EuPreCHO: European study on perioperative management and outcome following Preoperative Transthoracic Echocardiography in noncardiac surgery patients.

Short title / Study Identifier	EuPreCHO
Type of Research Project:	Multicentre Case Control Study
ClinicalTrials.gov ID	NCT06409234
Sponsor/Funder:	European Society of Anaesthesiology and Intensive Care (ESAIC) Rue des Comédiens 24, 1000 Brussels, Belgium Phone: +32 2 743 3290 E-mail: research@esaic.org ; EuPreCHO@esaic.org
Chief Investigators:	Prof. Michelle Chew, PhD Anaesthesia and Intensive Care ANOPIVA, Plan 14, Linköping University Hospital, S-58185, Sweden Prof Dr. Giovanna Lurati Buse, MSc University Hospital Düsseldorf Anesthesiology Department Moorenstr. 5 40225 Düsseldorf, Germany
Project Plan Version and Date:	Version 1.0, dated 04SEPT2024

Access To Research Documents

PROTOCOL SIGNATURE PAGE

Chief Investigators		
Name	**Signature**	**Date**
Prof. Michelle Chew, PhD Anaesthesia and Intensive Care ANOPIVA, Plan 14, Linköping University Hospital, S-58185, Sweden		
Prof. Dr. Giovanna Lurati Buse, MSc University Hospital Düsseldorf Anesthesiology Department Moorenstr. 5 40225 Düsseldorf, Germany		
Sponsor		
Name	**Signature**	**Date**
Pierre Harlet Research and Clinical Trial Lead European Society of Anaesthesiology and Intensive Care 24 rue des Comédiens 1000 Brussels, Belgium		

Local Principal Investigators ***(enter local details, as applicable)***		
Name - Place	**Signature**	**Date**

TABLE OF CONTENTS

SYNOPSIS (SUMMARY)

Chief Investigators:	Prof. Michelle Chew, PhD Anaesthesia and Intensive Care ANOPIVA, Plan 14, Linköping University Hospital, S-58185, Sweden Prof. Dr. Giovanna Lurati Buse, MSc University Hospital Düsseldorf Anaesthesiology Department Moorenstr. 5 40225 Düsseldorf, Germany
Project Title:	EuPreCHO: European study on perioperative management and outcome following Preoperative Transthoracic Echocardiography in noncardiac surgery patients.
Short Title :	EuPreCHO
CTGOV ID	NCT06409234
Protocol Version and Date:	Version 1.0 04SEPT2024
Project design:	International, prospective case control study
Background and Rationale:	In August 2022 the European Society of Cardiology (ESC) published updated guidelines [1] (previous version: 2014), which include new recommendations on preoperative transthoracic echocardiography (TTE). These updates have broadened the criteria for preoperative TTE. However, the impact of preoperative TTE on patient outcomes remains controversial, with most evidence derived from administrative databases [2-8]. There is a knowledge gap regarding how TTE information influences perioperative management in current daily practice and its subsequent impact on outcome. Additionally, a secondary analysis of a large international cohort suggests that the ESC criteria for TTE recommendations may not be efficient.
Objective(s):	**Main objectives:** EuPreCHO aims at answering the following three research questions (RQ) with regard to patients undergoing intermediate and high-risk noncardiac surgery procedures: 1. does the perioperative management of patients evaluated with vs those not evaluated with preoperative TTE differ in current clinical practice? 2. does the outcome of patients evaluated with vs those not evaluated with preoperative TTE differ in current clinical practice? 3. what factors (model) enhance the prediction of major pathologies in preoperative TTE? **Secondary objective:** To answer the question: does preoperative NTproBNP compared to preoperative troponin contribute to the prediction of major cardiac pathologies in patients that undergo preoperative TTE? **Tertiary objective:** To explore how information on TTE detected major pathologies compared to preoperative troponin and to preoperative NTProBNP information, respectively, contributes to the prediction of 1) disability-free survival and 2) major adverse cardiac events (should the number of events be sufficient).

Outcomes(s):	**RQ1**: Primary endpoint will be intensified perioperative management defined as one or more of the following: • discussion in preoperative multidisciplinary board and derived decisions (e.g. technique modifications, cancellations, postponing of scheduled procedure), • optimization of cardiovascular medication, • cardiological workup, • invasive or advanced intraoperative haemodynamic monitoring, • goal-directed haemodynamic management, • anaesthesia technique, • planned ICU/IMC admission or planned extended PACU stay, • postoperative troponin monitoring. **RQ2**: Primary endpoint will be disability- free survival at 30 days (12-item WHODAS questionnaire). Secondary endpoints will be: 30-day all-cause mortality, 30-day composite of all-cause death and myocardial infarction, 30-day major adverse cardiac events (cardiac death, myocardial infarction, cardiac arrest, coronary revascularization, acute heart failure/ decompensation of chronic heart failure), days-alive-and-out-of-hospital (DAOH) at 30 days, and in-hospital complications with Clavien-Dindo Class ≥3 [9]. Tertiary endpoints are ICU/IMC (re)-admission and length of ICU/IMC stay. **RQ3:** The endpoint will be a composite of major pathologies in TTE consisting in: • Moderate-severe left ventricular systolic dysfunction • Significant (Grade II or more) LV diastolic dysfunction with evidence of increased LV filling pressures • Significant right ventricular dysfunction • Severe left-sided valvulopathies
Inclusion / Exclusion criteria:	*Included* are inpatients planned for elective, inhospital, intermediate or high-risk noncardiac surgery procedures AND either aged ≥65 years or presenting ≥2 cardiovascular risk factors or with known cardiovascular disease. 'Exposed' will be patients in whom TTE was performed up to 6 months before surgery. 'Non-exposed' will be patients in whom TTE was NOT performed. *Exclusion criteria* are age <18 years, day surgery, urgent/emergency procedures, ICU patient at time of enrollment, cardiac surgery up to 30 days prior to the index noncardiac procedure, unwilling or unable to provide informed consent, unable to complete the WHODAS questionnaire (literacy or language barrier), previous enrollment in EuPreCHO (in case of repeated surgery)
Project assessments:	Baseline: 12-item WHODAS questionnaire [10, 11] and troponin measurement (where applicable + NTproBNP [1]); extraction of relevant clinical data (history of illness, planned operation, etc.) from medical charts; extraction of TTE findings from clinically indicated TTE. At discharge: extraction of relevant clinical data (ICU admission, in-hospital complications, length of stay, etc.) from medical charts. At day 30 after surgery: follow-up by mail or by phone for outcome assessment (12-item WHODAS questionnaire and the collection of information on postoperative events).

Number of Participants:	5393 exposed (TTE within 6 months before surgery) and 2696 non-exposed. *Of note, the 2:1 exposed-to-non-exposed ratio was chosen to reduce the burden for centres both in terms of data collection and in terms of preoperative biomarkers to be measured, while maintaining the power for the modelling to improve prediction of major pathologies in TTE.*
Project Duration, schedule:	Follow-up duration is 30 days.
Statistical Considerations:	RQ1: multilevel logistic regression with predefined variables. As alternative statistical approach (sensitivity analyses), we will calculate the propensity score for receiving TTE using logistic regression and insert it as a covariate in a logistic regression model, both bivariately and multivariately (double robust). RQ2: multilevel logistic regression with predefined variables. In sensitivity analyses, clinical factors will be substituted by clinical risk scores (RCRI, NSQIP MICA, AUB-HAS2 Cardiovascular Risk Index). As alternative statistical approach (sensitivity analyses), we will calculate the propensity score for receiving TTE using logistic regression and insert it as a covariate in a logistic regression model, both bivariately and multivariately (double robust). For DAOH, due to the expected non-normal distribution, a quantile regression will be conducted. RQ3: multivariable logistic regression with predefined covariates
Risk-Benefit statement:	The study is observational, i.e., it will collect pseudonymized data from preoperative TTE that are requested upon clinical decision of the attending clinicians (i.e., TTE is **NOT** study-mandated) and record information on the resulting perioperative management. Therefore, routine clinical management will not be affected. Study assessments consist of answering the WHODAS questionnaire and one preoperative blood sample (5 mL). Data handling will comply with the General Data Protection Regulation (GDPR) (EU) 2016/679. As such the risk associated with the study appears minimal. The benefit for future noncardiac surgery patients appears relevant as the data collected may contribute to more targeted, preoperative TTE therefore reducing potentially unnecessary testing and reducing procrastination of surgical procedures potentially resulting from “clogged” echo labs. On the other hand, the study will potentially identify risk groups where more targeted TTE will reduce the chance of missing relevant findings.

Abbreviations

ACC	American College of Cardiology
AIC	Akaike Information Criterion
ASA	American Society of Anesthesiologists
ASR	Annual Safety Report
AUC	Area under the curve
CAD	Coronary artery disease
CHF	Congestive heart failure
CI	Confidence interval(s)
COPD	Chronic obstructive pulmonary disease
CRF	Case report Form
eCRF	Electronic Case Report Form
ESAIC	European Society of Anaesthesiology and Intensive Care
ESC	European Society of Cardiologists
GDPR	General data protection regulation
GFR	Glomerular filtration rate
HR	Hazard Ratio
Hx	History
ICF	Informed consent form
ICH-GCP	Good Clinical Practice
ICU/IMC	Intensive care unit/intermediate care unit
ID	Identification
IRB	Institutional Review Board
MACE	Major adverse cardiac events
MI	Myocardial infarction
NSQIP	National Surgical Quality Improvement Program
NSQIP MICA	National Surgical Quality Improvement Program, Risk calculator for myocardial infarction
NTproBNP	N-Terminal PROhormone of Brain Natriuretic Peptide
OR	Odds ratio
PI	Principal Investigator
PVD	Peripheral vascular disease
RCRI	Revised Cardiac Risk Index (Lee-Index)
ROC	Receiver operating characteristics (curve)
SC	Steering Committee
SOP	Standard operating procedure
TTE	Transthoracic echocardiography
TOE	Transoesophageal echocardiography

1. ADMINISTRATIVE STRUCTURE

1.1 Steering Committee (SC)

Chief investigators are :

Prof. Michelle Chew, PhD
Anaesthesia and Intensive Care
ANOPIVA, Plan 14, Linköping University Hospital,
S-58185, Sweden

Prof. Dr. Giovanna Lurati Buse, MSc
University Hospital Düsseldorf
Anaesthesiology Department
Moorenstr. 5
40225 Düsseldorf, Germany

Prof. Michelle Chew and Prof. Giovanna Lurati Buse share the role of chief investigator.

Members of the steering committee:

Fernando Abelha, MD, PhD	Porto, Portugal
Gareth Ackland, PhD FRCA FFICM	London, UK
Kateryna Bielka, MD	Kiev, Ukraine
Bernardo Bollen Pinto, MD, PhD	Geneva, Switzerland
Stefan De Hert, MD, PhD	Ghent, Belgium
Jean-Luc Fellahi, MD, PhD	Lyon, France
Simon Howell MA (Cantab) MRCP FRCA MSc MD	Leeds, UK
Daniela Ionescu, MD, PhD	Cluj Napoca, Romania
Katarzyna Kotfis MD, PhD	Szczecin, Poland
Jan Larmann MD, PhD	Heidelberg, Germany
Purificación Matute, MD, PhD	Barcelona, Spain
Ekatarina Popova, MD, PhD	Barcelona, Spain
Christian Puelacher, MD,PhD	Innsbruck, Austria
Spadaro Savino, MD, PhD	Ferrara, Italy
Judith van Waes, MD PhD	Utrecht, The Netherlands
Peter Zahn, MD PhD	Bochum, Germany

Study Statistician:

He Zhang, PhD Linköping University, Sweden

Research Methodologist:

Malachy Columb, FRCA FFICM, Manchester University, UK

1.2 **Sponsorship**

EuPreCHO is sponsored by a grant from the European Society of Anaesthesiology and Intensive Care Clinical Trial Network (ESAIC CTN). The aim of ESAIC CTN is to provide an infrastructure for clinical research in the fields of Anaesthesia, Pain, Intensive Care and Emergency Medicine by transnational European collaborative studies. The Clinical Trial Network of the ESAIC can be contacted via:

ESAIC Research Department
European Society of Anaesthesiology and Intensive Care (ESAIC)
Rue des Comédiens 24
1000 Brussels, Belgium
E-mail: research@esaic.org; EuPreCHO@esaic.org

2. ETHICAL AND REGULATORY ASPECTS

2.1 Ethical Conduct of Study

The research project will be carried out in accordance with the GDPR (EU) 2016/679 and the principles enunciated in the Declarations of Helsinki (version October 2013) and of Taipei (version October 2016) by the World Medical Association, and by the ICH-GCP Guidelines E6(R2). Specific national and local regulatory authority requirements will be followed as applicable.

2.2 Risk categorisation

EuPreCHO is a prospective observational study. It will collect pseudonymised data from patients who are undergoing preoperative TTE that is requested upon clinical decision of the attending clinicians (i.e. TTE is **NOT** study-mandated) and record information on the resultant perioperative management. Therefore, routine clinical management according to the standards laid out in each institution will not be affected. The study assessments consist of the WHODAS 2.0 questionnaire preoperatively and at follow-up and the preoperative sampling of troponin.

Health risks are limited to the drawing of approximately 5 mL of blood ***once*** preoperatively (troponin; and where feasible NTproBNP will also be measured in the same sample). The blood sampling should be feasible at the time of blood sampling for clinical purposes (i.e., regardless of the patient's participation in the study) in most cases. Data handling represents the other potential source of risk. Data protection measures are reported in the section "8.3. Confidentiality, Data Protection".

2.3 Institutional Review Board (IRB)

In all cases, prior to study initiation, the local Principal Investigator (PI) at each centre must submit the study documents to the responsible IRB for ethical judgment and obtain documented proof that the study has been subject to IRB review and given approval/favorable opinion. No substantial changes will be made to the protocol without prior IRB approval, except where necessary to eliminate apparent immediate hazards to study participants.

In the unlikely event of premature study end or interruption of the study, a report will be sent to the IRB within 15 days. The regular end of the study is reported to the IRB within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter "2.8. Amendments, Changes". All communication, reports, and updates to the local IRB are the responsibility of the local PI.

2.4 Participant Information and Informed Consent

Written, informed consent, using the Informed Consent Form (ICF) approved by the responsible IRB, will be sought from each patient prior to inclusion. ICF and any other written information provided to the patient must be subject to IRB review and given approval/ favourable opinion.

Patient consent will be sought as follows: up to the date of the surgery, the patients will be presented with the IRB-approved ICF and sufficient time and information will be provided to allow the participant to make an informed decision about their participation in the study. This includes explaining the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort participation may entail. Each participant will be informed that their participation in the study is voluntary and that he/she may withdraw from the study at any time and without explanation, that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. In case of withdrawal from the study (procedures) no further data will be collected, while already collected, encoded data will be retained, and analysis may be performed up to the point of data collection. The participant will be informed that his/her medical records will be examined by authorised individuals other than their treating physician. The participant will read and consider the statement and will have the opportunity to ask questions before signing and dating the ICF and they will be given a copy of the signed document. Patients will confirm that they were given adequate time to reach a decision. The ICF must also be signed and dated by the investigator (or designee) and it will be retained as part of the study records.

The Sponsor provides templates of the Patient Information Sheet and Participant's ICF for the main study in English (see Appendix 1). Each centre/country will have their own approved translated ICF according to the local legislation. All translations and adaptation of the ICFs should be sent to the Sponsor (ESAIC) for validation. SOP and guidance published by the Sponsor should be followed in this regard.

2.5 Participant privacy

ESAIC as the Sponsor and the investigators affirm and uphold the principle of the participant's right to privacy and will comply with the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments guidelines as applicable. Specifically, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual subject medical information obtained for this study is considered confidential, and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by using subject identification codes and only encoded data will be recorded in the central database.

For data verification purposes, authorised representatives of the Sponsor or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants'

medical history. The study protocol and all study documents will be submitted by the local PI to the local data protection officer for review at each site where required by local regulation.

2.6 Early termination of project

EuPreCHO is an observational study. Therefore, premature termination of the study resulting from ethical or safety concerns is most unlikely. In case of insufficient participant recruitment, the study period may be extended to reach the calculated sample size.

2.7 Participants´ insurance

The study is observational, i.e., it will collect pseudonymized data from **non-**study mandated preoperative TTE and record information on the perioperative management, as decided upon by the clinicians. Clinical management is unaffected, and the study assessment consists in answering the WHODAS 2.0 questionnaire and in one preoperative blood sampling (5 mL). As such, the protocol does not mandate participants' insurance. In some rare jurisdictions, insurance might be required depending on **local** requirements. It is the responsibility of the PIs to check if local insurance requirements are applicable.

2.8 Amendments

Only the SC or persons delegated by the SC are entitled to amend the protocol. National Coordinating Investigators and Local PIs will receive timely notification of changes and will be required to submit amendments locally. Written approval of the amendment will be provided to the Sponsor and substantial amendments of the protocol will be only implemented after approval of the responsible IRB.

In consideration of the observational nature of the study, the necessity of protocol deviations to protect the rights, safety, and well-being of human subjects without prior approval of the Sponsor and the IRB appears remote. Such deviations must be documented and reported to the Sponsor and the IRB as soon as possible.

All non-substantial amendments like administrative changes will be communicated to the IRB as necessary by the PI. It is the local PI responsibility to communicate with their IRB.

2.9 Background

In Europe, nearly 40 million surgical procedures are performed every year [12]. With over 4 million deaths within 30 days of surgery yearly [13], postoperative mortality is a leading cause of death worldwide. Cardiac complications are frequent and associated with short- [14, 15] and mid-term mortality [16] after noncardiac surgery. The attributable fraction of myocardial injury to 30-day mortality after noncardiac surgery has been estimated to be 16% [17]. To mitigate cardiovascular risk, international societies have issued guidelines on perioperative management of patients at elevated

cardiovascular risk. In August 2022 the European Society of Cardiology (ESC) published updated guidelines [1] (previous version 2014) including recommendations on preoperative transthoracic echocardiography (TTE).

The 2022 update resulted in broadened criteria for preoperative TTE to include all patients with poor functional capacity, increased B-type natriuretic peptides (NPs) or new cardiac murmurs undergoing high-risk surgery (Class I recommendation). Further, the guidelines recommend considering preoperative TTE for patients with poor functional capacity, abnormal ECG, high B-type NPs or $\geq$1 clinical risk factor before intermediate risk surgery (Class IIb). Implementation of these updated recommendations would result in a substantial increase in the numbers of preoperative TTEs. Schweizer et al. [18] quantified in a one-day cross sectional study in a tertiary care centre that a preoperative TTE was recommended or should be considered in 17% of noncardiac surgery patients according to the updated guidelines. Our own unpublished data suggest that in a population at elevated cardiovascular risk (METREPAIR sample), the guidelines update would result in 33.4% (5177/15529) of patients receiving a stronger recommendation for preoperative TTE compared to the 2014 guidelines. Even most tertiary centres may not be able to manage such volumes without risking of delaying surgery or without reorganizing the logistics of preoperative TTE assessments [18]. Not only is the impact of preoperative TTE on outcome controversial and in most cases derived from administrative databases [2-8], there is also a knowledge gap in terms of what changes in perioperative managements are derived from TTE information in current daily practice in Europe and what their impact on outcome may be.

Of note, the updated criteria suggested by the 2022 ESC guidelines to define class of recommendation for TTE did not appear to improve the yield of pathological findings in a large sample of patients at elevated cardiovascular risk (unpublished data). Among the 3,285 (21.2%) patients in the METREPAIR sample that had undergone TTE within 6 months prior to noncardiac surgery, application of the updated guidelines would result in 11% [95%CI (6%-17%)] fewer patients with EF <40% (n=151) receiving a stronger recommendation for TTE whilst 26% [95%CI (25%-28%)] fewer patients with EF≥40% (n=3134) would receive a weaker recommendation for TTE, compared to the 2014 guidelines. Of particular concern are the results of a Monte Carlo simulation within the same sample (unpublished data). The model compared the number of performed TTE and number of detected EF<40% according to the 2014 and 2022 guidelines. In a sensitivity analysis, the model was run multiple times under assumption of a proportion of conducted TTE classified as IIb (“may be considered”) increasing from 0% to 100%. If 8% to 63% of TTE with a class IIb recommendation (“may be considered”) were conducted, the 2022 update resulted in a lose-lose situation - more TTE examinations would be performed, yet fewer cases with EF <40% would be detected. The range of between 8 to 63% of TTEs with a IIb recommendation performed is well within the probable proportion in clinical practice.

Performing all recommended and all "may be considered" TTEs according to the 2022 guidelines would result in 329 (95%CI 306-350) additional TTEs but only 6 (95%CI -2 to 13) additionally detected EF <40%. While the secondary analysis within METREPAIR suffered from being focused on EF only, it suggests that the criteria endorsed by the ESC guidelines to define the class of recommendation of TTE may not be efficient. Therefore, there is a need to refine criteria to guide the decisions to conduct TTE prior to noncardiac surgery procedures to improve the yield of major pathologies that may relevantly impact perioperative management.

2.10 **Rationale for the research project**

According to current guidelines [1], a relevant proportion of European patients planned for intermediate or high-risk noncardiac surgery procedure are supposed to undergo preoperative TTE. The risk-benefit balance of this approach is unknown and may result in delayed surgery from limited TTE availability and the inherent burdening of institutions without known clinical benefits.

Further, European anaesthesiologists are currently confronted with a guideline that they may not be willing to implement due to knowledge gaps or not be able to implement due to logistical barriers. Therefore, before considering reorganizing preoperative TTE logistics is an urgent need to generate knowledge on the outcome impact of TTE prior to noncardiac surgery and to establish criteria that may result in a more targeted use of preoperative TTE.

2.11 **Risk-Benefit Assessment**

The study is observational, i.e., it will collect pseudonymised data from preoperative TTE that are requested upon clinical decision of the attending clinicians (i.e., TTE is **NOT** study-mandated) and record information on the resultant perioperative management, as decided upon by the clinicians. Therefore, routine clinical management will not be affected. Of note in a recent cross-sectional study in a European tertiary care centre [18], the recommended to performed ratio was 0.21. As such, patients not receiving TTE evaluation prior to noncardiac surgery represent standard and not sub-standard care.

Study assessments consist of answering the WHODAS questionnaire and **one** preoperative blood sample (5 mL). All data processing will comply with the GDPR(EU) 2016/679. Before enrolment, ethical approval will be obtained in all centres and informed patient consent will be asked. As such the risk associated with the study appears minimal. The benefit for future noncardiac surgery patients appears relevant as the data collected may contribute to more targeted, preoperative TTE therefore reducing potentially unnecessary testing and reducing procrastination of surgical procedures potentially resulting from "clogged" echo labs. On the other side, more targeted TTE will reduce the chance of missing relevant findings.

3. OBJECTIVES, ENDPOINTS/OUTCOMES AND OTHER STUDY VARIABLES

3.1 Objectives

Main objective:

EuPreCHO aims at answering the following 3 questions with regard to patients undergoing intermediate and high-risk noncardiac surgery procedures [1]:

1) ***does the perioperative management of patients evaluated with vs those not evaluated with preoperative TTE differ in current clinical practice?*** Specific measures of intensified perioperative management to be assessed will include discussion in preoperative multidisciplinary board (e.g. modifications, cancellations, postponing of scheduled procedure), timeline between preoperative assessment and day of surgery, optimization of cardiovascular medication, invasive cardiological workup, invasive or advanced intraoperative haemodynamic monitoring, planned ICU/IMC admission or planned protracted monitoring in PACU;
2) ***does the outcome of patients evaluated with vs those not evaluated with preoperative TTE differ in current clinical practice?*** Specific outcomes of interest will be disability-free survival at 30 days (primary endpoint) assessed using the WHODAS 2 questionnaire, 30-day all-cause mortality, 30-day major adverse cardiac events, in-hospital complications with Clavien-Dindo Class ≥3 [9], ICU/IMC (re)-admission and length of ICU/IMC stay, days-alive and out of hospital at 30 days post-surgery (secondary).
3) ***what factors (model) enhance the prediction of major pathologies in preoperative TTE?*** Major pathologies detected on TTE include moderate-severe LV systolic dysfunction, significant (Grade II or more) LV diastolic dysfunction with evidence of increased LV filling pressures, significant RV dysfunction, and severe left-sided valvulopathies.

Secondary objectives:

To answer the question, if NTproBNP information compared to troponin information contributes to the prediction of major pathologies in preoperative TTE.

Tertiary objective

To explore, how information on TTE detected major pathologies compared to preoperative troponin and to preoperative NTProBNP information, respectively, contributes to the prediction of 1) disability-free survival and 2) major adverse cardiac events (should the number of events be sufficient).

3.2 **Endpoints´ definition and assessment**

3.2.1 RQ1: does the perioperative management of patients evaluated with vs those not evaluated with preoperative TTE differ in current clinical practice?

Primary endpoints for this analysis are an intensified perioperative management defined as one or more of the following:

- discussion in preoperative multidisciplinary board and derived decisions (e.g. modifications, cancellations, postponing of schedule procedure),
- changes of cardiovascular medication,
- cardiological workup (cardiac MRI, CCT, stress-imaging, coronary angiography, PCI, valvuloplasty or TAVI),
- invasive or advanced intraoperative haemodynamic monitoring (arterial line, central venous line, pulmonary arterial catheter, intraoperative TEE, PiCCO (Pulse index Continuous Cardiac Output) or other devices for cardiac output estimation,
- goal-directed haemodynamic management (as per locally implemented protocol),
- anaesthesia technique (e.g. regional),
- planned ICU/IMC admission or planned extended PACU stay.

These data will be extracted by trained personnel from clinical charts.

3.2.2. RQ2: does the outcome of patients evaluated with vs those not evaluated with preoperative TTE differ in current clinical practice?

To evaluate the effect of preoperative availability of recent TTE information on outcome among patients evaluated to vs not evaluated using preoperative TTE, disability-free survival at 30 days, assessed using the WHODAS 2 questionnaire [10, 11] will be the primary endpoint. The WHO assigns significant disability in presence of a WHODAS score of 25% [10, 11]. For calculation of the 12-item WHODAS score, the ordinal categories of Linkert scale for each item will be assigned numerical values (none=0 to extreme=4) for a total maximal score of 48 and transformed into the percentage of maximal disability score as published [19].

In EuPreCHO we will apply the definition of significant disability according to the WHO. (Note: while Shulman and co-workers [20] recently proposed WHODAS cut-off values specific for the postoperative setting, i.e. at 35%, these cut-offs have not been (extensively) externally validated, therefore EuPreCHO will use the WHO cut-off).

Secondary endpoints will be 30-day all-cause mortality, 30-day composite of all-cause death and myocardial infarction [21], 30-day major adverse cardiac events (cardiac death, myocardial infarction,

cardiac arrest, coronary revascularization [21], and acute heart failure/ decompensation of chronic heart failure). Of note the composite endpoint MACE also includes acute heart failure/decompensation of chronic heart failure that is not part of the MACE definition preferred by the Standardized Endpoints in Perioperative Medicine (StEP) initiative [21]. The decision to include acute /decompensated heart failure in the MACE composite was driven by the fact that preoperative TTE is conducted in a relevant proportion for heart failure evaluation and therefore the incidence of acute/decompensated heart failure is of particular relevance for the question addressed. Other secondary endpoint will include days-alive-and-out-of-hospital (DAOH) at 30 days[22] and in-hospital complications [23] with Clavien-Dindo Class ≥3 [9] . DAOH will be calculated as previously described DAOH at X days (DAOHx) is calculated from the day of the index procedure as: X- length of stay of index hospitalization (in days) – length of stay of any subsequent readmissions in days (including planned readmissions). If a patient died during the follow-up time X, his $DAOH_X$ will be set at 0 regardless of any time spent at home [22].Tertiary endpoint are ICU/IMC (re)-admission and length of ICU/IMC stay. For detailed definitions of the various endpoint, please refer to (Appendix 2). In the unlikely event of surgery cancellation, the patients will be followed-up 30 days after the decision to cancel the procedure.

Outcomes will be adjudicated by the local PI based on review of clinical documentation (charts and other relevant documents) using standardised definitions (Appendix 2). Adjudicators will be unaware of the preoprative availability or nonavailability of TTE information.

3.2.3 RQ3: what factors (model) enhance the prediction of major pathologies in preoperative TTE?

For the first question, our group of experts considered the following preoperative TTE findings as "major" pathologies in TTE, i.e., pathologies in preoperative TTE that may be reasonably expected to change perioperative management:

1) **Moderate-severe left ventricular systolic dysfunction**:
   - decreased contractility (LVEF ≤40% [24, 25] by Simpson's method or eyeballing) or based on corresponding qualitative statement in TTE report (e.g. "severe reduction"); and/or
   - any new (or previously undocumented) regional wall motion abnormalities (RWMA) on visual or myocardial strain analysis in conjunction with at least mildly reduced LVEF (41-49%) [24-26]

2) **Significant (Grade II or more) left ventricular diastolic function with signs of elevated filling pressures** defined by
   - E/A ratio >2 OR
   - E/A ratio <0.8 AND E>50cm/sec AND at least ≥ 2 additional criteria (Average E/e' ratio >14, peak TR velocity >2,8 m/sec, LA volume index >34 mL/m2) OR

- E/A ratio >0.8 to <2 AND at least ≥ 2 additional criteria (Average E/e' ratio >14, peak TR velocity >2,8 m/sec, LA volume index >34 mL/m2)) [27]
- OR corresponding diagnosis in the TTE report.

Of note only the most severe criteria, i.e criteria for patients with decreased LVEF and diastolic dysfunction plus increased LV filling pressures were used since in patients with normal LVEF because for this group of patients there is no grading of severity [27]

3) Significant right ventricular dysfunction

- RV failure phenotype defined septal flattening, paradoxical septal motion and a dilated IVC with no or small respiratory variations during spontaneous breathing
- Chronic cor pulmonale defined as a hypertrophic right ventricle with increased SPAP
- Acute cor pulmonale defined as a dilated RV (RV:LV>0.6) and paradoxical septal motion,
- Right ventricular failure defined as septal flattening, paradoxical septal motion and dilated inferior vena cava (IVC) with no or small respiratory variations during spontaneous breathing [28] OR
- acute RV dysfunction phenotype (defined as any one or more of tricuspid annular plane systolic excursion (TAPSE) <17mm, RV fractional area change <35%, RV free-wall strain, peak systolic (S') velocity of tricuspid annulus (<9.5 cm/s) measured with tissue Doppler, RV free wall strain > -20%) [29, 30] AND at least one sign of RV failure or increased SPAP [29] or based on corresponding diagnosis in TTE report.
- *Significant pulmonary hypertension* is defined as peak tricuspid regurgitant velocity >2.8m/sec + additional echocardiographic signs of RV dysfunction [29] or based on corresponding diagnosis in TTE report

4) Severe left sided valvulopathies

- Obvious anatomical abnormalities with colour Doppler suggesting major changes in flow [28]
- Severe mitral stenosis/regurgitation or severe aortic stenosis/regurgitation as defined by current ESC/EACTS guidelines [31]

The composite of these major pathologies will be the main dependent variable for RQ 3. This information will be extracted based on standardized definitions (Appendix 2) from TTE reports.

3.3 Other study variables

Exposures will include symptoms and clinical signs (dyspnoea, orthopnoea, chest discomfort, peripheral oedema, murmurs), clinical frailty scale [32, 33], cardiovascular history, renal function, self-reported functional capacity assessed using the ability to climb stairs [1] and level of regular physical activity assessed using the METREPAIR questionnaire [19] and preoperative troponin [7]. Where feasible, preoperative B-type natriuretic peptide [7] will also be collected (centres will be given the option to participate to the subcohort measuring preoperative B-type peptide at study inception).

Basic ECG information will be collected from clinically requested ECGs. The variables required to calculate the following scores will be collected from medical charts: RCRI [34], NSQIP MICA [35] and the AUB-HAS2 Cardiovascular Risk Index [36, 37].

4. PROJECT DESIGN

4.1 Type of research and general project design

EuPreCHO is a prospective, international, observational study. RQ3 (see 3.2) will be assessed in a cohort consisting of the exposed only. Any hospital in Europe or with comparable health care is welcome to participate as a study centre. Study centre registration occurs online via the dedicated "Call for Centres form" on the ESAIC EuPreCHO website. Eligibility to participation as centre will be assessed by the Sponsor and the SC under consideration of feasibility of the study protocol and administrative effort required (e.g single centre of limited size in a country where no other centres are registered). Final decisions in this regard rely with the Sponsor. **Centres will be asked to enroll a minimum of 50 exposed and 25 non-exposed subjects within the 12-month period planned for EuPreCHO enrollment**. Centres will need to conduct the study visits and collect study data including preoperative troponin, WHODAS, and 30-day follow-up.

Within the enrollment period, the start of recruitment for individual centres is at the discretion of the local PI, provided that there is a prior IRB approval. Recruitment across all centres will continue until enrollment of the planned sample size. After receiving IRB approval, it is mandatory that the study approval documentation coversheet is completed and signed by the Local PI and sent back to the ESAIC Research Department.

National coordinating investigators are anaesthesiologists/Intensivists or cardiologists appointed by ESAIC and the SC members to lead the project within individual countries and their responsibilities includes:

- Identify participating centres in their country and recruit local PIs in participating hospitals;
- Assist in the translation of study documents;
- Ensure that all necessary national or regional regulatory approvals are in place prior to start of patient inclusion;
- Assist and train the Local PI and monitor the conduct of the study according to GCP;
- Ensure good communication with ESAIC headquarters and the participating sites in his/her countries during all study steps including data cleaning.

Local PI are anesthesiologists, surgeons, or internal medicine or other specialists working in perioperative medicine in each participating institution who are responsible for the study at their centre. In particular, they will have the following responsibilities:

- Provide leadership for the study in their institution;
- Ensure all relevant regulatory/ethical approvals are in place for their institution;
- Ensure adequate training of all relevant staff prior to data collection;
- Supervise enrollment, daily data collection, and assist with problem solving;
- Adjudicate events
- Ensure timely completion of eCRF, follow-up assessments, and data cleaning queries. The Local PI is the main responsible for ensuring integrity of data collection. By signing the data on eCRF Local PI confirms the data integrity;
- Communicate with ESAIC headquarters and the relevant National Coordinating Investigator during all study steps including data cleaning.

4.2 **Procedures**

At screening day, usually during the preoperative evaluation by anaesthesiology, patients will be screened and informed. Patients will be given adequate time to reach a decision and asked if they are willing to give informed consent (for details see 2.4). If patients agree to participate in the study, and screening shows that they are eligible, they will be asked to complete the WHODAS questionnaire [10, 11] and, if clinically mandated blood samples are not available, blood (approx. 5 mL) will be sampled for preoperatively troponin measurement from the 'exposed' [1] (and where applicable for NTproBNP [1]). Relevant clinical data will also be collected (history of illness, planned operation, etc.). 'Exposed' will be defined as patients with TTE **up to 6 months before the date of surgery** (NOT up to 6 months of enrollment date). For procedures that are rescheduled i.e., date surgery was conducted was not equal to the initially scheduled date- a time window of **up to 8 months** will be accepted between TTE and surgery to define the exposure

At day 30 after surgery, patients will be contacted by mail or by phone for outcome assessment consisting in the WHODAS questionnaire and the collection of information on postoperative events (for details please refer to Appendix 2). The time window for follow-up may be extended up to day 51 (30+21) if the patient cannot be reached on the first attempt. Of note, follow-up can **NOT** be conducted before 30 days after surgery.

The choice on how to proceed to follow-up (mail vs phone) is at the discretion of the local PI, of note ESAIC will not cover stamp or phone cost. The figure in the Appendix 3 details the flow of study procedures.

4.3 Recruitment and Screening

Patients will be screened during their visit in the preoperative clinic. In addition, local PIs may also screen the surgical schedule of the upcoming days for eligible patients.

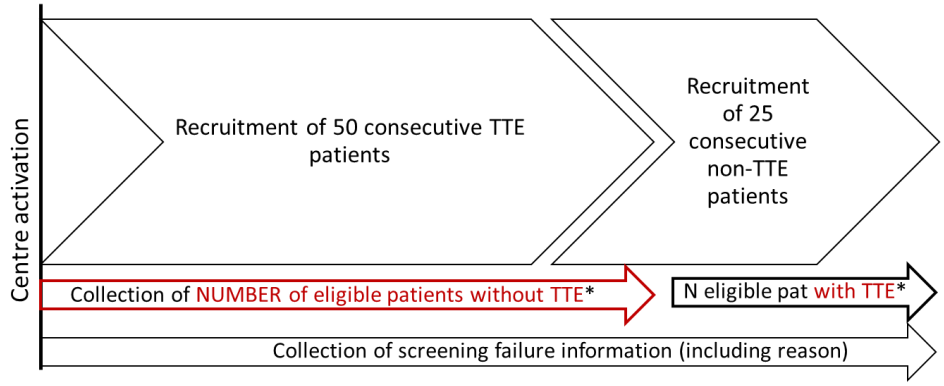
Recruitment will start with TTE patients (TTE recruitment period), i.e. centres will first only recruit consecutive exposed (TTE) patients until they reach their target number for exposed patients (50 patients) and thereafter enroll consecutive non-exposed patients (non-TTE recruitment period - 25 patients) to reach the 2:1 ratio (this sequence can be repeated) (see Figure). Centres are expected to switch to recruitment of non-exposed immediately after having enrolled their TTE patients to minimize temporal bias. Exception to the stepped recruitment may be made upon written request to the SC including extensive justification of why the local logistics do not allow for the proposed stepped recruitment. After careful consideration on a case-by-case basis, the steering Committee might approve the alternative approach.

It is mandatory for centres to keep screening logs (Appendix 4) to record the number of patients enrolled and not enrolled in the study, including the reason for non-enrollment (e.g. logistic issues or not consenting). Collecting information on the reason for non-enrolment is also essential for assessing selection bias and the STROBE flow chart. This screening log will be collected at the end of the recruitment period.

It is requested to specify for the TTE recruitment period the number of eligible patients that were not recruited because they did not undergo TTE within 6 months.

It is also requested to specify for the non-TTE recruitment period, the number of eligible patients that were not enrolled because they had received TTE.

Centres will be asked regularly to complete an online survey reporting the number of patients (TTE and non-TTE) recruited and non recruited. This report is essential to 1) monitor recruitment efficiency during the study and 2) assess the proportion of patients undergoing TTE in each centre.



*Centres will have different proportion of eligible patients submitted to TTE. To limit the burden for centres, we opted for a purposeful sampling in favor of TTE patients. For bias assessment it is of

UTMOST importance to quantify the proportion of eligible patients submitted to TTE in each centre. Therefore, it is mandatory to continuously collect information on the number of eligible patients non-submitted to TTE during the recruitment period of TTE patients and vice versa. This is done during screening. NOTE: *only the collection of the number is requested, not CRF completion.*

Of note, if a centre does not match the 2:1 ratio at the end of the study, for authorship rules only patients in a 2:1 ratio of TTE : non-TTE will be considered, e.g. a centre that enrolled 60 TTE and 50 non-TEE patients will be considered to have enrolled 60 TTE patients and 30 non-TTE patients (for details see 9.1.)

4.4 Methods to mitigate bias

EuPreCHO is an observational study and does not mandate preoperative TTE rather it collects the findings of clinically requested TTE. To meet the inherent selection bias, we will apply corresponding statistical approaches and monitor and document the proportion of conducted TTE in eligible patients across centres. Further, we will ask centres to provide information on the SOP/guidance documents they are using to regulate which patients are to be submitted to TTE and to provide common barriers for TTE conduction at their centres. To reduce attrition, study personnel will apply various communication channels of follow-up (postal, phone, social media as far as in accordance with data safety requirement). Using this approach, we previously reached >98% follow-up completeness at 30 days [38].

To mitigate the risk of assessment bias, all patients will be assessed by the same validated and simple questionnaire (12-item WHODAS 2) that requires approximately 5 (-10) minutes to complete [10, 11]. All data will be collected based on standardized definitions and categories. National PI and local PI will be trained in the definitions and will be asked to train their local personnel. Personnel assessing 30-day endpoints will not be aware of whether preoperative TTE has/has not been conducted.

5. PROJECT POPULATION

The target population consists of patients at elevated cardiovascular risk (for criteria see below) undergoing elective, intermediate or high-risk noncardiac surgery. The planned sample size is 5393 exposed and 2696 non-exposed (see sample size calculation, section 8.1.). Eligibility criteria are reported below.

5.1 Inclusion criteria

Patients planned to undergo elective, in-hospital intermediate or high-risk noncardiac surgery procedures according to the ESAIC guidelines [39] (Appendix 5) **AND**

- aged ≥65 years **OR**
- presenting ≥2 cardiovascular risk factors (hypertension, smoking, dyslipidaemia, diabetes, family history of CVD) **OR**
- with known cardiovascular disease

will be included.

Exposed will be patients fulfilling the inclusion criteria and in whom TTE was performed within 6 months before the date of surgery. Both TTE and focused TTE will be considered. ***Non-exposed*** will be patients fulfilling the inclusion criteria and in whom TTE was NOT performed within 6 months prior to surgery. If surgery is delayed, TTE should be performed not more than 8 months prior to surgery.

5.2 Exclusion criteria

- under 18 years of age
- day surgery
- urgent/emergency procedures
- current ICU patient (i.e. in ICU on day-1 or the day of the index surgery (day 0)),
- cardiac surgery within the last month prior to the index noncardiac procedure (**of note this does not include cardiological interventions like TAVI or valvuloplasty**),
- unwilling or unable to provide informed consent,
- unable to complete the WHODAS questionnaire (literacy or language barrier)
- Previous enrollment in EuPreCHO (in case of repeated surgery).

Of note, cancelled surgery does NOT represent an exclusion criterion and patients whose surgery was cancelled will be followed-up at 30 days after the decision to cancel the procedure.

Considering the minimal burden associated with participation (WHODAS questionnaire, one preoperative blood sample), participation in other studies does not preclude inclusion, provided the patient is consenting and the potentially concomitant inclusion is approved by the local IRB.

5.3 Criteria for withdrawal / discontinuation of participants

Due to the observational nature of the study, the protocol does not define any withdrawal/discontinuation criteria. Patients electing to withdraw from the study may do so at any point. In case of withdrawal from the study (procedures) no further data will be collected, while already collected, encoded data will be retained, and analysis may be performed up to the point of data collection. The planned sample size takes withdrawal and loss of follow-up into account as such withdrawn patients will not be replaced. However, the SC may decide upon potential extension of the recruitment period across centres, under consideration (among other) of the number of events already registered in the database at the relevant time point.

6. PROJECT ASSESSMENTS

6.1 Project flow chart(s) / table of procedures and assessments

Please see the figure in Appendix 3.

6.2 Assessments of endpoint outcome

The definitions and methods of assessment of the endpoints for the various RQs are detailed in 3.2.1-3.2.3.

6.3 Assessment of other study variables

The following data will be extracted from clinical charts by trained personnel: age, sex, weight, height, ASA classification, cardiovascular risk factors (hypertension, smoking, dyslipidaemia, diabetes, family history of CVD), relevant medical history, including symptoms and clinical signs (dyspnoea, orthopnoea, chest discomfort, peripheral oedema, murmurs), clinical frailty scale [32, 33], cardiovascular history, renal function, self-reported functional capacity assessed using the ability to climb stairs [1] and level of regular physical activity assessed using the METREPAIR questionnaire [19]. Basic ECG information will be collected (rhythms, conduction abnormalities (RBBB, LBBB), ischemic changes). Further, we will extract the variables for RCRI, NSQIP MICA, and AUB-HAS2 Cardiovascular Risk Index calculation, which includes information on the type (severity) and site of surgery.

For troponin, and where applicable NT-proBNP, measurement, blood will be collected preoperatively at the time of enrollment in the preoperative clinic or on the surgical ward at the time of clinically indicated blood samples. While not the preferred approach, sampling at the time of anesthesia induction will be accepted. Biomarkers will be analysed locally using the local high-sensitivity troponin and B-type natriuretic peptide assays. Centres will report the type of assay, the 99th percentile, and the actual concentration of the biomarkers. Since we expect that centres will use different assays, for analysis concentrations will be expressed as “multiples” of the 99th percentile of the relevant assay.

The decision to conduct the measurements daily or in batches is at the discretion of the local PI and local laboratory. In case of sample storage, storage temperature at –20°C is recommended. EuPreCHO does not plan storage of biological samples after measurement. The local laboratory will be responsible for sample destruction as per local practice after troponin (and where applicable NTproBNP) concentration has been measured and valid results have been obtained.

6.4 Assessment of safety and reporting

Study-related assessments in EuPreCHO are the completion of questionnaires and one preoperative blood sample (5 mL). As such, the potential for serious events appears too remote to justify systematic safety assessment and reporting.

7. STATISTICAL APPROACH

7.1 Determination of Sample Size

The sample size requirement for an independent cohort study assuming a probability of event in control group = 0.1 [20] , probability of event in experimental group = 0.08, with a controls per case subject = 0.5, Alpha = 0.05, Power = 0.8 are N = 4754 case subjects and 2377 controls for uncorrected chi-square test and N = 4903 case subjects and 2451 controls for corrected chi-square and Fisher's exact tests. Of note, the 2:1 exposed-to-non-exposed ratio (purposeful sampling) was chosen to reduce the burden for centres both in terms of data collection and in terms of preoperative biomarkers to be measured, while maintaining the power for the modelling to improve prediction of major pathologies in TTE (see below).

In a recent sample of patients at elevated cardiovascular risk (METREPAIR sample), 4.6% of patients submitted to TTE within 6 months before surgery presented an EF<40% and 6.6% severe valvular disease. Therefore, aiming for 500 patients with major pathologies in TTE to allow for robust multivariable modelling [40] and assuming a proportion of 10% of major pathologies in preoperative TTE, we will need to recruit 5000 patients submitted to preoperative TTE (exposed).

To account for loss of follow-up and missing data, we will aim at recruiting 5393 exposed and 2696 non-exposed (each+10% of planned sample size calculated for corrected chi-squared (RQ2) and +8% for the sample size estimated for RQ3 since RQ3 does not imply postoperative follow-up).

7.2 Data processing

In RQ 2, we expect DAOH to be non-normally distributed. We will not log transform the data, rather we will apply regression methods suitable for the non-normal distribution (quartile regression or zero-inflated beta-binomial regression, see below). For RQ 3 preoperative troponin concentrations will be modelled continuously and dichotomized at the 99th percentile.

7.3 Planned analyses

7.3.1 RQ1: does the perioperative management of patients evaluated with vs those not evaluated with preoperative TTE differ in current clinical practice?

We will report descriptive statistics as counts (percentages) for non-continuous data. Mean (standard deviation) or median (interquartile range) as appropriate will be used for continuous data. The impact of TTE (main independent variable) on the perioperative management will be assessed using multilevel logistic regression (hospital as cluster). Independent variables will include age, sex, ASA classification, the severity and site of surgery, frailty, functional capacity, history of cardiovascular disease (coronary artery, heart failure, stroke/TIA, peripheral vascular disease), chronic pulmonary disease, and renal failure (main analysis). In sensitivity analyses, these clinical

factors will be substituted by clinical risk scores (RCRI, NSQIP MICA, AUB-HAS2 Cardiovascular Risk Index).

As alternative statistical approach (sensitivity analyses), we will calculate the propensity score for TTE conduction using logistic regression and insert it as a covariate in a logistic regression model, both bivariately and multivariately (double robust).

A subgroup analysis in non-rescheduled patients will assess the impact of timeline between TTE and surgery with the hypothesis that more recent TTE results in more changes in intraoperative management or triage to IMC/ICU admissions.

7.3.2 RQ2: does the outcome of patients evaluated with vs those not evaluated with preoperative TTE differ in current clinical practice?

We will report descriptive statistics as counts (percentages) for non-continuous data. Mean (standard deviation) or median (interquartile range) as appropriate will be used for continuous data.

To evaluate the association between TTE conduction and 30-day outcomes, we will conduct multilevel logistic regression (hospital as cluster). Main independent variable will be the conduction/nonconduction of TTE. Other independent variables will include age, sex, ASA classification, the severity and site of surgery, frailty, history of cardiovascular (coronary artery, heart failure, stroke/TIA, peripheral vascular disease), chronic pulmonary disease, cancer and renal failure (main analysis). In sensitivity analyses, these clinical factors will be substituted by clinical risk scores (RCRI, NSQUIP MICA, AUB-HAS2 Cardiovascular Risk Index). For sensitivity analyses, p-value will be corrected for multiple analyses.

As alternative statistical approach (sensitivity analyses), we will calculate the propensity score for TTE conduction using logistic regression and insert it as a covariate in a logistic regression model, both bivariately and multivariately (double robust).

A non-normal distribution of DAOH is expected. Moreover, the distribution of DAOH may differ depending on the target population [41-44] .Therefore, a quantile regression, an established method in the literature on DAOH [22, 45, 46], will be the primary approach. Since according to Baldwin et al [47]: “there is always a risk that data will violate the assumptions” if required, DAOH may be alternatively modelled by zero-inflated beta-binomial regression, which is another common tool for DAOH investigation [42, 43, 48].

7.3.3. RQ3: what factors (model) enhance the prediction of major pathologies in preoperative TTE?

Only patients with TTE will be analysed. We will report descriptive statistics as counts (percentages) for non-continuous data. Mean (standard deviation) or median (interquartile range) as appropriate will be used for continuous data.

To establish a model for improving prediction of major pathological findings (binary outcome) in preoperative TTE, we will conduct multivariable logistic regression with predefined covariates. They will include symptoms and clinical signs (dyspnoea, orthopnoea, chest discomfort, peripheral oedema, murmurs), ECG abnormalities, clinical frailty scale [32, 33], cardiovascular history, renal function, self-reported functional capacity assessed using the ability to climb stairs [1] and level of regular physical activity assessed using the METREPAIR questionnaire [19] and preoperative troponin [7] (for B-type natriuretic peptide see below).

Model performance will be primarily assessed using the area under the curve (AUC) of the Receiver Operation Characteristic (ROC) curve. We will test for AUC superiority using the DeLong test for two correlated ROC curves [49]. The model will be internally validated using optimism-corrected concordance index performance (AUC), mean Brier score, and calibration intercept and slope. Model internal validation will be performed using bootstrap resampling methods at the cluster level (hospital) [50]. Decision curves will be calculated to provide an additional tool to assess predictive performance for comparison of the proposed model with the selection approach proposed by the ESC 2022 guidelines.

As alternative approach (sensitivity analysis), we will use classification and regression tree analysis to maximize of diagnostic odds ratio for pathological findings or other machine learning approaches.

Should the numbers of focused TTE be sufficient, we will conduct subgroup analyses in standard vs focused TTE.

Datasets to be analysed

All participating patients will be analysed as far as complete data for the specific research question (RQ1-3) are available. As such, we expect datasets for the different RQ to slightly differ. It may therefore become necessary to present baseline characteristics separately for the different RQ. Characteristics of patients with missing data (therefore excluded from the specific analysis) will be reported.

Handling of missing data

We will not impute missing data.

Ancillary analysis

Sensitivity and subgroup analyses

For each RQ1 and RQ2, we will conduct the following ancillary analyses:

- multilevel logistic regression modelling using clinical scores (each RCRI, NSQIP MICA, AUB-HAS2 Cardiovascular Risk Index) instead of the clinical risk factors (for details see above)
- propensity score calculation for TTE conduction and its introduction in the model (for details see above).

- should the numbers of focused TTE be sufficient, we will conduct subgroup analyses in standard vs focused TTE
- in non-rescheduled patients will assess the impact of timeline between TTE and surgery with assumption more recent TTE results in more changes in intraoperative management and triage to ICU admissions within the group of patients with TTE, we assess if outcome differs between patients with and without intensified perioperative management.

For RQ3, as sensitivity analysis, we will use classification and regression tree analysis to optimize patient selection for TTE (maximization of diagnostic odds ratio) or other machine learning approaches.

Secondary objectives

We will then compare model characteristics (AIC, ORs, decision analysis curves) and area under the ROC curve (de Long) of the main model vs the alternative model based on NTproBNP.

Tertiary objectives

We will compare model characteristics (AIC, ORs, decision analysis curves) and area under the ROC curve (de Long) of RCRI+age+information on pathologies detected by TTE vs RCRI+age+preoperative Troponin vs RCRI+age +NTproBNP for the prediction of 1) disability-free survival and 2) MACE at 30 days (provided that the number of events is sufficient). As a sensitivity analysis, we will replace the RCRI by the NSQIP MICA score as baseline model.

Deviations from the original statistical plan

We will state and justify any potential deviation from this initial analysis plan in the manuscript.

8. DATA AND QUALITY MANAGEMENT

8.1 Data quality

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirements.

Quality control measures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly, including written guidelines (in English for all countries) for data collection and entry, automated consistency checks, and training of National Coordinating Investigator and local PI. It will be responsibility of the National Coordinating Investigator, with support by the study coordinating office, to train local PI. Local PI will ensure that the data in the eCRF is carefully entered and verified regularly. It will be the responsibility of local PIs to conduct periodic and random checks to ensure data quality in her/his centre. On-site monitoring visits by the Sponsor are not planned.

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related sites, source data/documents and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities. Any agreements, made by the Sponsor with the investigator/institution and any other parties involved with the study, will be in writing in a separate agreement. No fee or financial compensation is given to PI and/or participating institution for patient recruitment.

8.2 **Data handling and record keeping / archiving**

Data will be entered into a secure on-line database protected by personal usernames and passwords and documenting the time and individual entering the data. The user should keep their log in details confidential. The language of the online database, eCRF, and the relative SOPs is English. Data will be collected directly from source documents and can be entered first into the encoded paper CRF (Appendix 6) or can directly entered into the eCRF. A copy of the original source documents will be stored within a locked cabinet/office accessible to authorised personnel only in accordance with local and national regulations.

An identifiable patient data page reporting the assigned patient identification code will be stored separately also in a locked cabinet/office (accessible to authorised personnel only) in order to record in-hospital outcomes, supply missing data points, and to allow potential monitoring visits by National Coordinating Investigators, Sponsor, IRB, or regulatory authorities. Signed ICFs which document that written informed consent was obtained prior to enrollment will be stored as described above. All local study documents will be archived as required by local legislation. Data will be stored 25 years in the central database. At the end of this period, the data will be destroyed or anonymized. Blood samples will not be stored after measurement and will be destroyed locally as per local practice by the laboratory.

8.3 **Confidentiality, Data Protection**

To safeguard patients' confidentiality, a patient identification code will be assigned to encode data. The confidential log linking patient identification code and identifiable patient data will be stored separately in a locked cabinet accessible to authorised personnel only and corresponding electronic files will be protected by personalised and confidential usernames and passwords. eCRF are identified through the patient identification code and will not include any names, initials, date of birth, or local hospital patient numbers; therefore, no patient identifiable data will be directly accessible from the eCRF. Data protection will be guaranteed through encoding and the use of a secured database with restricted access by individual log-in and gradated user rights. Only encrypted data will be stored centrally. The database will be hosted on servers physically located in the European Union and data can only be transferred to servers located in member States of the European Union or in other

countries where the level of personal data protection has been determined as adequate by the European Commission on the basis of the General Data Protection Regulation (GDPR, Article 45). Open direct access to all relevant trial information as well as source data/documents will be permitted for purposes of monitoring, audits or inspections to the Sponsor, national coordinators, IRB, or regulatory authorities. All handling of personal data will comply with the GDPR(EU) 2016/679, GCP Guidelines, and follow strictly the legal and applicable national requirements for data protection. All study documents will be submitted to the local data safety officer for approval.

The Sponsor may apply additional requirements, where applicable even if they are not expressly listed above.

9. PUBLICATION AND DISSEMINATION POLICY

9.1 Publication of results

The main results of EuPreCHO will be published in peer–reviewed international medical journals and presented at Euroanaesthesia and at national meetings. We plan to publish the findings of RQ 1 and 2 together in a paper and the results of RQ3 in a separate paper. As recommended by the International Committee of Medical Journal Editors (Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals, updated version 2023, https://www.icmje.org/icmje-recommendations.pdf accessed November 10th 2023) authorship will be considered based on:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or reviewing it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Members of the SC and other particularly committed investigators (see below) that fulfill those criteria will be part of the Writing Group. Draft and submitted manuscript will be shared within the Writing Group only. The members of the Writing group, named individually (=personal author name), and the group author name “EuPreCHO Investigators” will be authors of the publications. All individual authors have to meet all four criteria for authorship, including approval of the final manuscript, ability to take public responsibility for the work and full confidence in the accuracy and integrity of the work of other group authors. They will also be expected as individuals to complete disclosure form.

When submitting a manuscript, the corresponding author will include the group author name “EuPreCHO Investigators” as author in the byline. Since the group author name “EuPreCHO

Investigators" is included in the byline as author and the individual names of the investigators are reported at the end of the paper or in an appendix, MEDLINE will list the individual names of the group members . We will put every effort to ensure that all EuPreCHO Investigators will be considered as co-authors. However, depending on the policy of the journal, it may not be possible to define all members of the group author "EuPreCHO Investigators" as co-authors, as such contribution to data collection may only qualify to collaboratorship.

Each participating centre with 50 exposed and 25 non-exposed valid study subjects can designate one investigator to be mentioned in the publication(s). The enrollment of ≥ 80 exposed and 40 non-exposed and of ≥ 100 exposed and 50 non-exposed will entitle to 2 and 3 mentioned investigators, respectively. Centres recruiting ≥150 exposed and ≥75 non-exposed qualify for 4 investigators. Centres enrolling ≥200 exposed and 100 non- exposed will designate 1 member of the writing committee and 4 investigators (≥300 exposed and 150 non-exposed 2 members of the writing committee and 5 investigators) (see Table below).

Number of valid exposed patients (patients with TTE in the last 6 mt)	Number of valid non-exposed patients (patients without TTE in the last 6 mt)	Number of investigators reported under the group name "EuPreCHO Investigators" in the byline and individually at the end of the paper	Number of investigators with personal author name in the byline
50	25	1	0
80	40	2	0
100	50	3	0
150	75	4	0
200	100	4	1
300	150	5	2

Of note, the reported figures imply not only inclusion, but also completed data entry, and adequate answer to the queries for data consistency. **NOTICE: If a centre does not match the 2:1 ratio at the end of the study, for authorship rules only patients in 2:1 ratio of TTE:non TTE will be considered.**

If the number of recruited patients from a centre is too low to justify sufficient active involvement for co-authorship, the SC may decide on the legitimacy of authorship based on other contributions. The final decision will be left to the SC in consultation with the ESAIC. The local PI will be asked to submit names of staff actively involved from their institution in the End of Study Reporting Form (Appendix 7).

Presentation at international meetings will be restricted to the members of the SC or their delegates. National Coordinators will qualify for presentation at national meetings after approval by the SC and the Sponsor. ESAIC Clinical Trial Network will be acknowledged in all publications and presentations.

9.2 **Secondary analyses, nested substudies, and data sharing**

After database closure, the main publication(s) (RQ1-2 and separately RQ3) will be published within 4 years. After publication of the pooled results in the main publications, centres upon request will be allowed to use their own pseudonymised data for local presentation and publication. Duplicate data publication is not permitted.

The pseudonymised pooled dataset may be available for secondary analyses upon specific request in form of a detailed study proposal (including authorship rules) to the SC. The final approval of these potential secondary analyses rests with the SC. Prior to journal submission, any paper originating from the pooled data will be reviewed by the SC that is also entitled to require revisions. Authorship of any publication derived from the pooled data set will include the group name “EuPreCHO Investigators” and acknowledge the ESAIC as Sponsor and as such require approval by ESAIC. For transparency, the original paper(s) have to be referenced to in all articles of secondary analyses.

Local or national nested cohorts addressing additional questions, i.e., question not addressed in EuPreCHO, and collecting additional data while sharing part of the variables collected EuPreCHO, are allowed under the following conditions: nomination of a separate Sponsor (i.e., other than the ESAIC), separate ethical approval, separate informed consent, independent data management, and approval of a detailed study proposal by the SC. The Sponsor and the SC have the right to veto the nesting of a study into EuPreCHO. The publication of any study nested within EuPreCHO will occur after publication of the main results (RQ 1-2 and RQ3). For transparency, the original paper(s) should be referenced to in all articles of nested analyses. Authorship rules for potential publications derived from such nested cohort studies are to be submitted to the Sponsor and SC together with the study proposal.

Requests for data sharing for individual-level meta-analyses are to be addressed to the Sponsor and SC.

The Sponsor of the study (ESAIC CTN) can use anonymised pooled data for internal analyses, future research purposes and educational purposes.

9.3 **Data ownership and Transfer of data- EU/non-EU**

ESAIC is the owner of the pseudonymised pooled dataset of the study. Data can be transferred to another country (EU/non-EU) for future research purposes. ESAIC will ensure that either the country that receive the encoded- data is recognized as having an adequate level of data protection or appropriate safeguards will be put in place.

10. FUNDING AND SUPPORT

EuPreCHO is funded by a grant from the ESAIC CTN. The submission for national or local peer-reviewed grants to fund national or local implementation of the study is allowed conditional on prior written authorization from the Sponsor and the SC. Additional financial support, including from Industry, may be received for the study. This support would be organised by the Chief Investigators and may include the provision of laboratory kits (including shipment to/from local sites) at no cost to the Sponsor or sites. Any support that is received would not be in return for the Sponsor providing any service or good and is conditional on the written agreement from the Sponsor and the steering committee and in line with local regulations.
The SC members declare not to have any conflicts of interest (a declaration of conflict of interest will be signed by each SC member and kept by the Sponsor).

11. INSURANCE

EuPreCHO is a minimal-risk, observational study. Participant insurance might be required based upon individual agreement between local PIs and the relevant institutional legal department (see “2.7 Participants´ insurance”). The ESAIC has Public Liability insurance in place to cover the legal liability of the ESAIC as Sponsor in the eventuality of harm to a research participant arising from management of the research by the ESAIC, i.e., it specifically refers to data management and safety.
Of note, any clinical or data safety negligence on the part of its staff remains a responsibility of the centre.

12. REFERENCES

1. Halvorsen, S., et al., *2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery.* Eur Heart J, 2022. **43**(39): p. 3826-3924.
2. AbuSharar, S.P., L. Bess, and E. Hennrikus, *Pre-operative echocardiograms in acute fragility hip fractures: How effective are the guidelines?* Medicine (Baltimore), 2021. **100**(12): p. e25151.
3. Canty, D.J., et al., *One-year results of the pilot multicentre randomised trial of preoperative focused cardiac ultrasound in hip fracture surgery.* Anaesth Intensive Care, 2019. **47**(2): p. 207-208.
4. Chang, H.Y., W.T. Chang, and Y.W. Liu, *Application of transthoracic echocardiography in patients receiving intermediate- or high-risk noncardiac surgery.* PLoS One, 2019. **14**(4): p. e0215854.
5. Levitan, E.B., et al., *Pre-operative echocardiography among patients with coronary artery disease in the United States Veterans Affairs healthcare system: A retrospective cohort study.* BMC Cardiovasc Disord, 2016. **16**(1): p. 173.
6. Pallesen, J., et al., *The effects of preoperative focused cardiac ultrasound in high-risk patients: A randomised controlled trial (PREOPFOCUS).* Acta Anaesthesiol Scand, 2022. **66**(10): p. 1174-1184.
7. Tank, A., et al., *Evaluation of Appropriate Use of Preoperative Echocardiography before Major Abdominal Surgery: A Retrospective Cohort Study.* Anesthesiology, 2021. **135**(5): p. 854-863.
8. Wijeysundera, D.N., et al., *Association of echocardiography before major elective non-cardiac surgery with postoperative survival and length of hospital stay: population based cohort study.* BMJ, 2011. **342**: p. d3695.
9. Clavien, P.A., et al., *The Clavien-Dindo classification of surgical complications: five-year experience.* Ann Surg, 2009. **250**(2): p. 187-96.
10. TB, Ü., et al., *Measuring Health and Disability: Manual for WHO Disability Assessment Schedule (WHODAS 2.0)* 2010, World Health Organization 2010: Geneva
11. Ustun, T.B., et al., *Developing the World Health Organization Disability Assessment Schedule 2.0.* Bull World Health Organ, 2010. **88**(11): p. 815-23.
12. Rose, J., et al., *Estimated need for surgery worldwide based on prevalence of diseases: a modelling strategy for the WHO Global Health Estimate.* Lancet Glob Health, 2015. **3 Suppl 2**: p. S13-20.
13. Nepogodiev, D., et al., *Global burden of postoperative death.* Lancet, 2019. **393**(10170): p. 401.
14. Puelacher, C., et al., *Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization.* Circulation, 2018. **137**(12): p. 1221-1232.
15. Writing Committee for the, V.S.I., et al., *Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery.* JAMA, 2017. **317**(16): p. 1642-1651.
16. Puelacher, C., et al., *Long-term outcomes of perioperative myocardial infarction/injury after non-cardiac surgery.* Eur Heart J, 2023.
17. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study, I., et al., *Association between complications and death within 30 days after noncardiac surgery.* CMAJ, 2019. **191**(30): p. E830-E837.
18. Schweizer, R., M. Jacquet-Lagreze, and J.L. Fellahi, *Implementation of 2022 ESC guidelines for cardiovascular assessment before non-cardiac surgery: Major concerns to meet in the near future!* Eur J Anaesthesiol, 2023. **40**(6): p. 385-386.
19. Shulman, M.A., et al., *Measurement of disability-free survival after surgery.* Anesthesiology, 2015. **122**(3): p. 524-36.
20. Shulman, M.A., J. Kasza, and P.S. Myles, *Defining the Minimal Clinically Important Difference and Patient-acceptable Symptom State Score for Disability Assessment in Surgical Patients.* Anesthesiology, 2020. **132**(6): p. 1362-1370.
21. Beattie, W.S., et al., *Systematic review and consensus definitions for the Standardized Endpoints in Perioperative Medicine (StEP) initiative: cardiovascular outcomes.* Br J Anaesth, 2021. **126**(1): p. 56-66.
22. Myles, P.S., et al., *Validation of days at home as an outcome measure after surgery: a prospective cohort study in Australia.* BMJ Open, 2017. **7**(8): p. e015828.
23. Domenghino, A., et al., *Consensus recommendations on how to assess the quality of surgical interventions.* Nat Med, 2023. **29**(4): p. 811-822.
24. Authors/Task Force, M., et al., *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC.* Eur J Heart Fail, 2022. **24**(1): p. 4-131.
25. McDonagh, T.A., et al., *2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.* Eur Heart J, 2023. **44**(37): p. 3627-3639.

26. Knuuti, J., et al., *2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.* Eur Heart J, 2020. **41**(3): p. 407-477.
27. Nagueh, S.F., et al., *Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.* J Am Soc Echocardiogr, 2016. **29**(4): p. 277-314.
28. Robba, C., et al., *Basic ultrasound head-to-toe skills for intensivists in the general and neuro intensive care unit population: consensus and expert recommendations of the European Society of Intensive Care Medicine.* Intensive Care Med, 2021. **47**(12): p. 1347-1367.
29. Humbert, M., et al., *2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.* Eur Heart J, 2022. **43**(38): p. 3618-3731.
30. Lang, R.M., et al., *Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.* J Am Soc Echocardiogr, 2015. **28**(1): p. 1-39 e14.
31. Vahanian, A., et al., *2021 ESC/EACTS Guidelines for the management of valvular heart disease.* Eur Heart J, 2022. **43**(7): p. 561-632.
32. McIsaac, D.I., et al., *Prospective Comparison of Preoperative Predictive Performance Between 3 Leading Frailty Instruments.* Anesth Analg, 2020. **131**(1): p. 263-272.
33. Rockwood, K., et al., *A global clinical measure of fitness and frailty in elderly people.* CMAJ, 2005. **173**(5): p. 489-95.
34. Lee, T.H., et al., *Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery.* Circulation, 1999. **100**(10): p. 1043-9.
35. Gupta, P.K., et al., *Development and validation of a risk calculator for prediction of cardiac risk after surgery.* Circulation, 2011. **124**(4): p. 381-7.
36. Dakik, H.A., et al., *A New Index for Pre-Operative Cardiovascular Evaluation.* J Am Coll Cardiol, 2019. **73**(24): p. 3067-3078.
37. Dakik, H.A., et al., *AUB-HAS2 Cardiovascular Risk Index: Performance in Surgical Subpopulations and Comparison to the Revised Cardiac Risk Index.* J Am Heart Assoc, 2020. **9**(10): p. e016228.
38. Lurati Buse, G.A., et al., *Risk assessment for major adverse cardiovascular events after noncardiac surgery using self-reported functional capacity: international prospective cohort study.* Br J Anaesth, 2023.
39. De Hert, S., et al., *Pre-operative evaluation of adults undergoing elective noncardiac surgery: Updated guideline from the European Society of Anaesthesiology.* Eur J Anaesthesiol, 2018. **35**(6): p. 407-465.
40. Bagley, S.C., H. White, and B.A. Golomb, *Logistic regression in the medical literature: standards for use and reporting, with particular attention to one medical domain.* J Clin Epidemiol, 2001. **54**(10): p. 979-85.
41. Ariti, C.A., et al., *Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program.* Am Heart J, 2011. **162**(5): p. 900-6.
42. Lopes, R.D., et al., *Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial.* JAMA, 2021. **325**(3): p. 254-264.
43. Reilly, J.R., et al., *Hospital costs and factors associated with days alive and at home after surgery (DAH(30)).* Med J Aust, 2022. **217**(6): p. 311-317.
44. Wu, A., et al., *An evaluation of the outcome metric 'days alive and at home' in older patients after hip fracture surgery.* Anaesthesia, 2022. **77**(8): p. 901-909.
45. Jerath, A., et al., *Socioeconomic Status and Days Alive and Out of Hospital after Major Elective Noncardiac Surgery: A Population-based Cohort Study.* Anesthesiology, 2020. **132**(4): p. 713-722.
46. Jerath, A., P.C. Austin, and D.N. Wijeysundera, *Days Alive and Out of Hospital: Validation of a Patient-centered Outcome for Perioperative Medicine.* Anesthesiology, 2019. **131**(1): p. 84-93.
47. Baldwin, J.R., et al., *Protecting against researcher bias in secondary data analysis: challenges and potential solutions.* Eur J Epidemiol, 2022. **37**(1): p. 1-10.
48. Chen, Y., J. Lawrence, and N. Stockbridge, *Days alive out of hospital in heart failure: Insights from the PARADIGM-HF and CHARM trials.* Am Heart J, 2021. **241**: p. 108-119.
49. DeLong, E.R., D.M. DeLong, and D.L. Clarke-Pearson, *Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach.* Biometrics, 1988. **44**(3): p. 837-45.
50. Bouwmeester, W., et al., *Internal validation of risk models in clustered data: a comparison of bootstrap schemes.* Am J Epidemiol, 2013. **177**(11): p. 1209-17.

13. LIST OF APPENDICES

Appendix 01. Information sheet and Consent form

Appendix 02. Endpoint definition

Appendix 03. Flow chart of study assessment

Appendix 04. Screening Log

Appendix 05. List of procedural risk for common procedures

Appendix 06. Case Report Form

Appendix 07. End of study Report Form

14. PROTOCOL CHANGES HISTORY

Version Number	Change #	Page	Section	Description of changes