clinical epidemiologist
Amsterdam UMC: Locatie Academisch Medisch Centrum Amsterdam
Email: s.vandieren@amc.uva.nl
Tel.: +31 (0)205669111

1.3 In collecting data for my project, I will do the following:
Use existing data (please specify)
Use an MDS (Minimal Data Set)
Generate new data
The ACTION -trial is a prospective trial. For the conduct of this trial prospective daily care data (standard registered data per-operative and post-operative) will be used and new data will be generated with informed consent of the patient.

1.4 In my research, I will use:
A combination of quantitative and qualitative data
The following data will be collected: gender, weight, comorbidity, smoking status, co-medication, hospitalization in days (incl. ICU admittance), blood pressure, ASA-score, laboratory value's, specifications AAA, study arm, per- and postoperative observations (surgical and anesthesiological): dose heparin, administered heparin, ACT-value's and actions taken, postoperative observations: complications, physical parameters (RR, HR), laboratory, complications until 30 days postoperative. Subjects will be asked to fill in some multiple choice questionnaires.

1.5 I will be reusing or combining existing data, and I have the owner's permission for using or combining their data.
No, I will not be reusing or combining existing data

1.6 In collecting new data, I will be collaborating with other parties.
Yes, we have reached agreements on the user rights of the data used in the project. Yes, I will collect the new data in conjunction with other researchers or research groups It concerns a multi-centre prospective randomized trial,
27 sites. Dijklander Ziekenhuis is the sponsor. There will be a clinical trial agreement for participating centres.

1.7 I am a member of a consortium of 2 or more partners. Clear arrangements have been made regarding data management and intellectual property. (also consider the possible effect of changes within the consortium on issues of data management and intellectual property). Yes, clear arrangements have been made regarding data management and intellectual property through a consortium agreement
There will be signed an consortium agreement.

1.8 I can give an estimate of the size of the data collection; specifically, the number of participants or subjects ("n=") in the collection and its size in GB/TB
Yes (please specify)
N = 750 patients
375 patients are needed in each group to achieve a power of 80%. Including a drop out of 10%, a total of 750 patients is needed for the combined primary endpoints of TEC and mortality.

1.9 The following end products I will make available for further research and verification (please elaborate briefly). Several versions of processed data Documentation of the research process, including documentation of all participants
Data documentationaw data.
Data collection in CASTOR EDC. Castor complies with all applicable laws and regulations with regard to ICHG Good Clinical Practice (GCP) and the General Data Protection Regulation (GDPR). Following an audit – and improvement process CASTOR has been awarded a GCP compliance statement. All hosting platforms are certified for or compliant with relevant security certifications (ISO27001, ISO9001) and/or national or international standards (HIPAA, NEN7510). Statistic analysis SPSS software, version 23

1.10 During the project, I will have access to sufficient storage capacity and sites, and a backup of my data will be available. (please elaborate briefly)
Yes, I will make use of an external provider's services for storage and backup of my data
CASTOR EDC, a web based data management systeem, included automatic backups of all data and data changes of every participating centre.
Paper documents (signed informed consent, filled in questionnaires) will be filed for 15 year at each participating centre.

2. Legislation (including privacy)

2.1 I will be doing research involving human subjects, and I am aware of and compliant with laws and regulations concerning privacy sensitive data.
Wet op de Geneeskundige Behandelingsovereenkomst (Medical Treatments Contracts Act)
The Wet Medisch-Wetenschappelijk Onderzoek met Mensen (WMO, or Medical Research (Human Subjects) Act) applies to my project; I will have it reviewed by a Medical Research Ethics Committee.
In addition I will comply with the Kwaliteitsborging Mensgebonden Onderzoek (Quality Assurance for Research Involving Human Subjects)
Yes, I will involve human subjects in my research.
I will comply with the Algemene Verordening Gegevensbescherming (AVG)

2.2 I will be doing research involving human subjects, and I have (a form of) informed consent from the participants for collecting their data.
Yes (please describe the form this consent takes)
Written informed consent and the use of data, all legal demands are met.

2.3 I will be doing research involving human subjects, and I will protect my data against misuse.
Yes, the data will be pseudonymised. (please explain how this will be done, and by which organization) and
All data will be registered in CASTOR EDC.
Castor creates unambiguous identification codes for patients, which can be defined by the user. IDs are coded and confidential. They can also be automatically generated when a new patient is included.
Patients can answer the questionnaires at week 1, 4, 13, 23 and 26 post-operatively online in CASTOR
EDC. Patients will receive a reminder by email to complete the questionnaires.
The patients will sign a specific informed consent to provide their e-mail address.
After signing this specific informed consent the site staff will enter the patients e-mail address in CASTOR EDC.
This e-mail address will be encrypted and can only be seen by the site staff whom entered the patients e-mail address.

2.4 I will stick to the privacy regulations of my organization
Yes
My organization has privacy regulations.

3. Making data findable

3.1 The data collection of my project will be findable for subsequent research (note: this is a keyitem, which you should report to ZonMw at the end of your project).
Yes, it can be found through an online (metadata) catalogue or web portal (please specify)
Re3data.org DGF 20525 vascular and visceral surgery

3.2 I will use a metadata scheme for the description of my data collection.
Yes, I will use a metadata scheme specific for my field of research (please specify)
SNOMED CT direct via CASTOR EDC

3.3 I will be using a persistent identifier as a permanent link to my data collection (note: this is a key item, which you should report to ZonMw at the conclusion of your project).
Yes, I will be using the DOI code

4. Making data accessible

4.1 Once the project has ended, my data will be accessible for further research and verification.
Yes, after an embargo period (please explain)
Embargo period of 3 months, as demanded by ZonMW

4.2 Once the project has ended, my data collection will be publicly accessible, without any restrictions (open access).
No, there will be access restrictions to my data collection (please explain)
Permission to examine data will be granted after requests that will meet our terms of use

4.3 I have a set of terms of use available to me, which I will use to define the requirements of access to

my data collection once the project has ended (please provide a link or persistent identifier; also note that this is a key item, which you should report to ZonMw at the conclusion of your project).
Not yet, my institution will draft a set of terms of use with the help of a legal advisor

4.4 In the terms of use restricting access to my data, I have included at least the following:
A steering committee, program committee or project leader will be charged with approving data requests
Agreements on methodology
The approval of the participants allows for further research using this data set
The reimbursement of costs, for example in obtaining the data
The permitted period of use of the data set
The manner in which the data set can be accessed
Whether or not the data set may be linked with another data set (for reasons of privacy)
The sharing of data for commercial purposes, taking into account the provisions of state aid law
Collaboration in using the data set, including agreements on publication and authorship
Conditions related to data security

5. Making data interoperable

5.1 I will select a machine actionable data format, which will allow other researchers and their computers to read my data collection.
Yes (please specify)
CASTOR EDC and SPSS

5.2 I will select a metadata standard to allow my data collection to be linked to other collections (note: this is a key item, which you should report to ZonMw at the conclusion of your project).
Yes, I will select a metadata standard from the list published by Biosharing (please specify)
SNOMED CT via CASTOR EDC

5.3 I will be doing research involving human subjects, and I have taken into account the reuse of data and the potential combination with other data sets when taking privacy protection measurements.
Yes, the participants have given their permission for reuse of the data, and the data have been pseudonymised.

6. Making data reusable

6.1 I will ensure that the data and their documentation will be of sufficient quality to allow other researchers to interpret and reuse them (in a replication package).
I will document the software used in the course of the project (please specify)
I will perform quality checks on the data to ensure that they are complete, correct and consistent (please explain)
I will document the research process (please explain)
Research is depicted in study protocol
Data monitoring will be executed
Used software depicted in study protocol: CASTOR EDC and SPSS

6.2 I have a number of selection criteria, which will allow me to determine which part of the data should be preserved once the project has ended. (see also question 1.9)
Yes, in accordance with legal demands on quality-control after trial and restricted access.

6.3 Once the project has ended and the data has been selected, I can make an estimate of the size of the data collection (in GB/TB) to be preserved for long-term storage or archival.
Yes (please specify)
Around 10 Gb

6.4 I will select an archive or repository for (certified) long-term archiving of my data collection once the project has ended. (note: this is a key item, which you should report to ZonMw at the conclusion of your project)
Yes, and this archive has a data seal of approval (please specify the archive)
CentERdata, DANS

6.5 Once the project has ended, I will uphold the recommended data preservation period of at least 10 years.
Yes, in accordance with other guidelines (please explain, and specify the guidelines and the number of years)
15 year according to GCP

6.6 Data management costs during the project and preparations for archival can be included in the project budget. These costs are:
Amount_____(please elaborate)
€ 25.000

6.7 The costs of archiving the data set once the project has ended are covered.
Yes (please elaborate)
ZonMw grant

Appendix 5: Monitoring plan

MONITORING PLAN

ACTION-1 - study

ACT guided heparinization during open abdominal aortic aneurysm repair, a randomized trial

Table of content

Protocol	ACTION-1: ACT guided heparinization during open abdominal aortic aneurysm repair, a randomised trial NL: 6675902919 EudraCT: 2018-003393-27		
Registration ToetsingOnline	NL 6675902919		
Intern registration	WB 642		
Principal investigator / project leader	A.M. Wiersema, MD PhD		
Specialism	Vascular surgeon		
Sponsor	Dijklander Ziekenhuis		
IRB	Amsterdam UMC, location VUmc		
Approval IRB	To be requested		
Planned start-and end date	1 – Jan – 2020 until 1 – Dec – 2024		
Planned inclusion period	May 2020 – February 2024		
Total planned subjects	750		
Research type	**Negligible** ☐	**Moderate** **X**	**High** ☐
Type monitoring	**Mono center** ☐	**Multicenter incl.participating centra** **X**	
Total number of sites	**25**		
Type trial	**Pharmaceutical** **X**	**Medical device** ☐	**Overig, nl. interventie** ☐
Planned monitoring subjects	Percentage sample: ☐ 10% ☐ 20%		
Quality control by	Monitor CRO Julius Clinical CRA Dijklander Ziekenhuis		
Date initiation visit	Study still in initiation phase		
Date monitoring visit	Study still in initiation phase		

1. Rules and responsibilities

For the purpose of this study, all participating sites will be monitored by a Clinical Research Associate (CRA) of the sponsor Dijklander Ziekenhuis and a selection sites by a monitor of Julius Clinical, a Clinical Research Organisation (CRO). All monitors are qualified by education and experience to monitor the conduct of clinical research study sites according to applicable SOPs, Monitoring Visit Activities for Clinical Trials with an Investigational Product, ICH GCP and local requirements.

2. Introduction

This Monitoring Plan (MP) establishes the guidelines for conducting monitoring visits and related tasks for monitoring all participating sites in ACTION-1: ACT guided heparinization during open abdominal aortic aneurysm repair, a randomised trial, and is a requirement of the Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), Section 5.18.
This MP was developed by the Sponsor, Dijklander Ziekenhuis, in collaboration with the project leader, de heer dr. A.M. Wiersema, and the Clinical Research Organisation (CRO) Julius Clinical. Monitoring tasks will be performed in accordance with the protocol specific requirements, the SOP Monitoring, the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6 (R2) and other applicable requirements.

This MP describes the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. This monitoring plan includes the monitoring of critical data and processes. Specific attention will be given to those aspects that are not routine clinical practice and that require additional training.
This monitoring plan applies to 'WMO- studies' to which the NFU guideline 'Kwaliteitsborging mensgebonden onderzoek 2019'.
The purposes of the monitoring are to verify that:

- activities at the site are being performed according to ICH E6 (R1), Guideline for Good Clinical Practice E6 (R2), the Medical Research Involving Human Subjects Act (WMO), the clinical trial protocol, trial related procedures and applicable regulatory guidelines.
- the subject's rights and safety have been maintained,
- reliable, accurate and verifiable data have been obtained

3. Definitions and abbreviations

- BROK Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers
- CRA Clinical Research Associate
- CRO Clinical Research Associate
- eCRF Electronic Case Report Form
- GCP Good Clinical Practice
- GMP Good Manufacturering Practice
- ISF Investigator Site File
- SAE Serious Adverse Event
- SDV Source Data Verification
- SOP Standard Operating Procedures

- SUSAR Suspected Unexpected Serious AdverseReaction
- TMF Trial Master File
- WMO Wet Medisch-wetenschappelijk Onderzoek

4. Monitoring communication plan

The Monitor will send monitoring communication including site visit confirmation emails, agendas, follow-up emails etc, to the following (and in cc to the sponsor):

Role	Representative
Coordinating Site Lead PI (CPI)	A.M. Wiersema, MD, PhD
Study Contact	L.C. Roosendaal, MD

Participating Sites Contacts

Follows

5. On-site visit scheduling

The Monitor will contact the project leader (PL), the local principal investigator (PI) and site primary contact to schedule monitoring visits. The project leader will be informed of visit scheduling at participating sites.

Prior to the visit, the PI will receive a visit confirmation by email, including the agenda and a list of the files to be monitored. The Monitor will ensure that this information is communicated to the site personnel within a mutually agreed timeframe to allow sufficient time for record requests. The PI and research staff will be expected to secure a workspace for the Monitor and to be available during the visits to facilitate monitoring activities. Depending on how many subjects have been enrolled/randomized since the last monitoring visit, visits will take 1 day.

The monitor will be available at the end of each monitoring visit day to discuss findings and answer questions from the study staff. The Site PI and Primary Site Contact are also expected to be available for a wrap-up meeting at the conclusion of the visit, as schedules allow. These expectations will be explained in the visit confirmation email.

Each site will have an on-site monitoring visit at least once per year during the active phase of the study. The first on-site monitoring visit should occur within 6-8 weeks after including the first patient on a site. Thereafter, monitoring visits will be conducted annually until the last subject has completed the follow-up evaluations according to the protocol. Additional visits will only be scheduled if required.

6. Procedures

The procedure for the study specific monitoring plan will follow the overview below. This schedule is followed by an explanation of the specific components (see page 6):

Overview Clinical Monitor Plan ATCTION-1			
Start up/intiation	**On site monitoring**		**End of study**
Initation	**Monitoring eCRF** monthly	**On site monitoring visit**	**Study clossure**
Training site staff by video conference, study start checklist random on site monitoring visits	Check missing data, entry (S)Aes, progress data entry	1-2 times a year Check ISF, 25% informed consent procedure, 100% SAE procedure reported SAE's, eligibility check included patients, source data verification, Missed SAE's query proces and solving queries	The last monitoring visit on site will also be a study closure visit

6.1. Study start up / initiation

The site staff will be trained on site on the protocol and the ACT measurements during surgery by the investigators. The CRA will instruct the site staff by videoconference about GCP, safety, inclusion and randomization procedure, SOP's, informed consent procedure and the eCRF CASTOR EDC.

Before start of inclusion, a study start checklist will be completed by each participating site. Topics in this checklist:

- GCP and study specific training requirements
- local approval for the study
- adaptation patient informed consent forms to local situation
- storage of important documents in ISF study file
- procedures / SOPs
- description of critical points (see appendix 1).

The CRA sends a study start checklist to each local principal investigator (PI). The PI sends the completed and signed study start checklist to the CRA, including the completed and signed Delegation and responsibility log. Depending on these documents, the project leader allows the site to start including patients in the ACTION-1 -trial. The CRA will randomly conduct a study start site visit to check whether the local PI is adequately prepared for the conduction of the trial.

6.2. On-site monitoring visits

The principal investigators of all sites must be available for monitoring visits. An active study is defined as a study that is ready for inclusion, the site is including subjects, subjects are treated according to the study protocol or subjects are still being monitored for follow-up questionnaires.

6.2.1. Frequency of on-site monitoring visits

Monitoring visits will take place at least once a year at each site.
The visit will be evaluated with the local principal investigator or with a member of the research team appointed by the local principal investigator.

6.2.2. On-site monitoring activities

- Presence and completeness of the Investigator Site File (ISF) once a year.

An (electronic) folder, which for purposes of this MP will be defined as the Investigator Site File (ISF), will be maintained at each trial site and serve as the central source for essential document (ED) maintenance at the site. Documents with original signatures must also be maintained in a paper ISF. This includes study-level and subject-level documents (i.e. Clinical Trial Research Agreements and signed Information and Consent Forms [ICFs]).
The following documents represent a complete site essential document packet and are to be maintained in the ISF:

☐ The original IRB-approved versions of the protocol and amendments to the protocol, the IRB-approval of the protocol and protocol amendment(s), the signature pages, a sample of the Case Report Form (eCRF).
☐ All versions of the informed consent.
☐ The original product information.
☐ Annual reports, annual safety reports, expedited safety reports, notification of changes to the study team, submitted to IRB / local board of directors/ participating sites
☐ All correspondence between the PL/site PI and IRB/local board of directors. Including submissions, approvals and responses to questions/comments.
☐ Documented evidence (e.g. note to file) and reporting of non-compliance to GCP, SOPs, protocol to sponsor (protocol deviation form).
☐ Curriculum Vitae (CV) and GCP-certificate of the PI, the sub-investigator and all site staff involved.
☐ Delegation Log – up-to-date, all tasks appropriately delegated.
☐ Training Log – incudes trial-specific and GCP, valid for duration of involvement in study.
☐ Screenings log, listing all subjects with a signed informed consent and, whether the subject was included. For any subject not included in the study, the reason why they were not included.

The monitor will review the ISF for accuracy and completeness.

- **Essential Documents to be filed by the PL in the Trial Master File (TMF)**

The PL is responsible for maintaining the Trial Master File (TMF). The TMF is maintained in electronic and paper formats and owned by the PL. Documents with original signatures must be maintained in the paper TMF/ISF. This includes study-level and subject-level documents. All other essential documents will be maintained in the electronic TMF only.
Essential Documents that are common to all sites and essential documents specific to the PL must be filed in the TMF, including:

☐ DSMB-charter, communication with the DSMB and DSMB reports.
☐ Study team documentation: delegation and signature logs of each site, qualifications (CVs) and

training logs, copy of site initiation visit presentation and other training materials used at site.
☐ Templates of all site-specific patient informed consent forms.
☐ Study Contact List.
☐ Reported and line-listed SAEs / SUSARs
☐ Annual Safety Report to the IRB, acknowledgement of submitted reports (SAEs/SUSARs).
☐ Annual progress Report to the board of directors.
☐ Correspondence with ZonMw, the decision ZonMw.
☐ Financial documents.
☐ Copy of all agreements (e.g. clinical trial agreement (CTA), confidentiality agreement).
During the monitoring visits, the monitor will review the TMF for accuracy and completeness.

- **Source Data Verification**

Monitoring of data is necessary to verify the registered research date. The most direct way of doing this is by performing Source Data Verification (SDV). The monitor verifies the data quality by checking the data in the patient medical files versus the data in the eCRF CASTOREDC.
Based on a predefined list of variables for SDV, see annex 1.
At each on-site monitoring visit, the monitor will verify the following critical data/processes:
☐ Informed consent was obtained appropriately (25% check completeness & availability):
- Ensuring each subject entered into the study signed a correct version and IRB-approved informed consent forms.
- Ensuring whether informed consent forms was obtained before each subjects participation in the trial as mentioned in ICH-GCP (5.18.4e).
- Verification in the source document that the study was explained to the subject and that consent was obtained before conducting any study-related procedures.

☐ The investigator is following the IRB-approved protocol and all approved amendment(s), if any.
☐ The subjects enrolled in the study meet the protocol criteria for eligibility (100% check for the first 10 enrolled subjects per site, a random sample will be made upfront by the monitor).
A serious breach is deemed to have occurred if an ineligible subject is enrolled.

☐ For subjects that are randomized/receive the intervention, their medical record references the trial and indicates that the subject is receiving an intervention.

☐ Conduct and documentation (in medical records, CRFs, subject shadow files (if used), TMF) are complete, accurate, consistent and adhere to the protocol for procedures related to trial integrity, such as:
- The study blinding is maintained
- Dose modifications (and the reason for the dose modification) for the investigational product are documented for each subject in both the medical record and the CRF.

☐ Discrepancies between the source documents and the CRFs will be brought to the attention of the site staff and corrections made to the CRFs by the investigational site staff.
☐ 100% check on Serious Adverse Event (SAE) procedure for all reported SAE.
☐ 25% of all enrolled subjects check on missed SAEs.

☐ 25% of all enrolled subject SDV based on a predefined list of variables delivered by the sponsor. This list includes, but is not limited to, the primary endpoints of the study and other variables that have a clear relation to safety and validity of the study. This list is available during the first monitoring**.
☐ Check query process and assist investigators in solving unanswered queries, if applicable.

** Source Data Verification list, including the primary outcome measure and baseline characteristics, prepared by project group in consultation with the statistician and methodologist (see Appendix 2).

- **Review of investigator and site staff suitability**

At each monitoring visit, the Monitor should confirm the continued ability and commitment of the Investigator and site staff to conduct the study. This includes:
☐ Verify that the PI and site personnel are adhering to the protocol and conducting the study according to regulatory requirements, GCP and study-specific standard operating procedures (SOPs).
☐ Verify that the PI is providing adequate supervision to any individual or party to whom they have delegated trial-related duties and functions. Evidence of supervision may include email correspondence, meeting minutes with attendees listed etc.
☐ Review the delegations log and training log to ensure it is complete, current and delegation is in accordance with qualifications and training.

See appendix 3: Table: Monitors responsibilities, procedure and corrective actions.

6.3. Additional on-site monitoring visit

An additional on-site monitoring visit can be requested to assess a specific point. This can be requested by the project leader and / or the local principal investigator, in consultation with the monitor. An additional on-site monitoring visit can also be initiated by the monitor in case of doubt or questions about the quality of conduction of the study. The content of this extra on-site monitoring visit is tailored to the reason for the request.

6.4. Monitoring eCRF

Every three months the eCRF will be viewed, based on a predefined list of variables (which are clearly related to the safety and quality of the study, including primary outcome measure), the progress of data entry and questionnaires, and whether registered SAEs and / or SUSARs have been reported to ToetsingOnline. Findings will be reported in writing to the local principal investigator in copy to the project leader.

6.5. Close out visit

Upon termination of the trial, the trial will be closed at all relevant participating centers. During the last monitoring visit, after inclusion of the last subject on a site, study closure will be prepared. Answer the last queries, signing relevant documents (e.g. responsibility and delegation log, screening and randomization log, prepare archiving of the site file and other documents for 15 years.

7. Monitoring reports / follow up letter

Monitoring visit findings and resulting action items will be documented in monitoring visit reports. The monitor will complete a written monitoring visit report and provide a follow up letter to identified study team members as noted in Section within 10 business days of the visit. The follow-up letter should be signed and filed in the ISF and TMF. The Monitoring Visit Report is not for distribution to the site and should be filed in the TMF only.

The Monitor will work with designated site staff to resolve any outstanding action items as communicated in the follow-up letter. At a mutually agreed upon time, or 4 to 6 weeks post visit, whichever is earlier, the Monitor and site research staff designee will discuss via telephone conference or email all resolved, in process, and pending action Items. At this time the need for, and frequency of subsequent meetings will be discussed.

Appendix 1: Primary and secondary endpoints

Primary study endpoints

Combined incidence of all thrombo-embolic complications (TEC) and all-cause mortality within 30 days or during the same admission in hospital. TEC are any complication as caused by thrombus or embolus peri-operatively, including but not exclusively: myocardial infarction, leg ischemia, deep venous thrombosis, colon ischemia, TIA/stroke, graft thrombosis, per-operative thrombus requiring embolectomy or redo of an anastomosis, thrombus or embolus in organs or lower limbs and other peripheral thrombosis. Incidence of bleeding complications according to E-CABG classification, grade 1 and higher: per- or postoperative transfusion of 2 or more units of red blood cells, transfusion of platelets, transfusion of fresh frozen plasma or reoperation for bleeding during hospital stay.

Secondary endpoints

Complications (non-TEC), within 30 days postoperative or in the same admission, as defined by DSAA and suggested standards for reports on aneurysmal disease: all complications requiring re-operation, longer hospital stay, all other complications. Incidence of kidney injury as defined by RIFLE criteria: rise of serum creatinine > 100% or decrease of eGFR with 50%. Allergic reactions. ACT values (in intervention group), total heparin administration, protamine administration. Peroperative blood loss, blood transfusions either autologous or homologous, other blood products administration, total operative time, aortic clamping time, use of adjunctive hemostatic products, length of hospital (including ICU) stay. Health status as measured with the EQ-5D-5L. Economic and healthcare costs evaluation by IMCQ and IPCQ and addition of out-of-pocket expenses.

Appendix 2: Variable list Source Data Verification (SDV)

Baseline

- Use of medication: acetylsalicylic acid, Clopidogrel, other thrombocyte aggregation inhibitor + specification, vitamin K-antagonists + specification, DOAC + specification
- ASA-classification
- HB pre-op. (mmol/l)
- EGFR pre op. (ml/min)

Surgery

- Protocol deviation + if yes, specification
- Protocol violation + if yes, specification
- Additional procedure
  - Thrombo-embolectomy (if yes, + specification)
  - Re-do anastomosis (if yes, + specification)
  - Re-implantation renal artery (R, L or b
  - Extra bypass (if yes, +specification)
  - Other additional procedure (if yes, + specification)
- Blood transfusion (if yes + amount)
- Other blood products (FFP, platelets, other +specification, + amount)
- Heparin doses + time
- Protamine use + dose + time

Postoperative variables

- Blood transfusion postoperative + date
  - Packed cells + amount
  - FFP + amount
  - Platelets + amount
  - Other blood product + specification + amount

Postoperative complications

For all complications the Clavien-Dindo classification score will be evaluated. Following complications will be evaluated 30 days after surgery/during primary admission and 6 week after surgery.

Systemic and/or distant complications

- Cardiac complication
  - Type of cardiac complication:
    - Ectopic/arrhythmia
    - Congestive heart failure
    - Myocardial infarction
- TIA/CVA
- Deep venous thrombosis
- Pulmonary embolism
- Coagulation complication (no treatment, farmaca needed, operation or fatal)
  - Type coagulation complication:
    - Spontaneous bleeding
    - Thrombocytopenia
    - White clot syndrome
    - Thrombosis by ATIII or prot. C/S def.
    - HIT
- Renal insufficiency (>100% rise creatinine and/or >50% decrease EGFR) (No dialysis, dialysis (temporarily), permanent (dialysis, NTx)
  - Type renal insufficiency:
    - Contrast induced
    - Thrombo-embolic
    - Ischemic (ATN)
    - Pre-renal: hypovolemic
    - Post-renal: obstruction
- Bowel ischemia (conservative, surgery: thrombectomy, surgery: resection, fatal)
  - Location bowel ischemia:
    - Sigmoid
    - Colon
    - Ileum/jejunum
- Graft thrombosis (no therapy, revision/redo-surgery, tissueloss or amputation)
  - Unknown cause
  - Known cause
- Athero-embolus
  - No tissueloss
  - Minimal tissueloss/minor amputation
  - Major tissueloss/major

amputation

- Spinalcord ischemia (temporarily, small permanent deficit, major permanent deficit),
- Complication other than above + specification

Appendix 3: Table: monitors focus points, procedure and corrective actions

Focus points	Procedure	Corrective actions
Inclusion	Monitoring of the rate of inclusions and rate and drop out %.	Re-assess inclusion rate of subjects every 3 months and draw attention to the project leader, so that action can be taken.
Informed consent	100% control availability and completeness informed consent and written informed consent was obtained before each subject's participation in the trial (ICH-GCP 5.18.4).	In case of missing or incorrect informed consent; ASAP. completing missing and incomplete informed consent (no later than 1 month). An extra monitoring visit will be induced.
Progress data input (eCRF) CASTOR	Based on predefined list of variables that are clearly related to the safety and validity of the study, including primary outcome measure (see Appendix 2), monitoring progress of data input in the eCRF, monitoring of notifications / comments from project leader, principal investigator or research assistant.	Make adjustments ASAP based on the recommendations (completed within 1 months at the latest), In case of >15% deviation: re-assess following monitoring eCRF.
Progress questionnaires in eCRF	Checking eCRF progress of the completed online questionnaires.	Introduce discrepancies to the attention of investigator and / or project leader, so that any action can be taken.
SAE's and, in case of medicine trial, SUSAR's	100% verification reporting procedure and reporting based on imported eCRF (in accordance with ICH-GCP and SOP SUSAR and SAE reports).	Reporting incomplete or procedure incorrect: completing SAE and SUSAR reports (no later than 1 week), with deviation of> 15%: reassessing eCRF.
Eligibility check in-and exclusion criteria	100% of the first 10 enrolled subject and 25% of the remaining enrolled subjects per site (randomly selected by the monitor: check on eligibility included subjects in the study.	In case of deviation of > 15%: If there are incorrectly included participants in the study in relation to safety, all files of that specific study will be checked. A protocol deviation form must be completed.
Informed consent	100% control availability and completeness informed consent and written informed consent was obtained before each subject's participation in the trial (ICH-GCP 5.18.4)	In case of missing or incorrect informed consent; ASAP. completing missing and incomplete informed consent (no later than 1 month). An extra monitoring visit will be induced.

Investigator File and/or Trial Master File	Presence and completeness of digital and hard copy research file (in accordance with GCP guideline and SOP Study file TMF and ISF).	Completing research files (completed within 2 months at the latest), recheck at next Study Monitoring Visit.
Protocol deviations & violations	From five randomly chosen participants: check for completeness and correctness of protocol deviations & violations.	Update protocol deviations & violations within 2 months at the latest. In case of danger to the safety of participants, exclude participants from participation in the study. If >15% incorrect or incomplete tracking of protocol deviations & violations recheck at the next monitoring visit.
Source data verification on the basis of source documentation	25% check whether reliable, accurate and verifiable data is obtained of randomly selected subjects based on source documentation (i.e. original documents and patient records). Based on a predefined list of variables that are clearly related to the safety and validity of the study and delivered by the project leader (see Appendix 2).	If >15% incorrect data entry in the eCRF: 100% control of all imports based on the source documentation of that specific study.
Compliance study protocol	From five randomly chosen participants: check whether instructions (SOP's) for the execution of study procedures are present in the ISF and whether these procedures are complied according to the study protocol.	Ensure compliance according study protocol (completed within 1 months at the latest), review at the next study monitoring visit.
Study specific critical points regarding quality assurance (Appendix 1)	Check if the study specific critical points regarding quality assurance are proper documented in the source documents and eCRF.	Take action for non-executed critical points (action dependent on critical point) (completed within 1 months at the latest).

Appendix 6: Quality Assurance plan

QUALITY ASSURANCE PLAN

ACTION-1 -study

ACT guided heparinization during open abdominal aortic aneurysm repair, a randomised trial

Table of content

Protocol	ACTION-1: ACT guided heparinization during open abdominal aortic aneurysm repair, a randomised trial NL: 6675902919 EudraCT: 2018-003393-27		
Registration ToetsingOnline	NL 6675902919		
Intern registration	WB 642		
Principal investigator/ project leader	A.M. Wiersema, MD PhD		
Specialism	Vascular surgeon		
Sponsor	Dijklander Ziekenhuis		
IRB	Amsterdam UMC, location VUmc		
Approval IRB	To be requested		
Planned start-and end date	1 – Jan – 2020 until 1 – Dec – 2024		
Planned inclusion period	May 2020 – February 2024		
Total planned subjects	750		
Classification of risk	**Negligible** ☐	**Moderate** X	**High** ☐
Type monitoring	**Mono center** ☐	**Multicenter incl.participating centra** X	
Total number of sites	**25**		
Type trial	**Pharmaceutical** X	**Medical device** ☐	**Overig, nl. interventie** ☐
Planned monitoring subjects	Percentage sample: ☐ 10% ☐ 20%		
Quality control by	Monitor CRO Julius Clinical CRA Dijklander Ziekenhuis		
Date audit 1	Study still in initiation phase		
Date audit 2	Study still in initiation phase		

1. Introduction

The ICH (1.6) describes audit as a systemic and independent examination of trial related activities and documents to determine whether the trial related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures, good clinical practice (GCP), and the applicable regulatory requirement(s).

2. Responsibilities

For the purpose of this study Julius Clinical, a Clinical Research Organisation (CRO), is contracted to perform two site audits to assure quality of the ACTION-1 study ACT guided heparinization during open abdominal aortic aneurysm repair, a randomised trial. The quality assurance manager (QAM) of Julius Clinical is properly educated and experienced to conduct two site audits to assure the quality of the conduct of clinical research at study sites according to the study protocol, applicable SOPs, ICH GCP and local requirements.

3. Purpose and scope of the audit

The purposes of the audits are to verify that:

- The investigator sites have the appropriate facilities, equipment, personnel, experience and procedures in place to conduct of the study protocol.
- Activities at the site are being performed according to ICH-GCP, trial protocol, trial related procedures and applicable regulatory guidelines.
- The participant's rights and safety have been maintained.
- Trial related procedures have been satisfactorily implemented during the trial.
- Early detection and collection and prevention of any existing problems or potential problems with a system and/or process.
- Early detection of any existing problems or potential problems occurring at an institution entrusted with trial-related duties.
- Confirmation of the appropriate conduct of a trial, the reliability and verifiability of data obtained, and the condition of record keeping at a participating medical institution(s) through direct access.

All audits will be conducted according to this audit plan which will be revised when the sites have been selected for audit.

4. Planning and confirmation

The auditor will confirm mutually convenient dates with the principal investigator, ensuring that study personnel will be available during the audit, with at least three weeks' notice. The auditor will then forward an audit confirmation letter with an accompanying agenda to the Principal Investigator, study coordinator, monitor and sponsor.

5. Document review in preparation of the audit

The auditor will request the following documents and any amendments in preparation for the audit:

- Protocol version_____, dated _____
- Summary Product Characteristics (SPC heparine), version_____, _____
- SOPs relating to site qualification, site initiation, site monitoring, project management and monitoring plans, safety plan, site activation (green light) and unblinded monitoring plan.
- SOPs relating to monitor qualification and training.
- Trial Master File – central documents and site specific documents in accordance with section 8, ICH GCP.
- The auditor will request access and training regarding the eCRF prior to the audits.

6. On-site audit

6.1. Introduction meeting

The auditor will hold an introductory meeting with the Site Staff to explain and review the following:

- Scope and purpose of the audit,
- Audit agenda,
- Confirm the auditees' availability during the audit.

6.2. Site staff interview

The auditor will interview the Site Staff to ascertain how the trial is conducted at the site and to confirm roles and responsibilities. The processes for the following areas will be confirmed:

- Roles and responsibilities, delegation.
- GCP training, clinical trial experience.
- Study oversight, meetings, review of results.
- Participant recruitment.
- Informed consent procedure.
- Screening and randomization procedure.
- Source data including responsibilities, location, availability and archive.
- Access to electronic systems (electronic patient files, laboratory results, eCRF).
- Completion of study procedures.
- IP: check SOP compliance.
- Maintenance of essential documents.
- Correspondence with the sponsor.
- IRB/IEC and Regulatory Authority approvals and correspondence
- Safety Reporting.

6.3. Essential documents

The auditor will review the Investigator Site file. The essential documents will be verified against the site file index as well as the documents listed per section 8, ICH GCP.

6.4. Informed consent verification

The auditor will review 25% of the participants' informed consent forms and will verify the following:

- Participant number and initials.
- Subject signature and dated by subject.
- Name of investigator/designee taking consent.
- Version date of the form.
- IEC/IRB approval of the form.
- Witness signature and date, if applicable.

6.5 Source data verification (SDV)

- The auditor will verify that source data is available for all subjects.
- The auditor will perform 100% SDV on the subjects' CRFs at the site (where 'n' is the total number of subjects randomized/enrolled into the trial site). Where time permits, the auditor will review additional CRFs.
- If the scope of SDV is amended during the audit, the amendment will be documented in the Audit Report.
- CRFs for SDV may be selected according to the following criteria:
  - ☐ Subjects from the beginning, middle and end of recruitment period,
  - ☐ Subjects with SAEs,
  - ☐ Subjects relating to deviations documented in the monitoring reports.

6.6 Interview

The auditor will interview the site staff and review their role, experience, training, responsibility regarding the site, communication with project manager, report writing, follow up of issues documented in visit reports, non-compliance reporting, protocol deviations and issue escalation.

6.7 Concluding the audit

- At the end of the audit, the auditor will conduct a closing meeting with the PI and site staff to discuss the audit findings and conclusions of the audit process in a manner that they are clearly understood and acknowledged by the auditee(s).
- Every attempt should be made to resolve any diverging opinions concerning the audit evidence and/or findings and unresolved points should be recorded.
- The auditor will inform the auditee that evidence of correction will be requested for all critical and major findings.

6.8. Audit visit acknowledgement

A letter of acknowledgement will be sent to the auditees within five (5) days of the audit.

7. Audit reporting

The auditor will prepare the audit reports within 20 business days of completing the audit(s) and forward the reports to the auditee, the project leader and the sponsor.

Upon Client approval, the observations will be forwarded to the respective auditee and monitor for response and follow up.
Responses are expected within twenty (20) business days of receipt and upon review and approval from the auditor, an audit certificate will be issued to the auditee and copied to the sponsor.

Delays in receiving responses from the auditee will be escalated to the sponsor.

This Quality Assurance plan will be formalized and accorded by Julius Clinical.