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Faculty of Medicine

Department of Clinical
Research (DCR)

CTU Bern

Statistical Analysis Plan

Study title: Effects of hemodynamic monitoring using the ImaCor single use transesophageal echocardiography probe in critically ill patients - a randomized controlled trial

Study acronym: ImaCorII

CTU project number: 0350

ClinicalTrials.gov identifier: NCT02048566

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Change history:

Version	Date	Major changes

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1. Purpose

This statistical analysis plan (SAP) describes detailed aspects of data preparation and analysis, and was setup before starting the final analysis. The SAP is based on the final study protocol (Version 4.0, January 2018).

2. Study synopsis

The summary of the protocol is only available in German, and will thus not be copied in the SAP.

Hypothesis: The study hypothesis is that hemodynamic monitoring using hTEE in critically ill patients with hemodynamic compromise allows for an expedited reversal of circulatory impairment compared to standard ICU monitoring.

Primary Objective*: To assess the impact of hemodynamic monitoring using the ImaCor ClariTEE technology on time to reversal of shock in hemodynamically compromised patients in comparison to standard monitoring.

Secondary Objective: To assess the safety and tolerability of the ImaCor ClariTEE probe.

Study design: Open-label, randomized controlled, single-centre trial. Subjects will be randomized into four groups in a two by two factorial study design. Assessed factors are the method of monitoring (use of hTEE monitoring vs. conventional monitoring) and the frequency of monitoring (use of per-protocol intervals for hemodynamic assessment vs. standard assessment intervals).

Primary outcomes: Time to resolution of hemodynamic instability defined as systemic mean blood pressure (MAP) > 60mmHg for at least 4 hours after discontinuation of vasopressors or inotropes. The criterion is considered fulfilled if >90% of MAP measurements occurring every 1-2 minutes is > 60mmHg for a 4 hour period.

Secondary outcomes: Time to death. Time to resolution of clinical signs of hypoperfusion as a composite of capillary refilling time < three seconds, urine output > 0.5 mL/kg/h for at least 4 hours, and blood lactate < 2 mmol/L. Use of pulmonary artery catheter (yes/no), central venous catheter (yes/no), or conventional echocardiography (yes/no). Occurrence of adverse events assumed to be due to prolonged hemodynamic impairment and treatment with vasopressors/inotropes (as binary yes/no outcomes): cardiac arrhythmias, excessive vasoconstriction, and secondary infections.

Please see the protocol (Version 4.0, January 2018) for a detailed description of the study.

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3.   Study objectives

3.1.   Primary objective

The primary objective of the study is to assess the impact of hemodynamic monitoring using the hTEE technology on time to reversal of circulatory shock in hemodynamically compromised patients in comparison to standard monitoring.

3.2.   Secondary objectives

Secondary objectives include the assessment of safety and tolerability of the hTEE probe.

4.   Study design

4.1.   General design

This is an open-label, randomized controlled, single-center trial. The study follows a two by two factorial design. Subjects are randomized into four groups: Use of hTEE monitoring vs. conventional monitoring, and use of per-protocol intervals for hemodynamic assessment vs. standard assessment intervals.

4.2.   Sample size

Sample size calculation is based on a retrospective analysis of a sample of 159 patients admitted to ICU of Inselspital Bern during a three-month period, which fulfilled the study entry criteria. Median time to resolution of hemodynamic instability as defined by discontinuation of vasopressors or inotropes in this sample was 18.5 hours. We used the Stata command artsurv to calculate the sample size (Barthel et al). We applied the unweighted logrank test and derived expected probabilities of hemodynamic stabilization and loss-to-follow up (i.e. death) over time from the retrospective analysis. To identify a clinically relevant reduction of time to resolution of hemodynamic instability of 25% (i.e. from 18.5 to 14.0 hours) we calculated a required sample size of 458 patients to achieve a power of 80% at a two-sided alpha level of 0.05 for the main effect (comparison of monitoring with/without hTEE). To account for an estimated drop-out rate of 10%, we choose a sample size of 125 patients for each of the four groups or 500 patients in total.

4.3.   Randomization

Subjects were randomized to a total of four groups by block randomization using sequentially numbered, identical, opaque, letter-sized, sealed envelopes, selecting a block size of four.

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Due to logistical reasons (2 hTEE devices available for the study) inclusion of a maximum of
two patients into the groups applying hTEE was possible at the same time. Randomization
and recruitment was therefore interrupted as soon as a second patient has been randomized
into a treatment group in which hTEE was applied to preserve allocation concealment.
Randomization and recruitment have been restarted as soon as at least one hTEE device
has been available for further patients.

4.4. Blinding

This is an open-label study, as the method used cannot be concealed from the physician.
The patient is usually not in a condition to realize the treatment he is assigned to. The
physician assessing stability of the patient is not blinded to the treatment of the patient, or to
additional information available like conventional monitoring.

The trial statistician will not be blinded. Blinding of the statistician would not be feasible,
because the trial is open-label and the database contains information on the study arm in
several forms.

5. Hypothesis

The primary study hypothesis is that hemodynamic monitoring using hTEE in critically ill
patients with hemodynamic compromise allows for an expedited reversal of circulatory
impairment compared to standard ICU monitoring. The secondary hypothesis is that more
frequent monitoring results in shorter reversal of hemodynamic shock as compared to
standard monitoring.

6. Study endpoints

6.1. Primary endpoints

The primary study outcome is the time from study inclusion to resolution of circulatory shock.

- Time to resolution of hemodynamic instability defined as systemic mean blood
  pressure (MAP) > 60mmHg for at least 4 hours after discontinuation vasopressors or
  inotropes (dobutamine, milrinone, norepinephrine or epinephrine). The criterion is
  considered fulfilled if >90% of MAP measurements (occurring every 1 - 2 minutes) is
  > 60mmHg for a 4 hour period.

6.2. Secondary endpoints

- Time to death

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- Time to resolution of clinical signs of hypoperfusion as a composite of capillary refilling time < three seconds, urine output > 0.5 mL/kg/h for at least 4 hours, and blood lactate < 2 mmol/L.
- Use of conventional hemodynamic monitoring (3 binary endpoints):
  - pulmonary artery catheter (yes/no),
  - central venous catheter (yes/no),
  - conventional echocardiography (yes/no)
- Occurrence of adverse events assumed to be due to prolonged hemodynamic impairment and treatment with vasopressors/inotropes (as binary yes/no outcomes):
  - cardiac arrhythmias: non sustained ventricular tachycardia (≥ 4 beats), sustained ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter, other supraventricular tachycardia, new onset AV block (I/II/III), or asystole,
  - Excessive vasoconstriction: occurrence of acute myocardial infarction, skin necrosis, or secondary bowel or limb ischemia or stroke,
  - Secondary infections (catheter related infections, VAP, new onset of sepsis).

6.3.   Further outcomes of interest

Following outcomes will only be analysed descriptively:

- Length of time with need for organ support (mechanical ventilation, renal-replacement therapy)
- Length of stay (LOS) in the ICU
- LOS in hospital
- Death during ICU admission
- Death during hospital admission

6.4.   Safety endpoints (specific for use of hTEE only)

Occurrence of complications potentially attributed to the use of hTEE

  - Oral, pharyngeal, esophageal or gastrointestinal bleeding or injury
  - Need for additional sedation and/or muscle relaxants for hTEE probe placement and hTEE assessment

7.   Data management

7.1.   Data export

Clinical study data are in a database format (REDCap) and will be imported into R by the trial statistician for data preparation, validation and analysis. The database system was set up by the investigators, and thus contains no data validation and error checks.

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7.2. Data validation

All variables used in the analysis, including the derived variables, will be checked for missing values, outliers, and inconsistencies and queried.

7.3. Data preparation

The primary endpoint will be derived as the difference in hours between the date and time of randomization and the date and time of resolution of clinical shock. The competing risk of death for the primary outcome will be derived as the difference in hours between the date and time of randomization and the date and time of discontinuation of therapy before death.

Secondary and further endpoints will be derived as follows:

- Time to death (in hours) will be derived as the difference in hours from randomization to discontinuation of therapy before death.
- Time to resolution of clinical signs of shock will be derived as the difference in hours from randomisation to the latest time of any of the three: first lactate below 2 mmol/L, urine output above 0.5 ml/kg body weight or first capillary refilling time below three seconds
- Pulmonary artery catheter is yes if it was yes during any assessment
- Central venous catheter is yes if it was yes during any assessment
- Conventional echocardiography will be regarded as yes if TEE or TTE was used during any assessment
- Cardiac arrhythmias will be derived from any non sustained ventricular tachycardia (≥ 4 beats), sustained ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter, other supraventricular tachycardia, new onset AV block (I/II/III), or asystole
- myocardial infarction, skin necrosis, and stroke will be taken as is
- secondary bowel or limb ischemia will be derived from any bowel ischemia or any limb ischemia
- secondary infections will be derived from any catheter infection, VAP infection or sepsis
- Length of time with organ support (in hours) will be derived from length of time with mechanical ventilation and/or renal replacement therapy. If a patient received both, times will be added. If therapies are overlapping, time will only be counted once.
- Length of time in ICU (in hours) will be taken from eCRF as is.
- Length of time in hospital (in hours) will be taken from eCRF as is.

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8. Study populations

8.1. Patient flow

A CONSORT patient flow diagram will be drawn following the CONSORT 2010 standards (http://www.consort-statement.org/consort-2010).

8.2. Definition of populations for analysis

8.2.1. Full analysis set (FAS)

The full analysis set consists of all randomized patients fulfilling all inclusion criteria, regardless of whether they actually received the allocated monitoring or not or any subsequent protocol deviations during follow up visits. Patients will be analysed in the group they were randomized regardless of any cross-overs or loss to follow-up (intention-to-treat principle). This corresponds to the treatment-policy estimand.

8.2.2. Per-protocol (PP)

The per-protocol population consists of all subjects in the FAS who did not have any protocol deviations during follow up that could confound the interpretation of analyses conducted on the FAS. The following are common major protocol deviations:

- General protocol violations:
    - No hemodynamic instability at screening (i.e. MAP ≥ 60 mmHg)
    - No signs of hypoperfusion or organ dysfunction at screening (i.e. capillary refilling time < 3 seconds, urine output ≥ 0.5 ml/kg/h, lactate ≤ 2 mmol/l)
    - Oesophageal conditions not allowing use of TEE, i.e.
        - Unrepaired tracheoesophageal fistula
        - Prior oesophageal or gastric surgery
        - Oesophageal obstruction or stricture
        - Oesophageal varices or diverticulum
        - Gastric or oesophageal bleeding
        - Recent oesophageal surgery
- Protocol violations in monitoring method:
    - Use of hTEE in conventional monitoring arms and vice versa
- Protocol violations in monitoring interval:
    - Mean interval among monitoring shorter than 6 h for the standard interval arms, and longer than 6 hours for the per-protocol interval arms.

8.2.3. Safety population

The safety population consists of all subjects that received a hTEE or a conventional monitoring and will be evaluated according to the intervention actually received.

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8.3. Definition of sub-group populations in different analyses

Subgroups will be defined by the method (hTEE vs. standard monitoring) and the frequency (per protocol vs. standard interval) of hemodynamic monitoring.

9. Statistical analysis

9.1. General

The primary analysis will be based on the FAS, analysing all patients in the treatment group they were randomized to. We will first test the primary hypothesis, the difference in time to hemodynamic stabilization between the hTEE and standard group. Second, we will evaluate the difference between the protocolled and standard monitoring. Differences in the primary outcome will be assessed using the Fine-Gray competing risk model accounting for the competing risk of death (Fine and Gray 1999).

9.2. Demographics and baseline characteristics

The patient characteristics of the FAS at baseline will be presented in a table, stratified by the four intervention arms (defined by both methods and both frequencies of hemodynamic monitoring), as number and percentage for categorical and mean and standard deviation for continuous variables. For data severely deviating from a normal distribution, we will present median and interquartile ranges. No statistical comparisons of patient characteristics at baseline will be performed. The following variables will be considered:

- Age
- Gender
- Weight
- Height
- Patient admission from: emergency department, ward, external ICU, coronary laboratory, op, and other
- Admission diagnosis: cardiovascular, gastrointestinal, metabolic, neurological, renal or genitourinary, respiratory, trauma, infectious
- Comorbidities: septic shock, chronic lung disease, chronic cardiovascular disease, chronic liver disease, chronic renal failure, immunosuppression, lymphoma, metastatic cancer, leukaemia or myeloma,
- Apache II score,
- SAPS II score, and
- SOFA score.

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9.3. Procedural characteristics

Procedural characteristics will not be shown.

9.4. Compliance to interventions

To validate compliance to the method of monitoring (only hTEE), we will descriptively present the duration of hTEE, and the number and percentage of early termination of hTEE monitoring. The frequency of hemodynamic monitoring will be validated by the time interval between examinations (based on date and time of examinations) and presented descriptively in each group.

9.5. Primary analysis

The primary analysis will be based on the FAS. Since the primary outcome is a time to event outcome, no multiple imputation will be used.

9.5.1. Primary comparison between hTEE and standard monitoring method

We will first test the primary hypothesis, the difference in time to resolution of circulatory shock between the hTEE monitoring and standard monitoring group (i.e. monitoring factor only).

Primary analysis of primary endpoint
The analysis of the primary endpoint will be a superiority analysis based on the full analysis set, asking whether hTEE monitoring is superior in time to resolution of circulatory shock as compared to standard monitoring. We will use a Fine-Gray competing risk regression model accounting for the competing risk of death (Fine and Gray 1999), adjusted for the frequency of monitoring (protocolled vs standard).

The primary outcome will be censored after 6 days in the primary analysis, because continuous hTEE monitoring was only continued for 72h after randomisation. Patients which were discharged without reaching the primary endpoint before 6 days will be censored as well. The strength of the association between each covariate and the outcome is reflected by the sub-hazard ratio in these competing risks models. The sub-hazard ratio is the ratio of the hazard associated with the cumulative incidence function under different values of the covariate, taking into account the hazard of the competing event (death).

Primary analysis of secondary endpoints
The secondary outcome time to death will be evaluated using Cox proportional-hazards regression. Other secondary time-to-event outcomes will be analysed using competing risk models as described above. Binary outcomes will be analysed using logistic regression, All models will be adjusted for the frequency of monitoring (protocolled vs standard).

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9.5.2. Secondary comparison between protocolled vs standard monitoring frequency

Second, we will test the secondary hypothesis, the difference in time to resolution of circulatory shock between the protocolled and standard frequency monitoring group, adjusted for the method of monitoring.

We will analyse primary and secondary endpoints as described above. All models will be adjusted for the method of monitoring (hTEE vs standard).

We will also test for an interaction between the method (hTEE vs standard) and frequency of hemodynamic monitoring (protocolled vs standard) in order to assess if effects are different depending on the method and frequency of monitoring, entering an interaction term in the models described above.

9.6. Secondary analyses

Secondary analyses will include a per-protocol analysis as well as sensitivity analyses.

First, we will perform a per-protocol analysis based on the per-protocol analysis set.

Second, we will evaluate the primary endpoint censoring after 3 days and after 28 days using the FAS.

Finally, we will perform subgroup analysis for the method (hTEE vs. standard monitoring) and the frequency (per protocol vs. standard interval) of hemodynamic monitoring using the FAS.

9.7. Evaluation of safety parameters

All safety analyses will be performed using the Safety Set.

SAEs will be deemed treatment emergent if the onset date is on or after the date of first study treatment. SAEs will be summarized by presenting for each treatment arm the total number of any SAE, the total number of any SAE by type, and the number and percentage of patients having any SAE, and any SAE type. Only SAEs that might be treatment related were collected and will be reported.

All other information collected (e.g., severity or relationship to study treatment) will be tabulated and listed as appropriate.

9.8. Interim analyses

No interim analysis is planned.

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9.9. Methods for handling missing data

The primary outcome is a time to event outcome. Thus, data in the primary outcome will be censored if a patient is lost to follow-up (e.g. discharged before reaching the primary endpoint). Secondary time-to-event outcomes will be handled likewise. Missing binary data will be assumed as being absent. For the descriptive analysis of continuous outcomes, an available case analysis will be performed.

9.10. Statistical software

All analyses will be performed in the current version of Stata. The version of Stata will be listed in the statistical report.

10. Deviations from the protocol

Header	Change	Reason
Primary objective	Removed the duration and amount of vasopressor use from the primary objective	Clarifies primary outcome
Secondary endpoint	Time to death instead of death during ICU or hospital stay	Analyse as time to event outcome
Secondary endpoint	Defined composites of adverse events as outcomes	Adverse events of interest were listed in the protocol, without defining composites
Descriptive endpoints	Moved following outcomes from secondary endpoints Length of time with need for organ support (mechanical ventilation, renal-replacement therapy) Length of stay (LOS) in the ICU LOS in hospital Death during ICU admission Death during hospital admission	Only descriptive analysis of these outcomes is planned
Statistical analysis	Use of a competing risk model for the primary outcome	To account for the competing risk of death
Primary analysis	Defined the method of monitoring as primary comparison, and the frequency of monitoring as secondary comparison.	We do not have power to analyse the data as factorial.

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11. References

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