Protocol Full Title prospective cohort study:

Assessing the incidence of postoperative delirium following aortic valve interventions

Protocol Acronym/short title:

POD following TAVI or SAVR

Version and date of final protocol:

DH062018 version 02, 13-08-2018

Sponsor:

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1. Study Synopsis

Title of clinical trial	**Assessing the incidence of postoperative delirium following aortic valve interventions**
Protocol Short Title/Acronym	Postoperative delirium following TAVI or SAVR
Sponsor name	UZ Leuven
Principal Investigator	Danny Hoogma
Medical condition or disease under investigation	Postoperative delirium (POD)
Purpose of clinical trial	Identifying the incidence of POD following aortic valve interventions using either trans-femoral or trans-apical transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) in the elderly population age ≥70y.
Primary endpoint	Incidence of POD during the first five postoperative days assessed daily by using the 3-minute Diagnostic confusion assessment method (3D-CAM) or the derived version for intensive care unit (CAM-ICU)
Secondary endpoints	- Onset moment of POD (from surgery until postoperative day 5)

	- Duration of POD - Severity of POD (assessed with the delirium severity measure-based CAM (CAM-S Long) - Incidence of subsyndromal delirium (SSD) - Intensive care unit (ICU) length of stay - Hospital length of stay - Early safety (at 30 days) defined by the Valve Academic Research Consortium (VARC)-2 - Clinical efficacy (at 6 months) as defined by VARC-2 - Discharge destination
Recorded baseline data	- EuroQol five dimensional questionnaire five levels (EQ-5D-5L) validated Dutch version and EuroQol Visual Analogue Scale (EQ-VAS) - Instrumental Activities of Daily Living - Anticholinergic Loading Scale - Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) - Mini Mental State Examination (MMSE) - Clock completion - European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) - Tilburg Frailty Indicator - Essential Frailty Toolset
Trial Design	This prospective cohort study will be performed at the University Hospital of the KU Leuven. An

	investigator will assess the primary outcome parameters. Perioperative data will be collected by the attending anaesthesiologist, written and electronically.
Sample Size	We expect, based on institutional data, that 250 patients will meet the inclusion criteria, with 70 patients having a TAVI and 180 a SAVR.

Summary of eligibility criteria	Inclusion criteria are as follows:
	- Patients scheduled to undergo elective
	  ○ TAVI
	  ○ SAVR (with or without coronary artery bypass grafting (CABG))
	- Age ≥ 70 years
	- Patient able to read and understand the research materials
	
	Exclusion criteria are as follows:
	- Inability to give informed consent
	- Presence of delirium at baseline as screened with the 3-minute Diagnostic Confusion Assessment Method (3D-CAM)
	- Combined surgical procedures (other valve surgery)

Maximum duration of follow-up of a subject	Incidence of POD during the first five postoperative days, if positive, patients will be followed-up until POD has resolved or until discharge. Follow-up by

	phone for mortality and ADL at 30 days and 6 months postoperative.
Version and date of final protocol	DH062018 version 2, 13-08-2018

2. Background and rationale

Contents summary

Postoperative delirium (POD) is a common complication after cardiac surgery, causing a significant burden on the patient's well-being and the community. Identifying patients at risk might significantly reduce the overall morbidity and mortality. Currently, data regarding the incidence of postoperative delirium in patients undergoing modern techniques of aortic valve interventions, is lacking. The objective of this study is to determine the incidence of POD in elderly patients undergoing aortic valve interventions including transcatheter aortic valve implantation (TAVI) and minimally invasive or median sternotomy surgical aortic valve replacements (SAVR).

Background

POD is characterized by acute and fluctuating cardinal features of inattention and disorganized thinking, affecting up to 82% of patients older than 60 years[1,2].

POD can be clinically categorized into three motor subtypes: hypoactive, hyperactive and mixed. As clinical symptoms are frequently uncharacteristic and hence overlooked, several standardized diagnostic tests have been developed and validated of which the Confusion Assessment Method (CAM), 3-minute Diagnostic Confusion Assessment Method (3D-CAM) and its derived version for patients on the intensive care unit (CAM-ICU) are the most commonly used methods[3-5].

Plenty of risk factors are associated with POD, with some predisposing the patient to the development of POD and others precipitating POD. Predisposing factors are patient-related, are present already preoperatively and can usually not be modified: advanced age, cognitive impairment, low level of education, anemia, dehydration, malnutrition and electrolyte abnormalities. Two validated risk models are available for the prediction of POD in cardiac and non-cardiac surgery[6]. In contrast, precipitating factors typically prevail in the immediate perioperative phase and are potential candidates for preventive strategies. Blood pressure

fluctuations[7] but also several medications including anticholinergics, antidepressants, benzodiazepines and ketamine[3] or high dose of sufentanil or fentanyl[8] have been associated with an increased risk of POD. Furthermore, prolonged ventilation or the stay in the intensive care unit (ICU) increases the risk for POD[9,10]. As such, an enhanced recovery program with early extubation and avoidance of the ICU-setting is a promising strategy to reduce the incidence of POD[11-13].

POD has been consistently associated with short-term complications. While older studies neglected the effects on long-term outcome, POD appears to have a more profound and long-lasting effect than initially thought[14]. Prospective studies have shown that patients with POD have an increased length of stay (LOS) in the intensive care unit, higher complication-rate, an increased hospital LOS and perioperative mortality[15,16]. POD is also associated with functional decline, increased use of hospital resources and health care costs [17].

The pathophysiology of postoperative cognitive disorders is still far from being understood. The pathogenesis of POD is multifactorial and several pathophysiological mechanisms have been suggested to be in close interplay with each other[18]. A first mechanism would be *neuroinflammation*. Perioperative surgical stress and the cardiopulmonary bypass (CPB) cause a systemic inflammatory response syndrome (SIRS) with the release of cytokines, chemokines, and other inflammatory mediators, probably resulting in the disruption of the blood-brain barrier. The peripheral inflammatory stimulus is then amplified within the brain by the microglia, causing neuroinflammation and ultimately neuronal dysfunction or even neuronal death[19]. Risk factors for a weakening of the blood-brain barrier also include older age and exposure to anesthetics. Moreover, it has been suggested that sedation causes acute hypoxia in endothelial cells, resulting in swelling of capillaries. This endothelial dysfunction affects the integrity of the blood-brain barrier. Subsequent reperfusion leads to production and release of active metabolites causing a chemotactic activation of activated neutrophils, eventually leading to nervous system injury [20,21]. Secondly, after clinical observations the neurotransmitter hypothesis was proposed. The use of substances that alter neurotransmitter

function resulting in either increased cerebral dopamine levels or reduced levels of acetylcholine appeared to cause delirium[18,22,23]. The cholinergic system is one of the essential modulatory neurotransmitter systems in the brain, controlling awareness, attention, sleep and memory. Thus, drugs with an anticholinergic potential may precipitate the development of delirium. Even if not exposed to these drugs, patients still could have low cholinergic activity. There is evidence for endogenous anticholinergic substances produced during acute illness, hypoxia, hypoglycemia or immobilization[18].

Surgical aortic valve replacement is a well-known technique performed via limited or full sternotomy using CPB and myocardial arrest. In our institution CPB is performed with mild to moderate hypothermia on a conventional CBP circuit with cardiac arrest induced by antegrade or retrograde infusion of cold crystalloid cardioplegic solution. Prior to CPB, heparin is administered to achieve an activated clotting time of > 400 s. Extracorporeal circulation is performed with 2.2-2.5 L min^{-1} m^{-2}. After weaning from CBP, heparin is antagonized with protamine[24].

TAVI is a less invasive technique compared to SAVR[25], being at least non-inferior to SAVR with regard to mortality and morbidity in patients at high or intermediate surgical risk[26]. During this procedure, a bioprosthetic valve is suspended within an expandable metal stent and deployed on the end of a delivery catheter. Before deployment of this valve, a balloon aortic valvuloplasty is performed. Both procedures are facilitated with brief periods of rapid ventricular pacing to interrupt cardiac output[27].

TAVI stimulated the interest in surgical techniques using rapid deployment of stent-mounted valve prostheses[28], dramatically reducing aortic crossclamp and CPB times when compared to the implantation of conventional aortic valve protheses. In our institution, the Perceval S (Sorin Biomedica Cardio Srl, Sallugia, Italy) bioprothesis is routinely used in elderly patients[29].

Given the reduction in surgical invasiveness from conventional SAVR over mini sternotomy SAVR using rapid-deployment prostheses to TAVI, the systematic use of fast-track protocols

in minimal invasive SAVR and in TAVI, and the avoidance of CPB in TAVI, we suggest that the incidence of POD is reduced in parallel. One prospective study compared the incidence of POD after TAVI to SAVR. A high incidence of POD 44% and 66% respectively was identified in these patients. Although procedure time is recorded, there is no description of the procedure, nor is there any POD severity or long-term outcome reported[30]. A retrospective cohort study identified an incidence of 27% for POD following TAVI, with only 12% POD following transfemoral-TAVI[31]. Some retrospective studies showed almost no difference in the POD incidence between TAVI (19-29%) or SAVR (20-33%)[32,33], however, after propensity matching SAVR-treated patients developed POD more frequently[32]. Considering the controversial results, there is currently no valid data regarding the comparative incidence of POD after modern aortic valve interventions.

We hypothesize that in older patients, the incidence of POD is lower in patients undergoing TAVI than in patients undergoing minimally-invasive SAVR with mini sternotomy than in patients undergoing conventional SAVR with full median sternotomy.

3. Trial objectives and Design

3.1 Trial objectives

The primary aim of this study is to identify the incidence of POD following aortic valve interventions using either trans-femoral or trans-apical TAVI, compared to SAVR using mini sternotomy or median sternotomy in the elderly population age ≥70y.

3.2 Primary endpoint

Incidence of POD during the first five postoperative days.

POD screening will be carried out using the 3D-CAM or CAM-ICU (only for intubated patients). Several features will be assessed: 1/ Acute onset, 2/ Inattention, 3/ Disorganized thinking, 4/ Altered level of consciousness. The diagnosis of full syndromal delirium by CAM requires the presence of both features 1 and 2 combined with the presence of either 3 or 4.

Throughout the ICU/CCU/PACU-stay, patients will be assessed for POD once daily by a trained research nurse using the CAM-ICU or 3D-CAM, if positive, severity of POD will be assessed with the delirium severity measure based on CAM long version (CAM-S Long)[34]. In addition, a daily chart review will be performed for the results of the Intensive Care Delirium Screening Checklist (ICDSC)[35] and to check whether anti-psychotic therapy was administered. If a Richmond Agitation-Sedation Scale (RASS)[36] of < -3 is found in the chart, this patient will be considered unconscious and unevaluable for POD.

After transfer to the ward, patients will be assessed once daily by a trained research nurse for the presence of POD using the 3D-CAM and if needed a CAM-S Long. Patients' charts will be checked daily over the previous 24-hours to identify key words suggestive for POD, to check whether anti-psychotic therapy was administered[37] and for the results of the Delirium Observation Scale (DOS)[38].

3.3 Secondary endpoints

Secondary endpoints, within the group of patients who develop POD, include onset moment of POD (from surgery until postoperative day 5), duration of POD, and severity of POD as assessed with CAM-S long. Moreover, we will assess the incidence of subsyndromal delirium [full syndromal delirium (FSD) versus subsyndromal delirium (SSD): FSD will be defined as demonstrating abnormalities in features 1 + 2 + (3 or 4) of the CAM-test. SSD will be defined as having one or more CAM symptoms, but not fulfilling criteria for FSD].

Other secondary endpoints include the determination of the predictive value of frailty scales on several outcome parameters. After discharge early safety (at 30 days) and clinical efficacy (at 6 months) will be recorded as defined by the Valve Academic Research Consortium (VARC)-2[39]. Also effects on the Cognitive Failure Questionnaire (6 months) [40] and EQ-5D-5L (6 months) will be evaluated.

3.4 Trial Design

This prospective cohort study will be performed at the University Hospital of the KU Leuven. An investigator will assess the primary outcome parameters. Perioperative data will be collected by the attending anaesthesiologist, written and electronically.

3.5 Trial Flowchart

Eligibility for enrolment will be based on screening of the patients' chart. Preoperatively, the investigator will obtain written informed consent and record baseline data (demographic data, routine clinical examination, surgical and medical history, EuroSCORE II, results of standard laboratory parameters and other tests). During a preoperative visit window, (1 day to a maximum of 6 weeks before cardiac surgery), the 3D-CAM, the Mini Mental State Examination (MMSE)[41], clock completion[42], self-administered Instrumental ADL (IADL) [43], Tilburg Frailty Indicator[44], Essential Frailty Toolset (EFT)[45], self-administered EuroQol five dimensional questionnaire five levels (EQ-5D-5L) validated Dutch version and EuroQol Visual Analogue Scale (EQ-VAS) [46] and an interview with a family member using the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[47] will be performed.

The day of or before surgery the 3D-CAM will be assessed.

Anaesthesia

In general, management will be performed according to the following institutional standards. It is however possible that the attending anaesthesiologist changes this management to optimise the patients' care.

SAVR / transapical TAVI

General anaesthesia

Prior to anaesthesia, patients must be in a fasting state for 6 hours. Premedication is only given if explicitly requested by the patient and consists of alprazolam 0.5 or 1 mg.

After 5 minutes of pre-oxygenation (FiO_2 = 1.0), general anaesthesia will be induced with a combination of remifentanil 0.5 μg kg^{-1} min^{-1} followed by a bolus of propofol 0.5-1 mg kg^{-1}. Tracheal intubation will be facilitated by a bolus administration of rocuronium 1.0 mg kg^{-1}. Further curarization will be left upon the discretion of the attending anaesthesiologist.

General anaesthesia will be maintained with sevoflurane 1.5-2.0 % (FiO_2 = 0.4-0.5), titrated to achieve a bispectral index (BIS) of 40-60. A continuous infusion of dexmedetomidine 0.5 μg kg^{-1} h^{-1} is started. Analgesia is achieved with a continuous infusion of remifentanil (0.15-0.30 μg kg^{-1} min^{-1}), starting after induction and adjusted depending on patients' reactions, spontaneous movements, sweating and/or sudden increase in heart rate or arterial pressure. After completion of surgery the treatment differs depending on surgery and ICU or PACU admittance.

- For TAVI, postoperative analgesia will be provided by local infiltration of the wound with 10-20 ml levobupivacaine 0.5%. Patients are to be extubated on table and transferred to the ICU afterwards.
- For SAVR, postoperative analgesia will be provided by a bolus of intravenous (IV) morphine 0.1-0.2 mg kg^{-1} at end of surgery. Patients are transferred intubated to the ICU or PACU under mono-sedation with propofol (using a target-controlled infusion (TCI) with 1.0μg/mL) and remifentanil (0.1 μg kg^{-1} min^{-1})

Transfemoral TAVI

Sedation

Prior to anaesthesia, patients must be in a fasting state for 6 hours. Premedication is only given if explicitly requested by the patient and consists of alprazolam 0.5mg.

Oxygen will be administered with a face mask (5 L min^{-1} O_2) and sedation is provided with a continuous infusion of remifentanil (0.05-0.10 μg kg^{-1} min^{-1}) and a TCI of propofol with calculated plasma concentrations of 0.2-1 μg ml^{-1} titrated, targeting a BIS of 60-80. Local

anaesthesia of the groin will be achieved with 10-20 ml levobupivacaine 0.5% to provide surgical anaesthesia. After completion of surgery, propofol and remifentanil will be stopped. Patients will be transferred awake and cooperative to the ICU.

Monitoring and hemodynamic management

Hemodynamic and respiratory monitoring will be provided according to our institutional routine. Patients will be instrumented with peripheral intravenous, arterial and central venous catheters. Depending on the intervention and the co-morbidities, a thermodilution or pacing pulmonary artery catheter will be placed.

Whenever available, the following parameters will be recorded digitally every minute from the pre-anaesthetic period to the end of surgery: peripheral oxygen saturation (SpO_2), heart rate (HR), invasive arterial blood pressure (IBP), central venous pressure (CVP), cardiac output (CO), mixed venous oxygen saturation (SvO_2), mean pulmonary artery pressure (MPAP), fraction of inspired oxygen (FiO_2), end-tidal carbon dioxide ($etCO_2$), body temperature, BIS, cerebral tissue oxygenation (rSO_2), urine output and blood loss. Transoesophageal echocardiography (TEE) will be performed during anaesthesia according to our institutional standards.

For SAVR, blood gas analysis will be performed at the following time points: T0 = prior to induction, T1 = after induction, T2 = after sternotomy, T3 = after weaning from CPB, T4 = after sternal closure and T5 = end of surgery. In TAVI, blood gas analysis will be performed at the following fixed time points: Ta = prior to sedation/induction, Tb = after placement of central venous catheter, Tc = after deployment of aortic valve, Td = end of surgery. Further blood gas analyses will be left upon the discretion of the attending anaesthesiologist

Intraoperative hemodynamic management will be standardized according to our clinical routine. Basic fluid substitution will be performed with 1 ml kg^{-1} h^{-1} balanced crystalloid solution. Hemodynamic stability will be defined as mean arterial blood pressure of >70 mmHg (50-60 mmHg during CPB) and SvO_2 > 70 %. In case of hypovolemia (detected by TEE or visual

inspection of the heart chambers), a colloid solution will be infused. In case of anaemia, defined as a haemoglobin content less than 8.0 g dL^{-1}, packed red blood cells (RBCs) will be transfused. In case of unstable haemodynamics despite adequate volume loading, a norepinephrine infusion will be started. Administration of other vasopressors, inotropes, PC, fresh frozen plasma (FFPs) and platelets will be left at the discretion of the attending anaesthesiologist.

Postoperative treatment

Intensive care unit treatment

After SAVR, sedation on the ICU will be maintained with a propofol infusion of 2-3 mg kg^{-1} h^{-1}. Analgesia will be achieved with a continuous infusion of fentanyl, supplemented by systemic acetaminophen (15 mg kg^{-1}, administered IV every 6 hours) during the first postoperative day. Standard tracheal extubation and patients discharge criteria will be applied.

Following TAVI, the patient will be transferred to the ICU awake and extubated. Analgesia for these patients will be achieved with intermittent intravenous administration of tramadolhydrocholoride (1 mg $kg^{-1,}$ every 6 hours if needed), supplemented by systemic acetaminophen (15 mg kg^{-1}, administered IV every 6 hours).

Post anaesthesia care unit treatment in patients receiving fast-track anaesthesia

Following SAVR, patient that are transferred to the PACU will be sedated with propofol or dexmedetomidine. Analgesia will be achieved with infusion of remifentanil and subcutaneous morphine, supplemented by systemic acetaminophen (15 mg kg^{-1}, administered IV every 6 hours) during the first postoperative day. Standard tracheal extubation and patients' discharge criteria will be applied. PONV prophylaxis is continued with administration of dexamethasone 5 mg IV every 12 hours and ondansetron 4 mg IV every 6 hours. Transfer to the ward will be done once standard discharge criteria are fulfilled.

Standard hospital care

A bundle of non-pharmacological interventions is applied to prevent delirium, including: early mobilization; detection and treatment of pain; early removal of catheters, drains and probes; timely recognition of medical problems and treated accordingly; avoidance of precipitating pharmacological triggers of POD. Whenever POD is detected, known precipitating factors will be corrected and non-pharmacological measures based on our institutional and hospital-wide standard operating procedures will be initiated. Only if this proves to be insufficient, pharmacological treatment will be initiated.

4. Selection and withdrawal of subjects

Patients will be recruited by the principal investigator or co-investigator. Detailed information about the study design, background and protocol will be given. Questions brought forward by the patient will be answered. The eligible patient who is willing to participate will sign a written informed consent before any study procedure.

4.1 Inclusion criteria

- Patients scheduled to undergo elective
    - TAVI
    - SAVR with or without CABG
- Age ≥ 70 years
- Patient able to read and understand the research materials

4.2 Exclusion criteria

- Inability to give informed consent
- Presence of delirium at baseline as screened with the 3-minute Diagnostic Confusion Assessment Method (3D-CAM)
- Other combined surgical procedures (e.gother valvesurgery)

4.3 Expected duration of trial

The enrolment period is planned over 24 months, starting September 2018 and ending August 2020. A subsequent period of 6 months is planned for the primary data evaluation and statistical analysis. An additional 3 months is planned for the assessment of 6-month follow-up, including additional data evaluation, statistical analysis and publication of the results.

5. Trial Procedures

5.1 By visit

Baseline measurement visit (Visit 0)

- MMSE
- Clock completion
- 3D-CAM
- Self-administered IADL
- Self-administered EQ-5D-5L and EQ-VAS
- EuroSCORE II
- IQCODE
- Tilburg Frailty Indicator
- Essential Frailty Toolset
- Anticholinergic Loading Scale[48]
- Geriatric Depression Scale

Anaesthesia for aortic valve intervention (Visit 1)

- Perioperative hemodynamic and respiratory monitoring parameters
- Duration of surgery, CPB and aortic cross clamp time
- Minimum core temperature
- Doses of vasopressors/inotropes

Visit 2 (first morning ICU/PACU))

- CAM-ICU (intubated and/or analgosedated patients) / 3D-CAM (awake and extubated patients), in case of a positive result CAM-S Long.
- Daily chart review keywords indicative for POD and administration of antipsychotic drugs
- Extubation time
- Time of chest drain removal
- Anticholinergic Loading Scale

Visit on the ward, daily until postoperative day 5 (Visit 3-6)

- 3D-CAM, in case of a positive result: CAM-S Long
- Daily chart review for keywords indicative for POD, administration of antipsychotic drugs and DOS.
- Anticholinergic Loading Scale

30-day chart review

- Hospital length of stay
- Intensive care unit length of stay (ICU-LOS)
- Early safety (at 30 days) as defined by VARC-2
- Discharge destination

6-months interview (by phone and mail)

- Self-administered IADL
- Self-administered EQ-5D-5L and EQ-VAS
- Cognitive Failure Questionnaire
- Clinical efficacy (at 6 months) as defined by VARC-2

Patients in which POD develops during the first five postoperative days will be followed using CAM-ICU/3D-CAM until POD has resolved or until discharge.

5.2 Laboratory tests

Data will be used from standard pre- and postoperative laboratory tests. At the beginning and at the end of surgery, 2 blood samples will be collected to examine the presence of neural injury markers.

6. Assessment of Safety

All patients will receive routine anaesthetic/surgical/interventional care according to our institutional standards. All procedures will be carried out in a cardiac surgical operation theatre fully equipped with all the necessary infrastructure for advanced cardiopulmonary monitoring and resuscitation. Patients will not receive any investigational treatment.

This study has primarily an observational character consisting of completing several questionnaires with the exception of obtaining a blood sample at the end of surgery. As such, the potential for serious events appears too remote to require their definition, assessment or documentation. However, a variety of important safety parameters will be assessed as secondary endpoints, including early safety (at 30 days) and clinical efficacy (at 6 months) using the global VARC-2 criteria.

7. Statistics

7.1 Sample size

Based on an expected accrual of 250 patients in total, assuming 70 and 180 patients in the TAVI and SAVR group, respectively, there will be 89% power to detect a difference of 15 percentage points in POD (5%POD in TAVI group and 20% POD in SAVR group).

The calculated power is an approximation, since the primary analysis will not be based on a classical Chi^2 test, but on the calculation of a relative risk, taking into account differences in number of evaluable days and differences in patient mix (using IPTW, cfr. Statistical analysis).

7.2 Analysis

For the evaluation of POD within 5 days (primary outcome), the relative risk (and 95% confidence intervals) will be reported. The estimate will be obtained from a Poisson regression model[49] with the (log) number of evaluable days as offset (for some patients the number of evaluable days will be lower than 5 if the patient is considered unconscious (RASS score <-3) or died within the first 5 days).

Secondary outcomes which are dichotomous will also be evaluated using relative risks.

The potential difference in patient-mix between patients in the SAVR and in the TAVI group, caused by the observational character the study, can induce bias when comparing primary and secondary outcomes between the groups. To reduce the risk of bias, each subject will be weighted by its inverse probability of being in its specific group, conditional on the following variables suspected a priori to be related to POD (and potentially to other outcomes: EuroSCORE II, TFI, EFT). The objective is to create a weighted sample in which the distribution of these variables is the same in both groups. The probabilities of group membership are also known as propensity scores[50] and will be obtained with an approach proposed by McCaffrey et al [51](this approach will be followed instead of a classical multivariable logistic regression model to avoid weights to be too extreme). Each individual is weighted by the inverse of its probability to belong to its group. Thus, the more typical a subject is for the group it belongs to, the lower its weight will be. The weights will be normalized to the sample size in each group, meaning the sum of weights in each group equals the sample size of that group. This approach is known as inverse probability of treatment weighting[52]. It uses the propensity score to construct weights, contrary to the more classical approaches where the score is used as a covariate in the analysis or is used to create a matched sample. All statistical analyses earlier mentioned will include the IPTW.

All analyses will be performed using SAS software, version 9.4 of the SAS System for Windows. Copyright © 2002 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

An investigator or a study nurse will review completed CRFs for completeness and correctness before digitalization and statistical analysis. At this time point, missing data will be identified, if possible drawn from source data and filled into the CRFs. Missing data not being found back in source data will not be expected. Any deviations from the original statistical plan will be described and justified in the protocol and in the final report.

8. Quality assurance

The primary investigator and the principle study nurse of the investigational team have followed various certified courses in “Good Clinical Practice”. Further study personal will work under close supervision of these GCP-trained investigators.

9. Direct access to source data and documents

The investigator(s) and the institution will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (ie patients’ case sheets, blood test reports, X-ray reports, histology reports etc).

10. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to Ethics Committee of the University Hopitals Leuven.

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Study Site shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the Ethics Committee, if

required. The Study Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator shall treat all information and data relating to the Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).

11. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance."

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