The Statistical Analysis Plan of the HERO Study

This Statistical Analysis Plan (SAP) was written according to the guidelines proposed by Yuan et al. and by Gamble et al. for randomized clinical trials.

1. SAP versions, dates and reasons for revision

Version #1: March 10th, 2026.

2. Trial registration number

NCT07544771

3. Study title

Randomized comparison of HeartLogic™ remote monitoring versus traditional face-to-face follow up in patients with heart failure. HERO study

4. SAP contributors with roles and responsibilities

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5. Background and rationale of study

Heart failure (HF) affects >50 million people worldwide and is associated with significant morbidity and a mortality in excess of 40% 5 years after diagnosis. HF is associated with a high readmission rate, which is estimated to be 25% within the first 30 days after diagnosis, accounts for 1 to 2% of all hospitalizations and is the major economic burden related to HF.

Remote monitoring of patients with HF is a promising development which may enable treatment of subclinical HF decompensation to prevent overt clinical deterioration and rehospitalization. HeartLogic™ is an algorithm currently only available on Boston Scientific implantable cardioverter defibrillators designed to predict acute episodes of HF in advance which can be monitored remotely. It uses various biometric data (nocturnal heart rate, S1 and S3 heart sounds, respiratory rate, relative tidal volume, activity level and chest impedance) to compute an index. In the event of a rise in HeartLogic™ index, ambulatory therapeutic adjustments can be implemented, potentially avoiding an unscheduled hospitalization for HF. Initial experience with this algorithm has been evaluated in the Multisense study, which found that HeartLogic™ index ≥16 predicted acute episodes of HF an average of 34 days in advance with sensitivity of 70% and specificity of 85.7%. Other studies have assessed the HeartLogic™ algorithm, but were carried out without the goal of pre-emptive therapeutic adjustment to reduce HF events in case of a HeartLogic™ alert.

6. Study type

This is a prospective, multicenter (15 centers), open-label, randomized trial with two parallel arms.

7. Objectives and related endpoints (units and calculations used to derive outcomes)

7.1. Primary objective

The primary objective is to demonstrate the superiority of remote management guided by the HeartLogic™ index over traditional face-to-face follow-up in reducing the 12-month proportion of at least one of the following events in patients with HF: death, unscheduled hospitalization for HF, or deterioration in quality of life.

The primary outcome is the proportion of patients, at 12 months, who are alive with no unscheduled hospitalization for HF and no deterioration in quality of life. Deterioration in quality of life is defined as a reduction of 5 points or more in the Overall Summary Score of the Kansas City Cardiomyopathy Questionnaire (KCCQ) between inclusion and 12 months' follow-up.

7.2. Secondary objectives

The secondary objectives are to compare, over a 12-month period post-implantation, remote management guided by the HeartLogic™ index versus traditional face-to-face follow up in terms of:

1. Win ratio based on mortality, unscheduled hospitalization and quality of life deterioration. The win ratio will be constituted by the three following outcomes in this order of priority: the time-to-death, the time-to-unscheduled hospitalization for HF, and a 5-point difference in the Overall Summary Score of KCCQ between baseline and 1 year of follow-up.
2. Unscheduled hospitalization for HF. This endpoint will be analysed as the cumulative incidence function of first unplanned HF hospitalization, with all-cause death treated as a competing event. Unscheduled hospitalization for HF is defined by the *Standardized Definitions for Evaluation of Heart Failure Therapies*. Hospitalization motivated by a worsening of the HF requiring an increase in diuretic treatment, whether intravenous or per-os. A scheduled hospitalization for systematic follow-up, pre-transplant assessment or iron injections is not considered to be an unscheduled hospitalization(1).
3. HF-related mortality. This endpoint will be analysed as the cumulative incidence of HF-related death (i.e. Pump failure death) as defined by the *Standardized Definitions for Evaluation of Heart Failure Therapies*.
4. Cardiovascular mortality. This endpoint will be analysed as the cumulative incidence of cardiovascular death as defined by the *Standardized Definitions for Evaluation of Heart Failure Therapies*. Cardiovascular death is defined as a death with a defined cardiovascular cause such as acute myocardial infarction, arrhythmia or conduction system disturbance, cardiogenic shock, cardiovascular device failure, cardiovascular hemorrhage, cardiovascular infection, cardiovascular procedure-related, HF, peripheral arterial disease, thromboembolism, stroke, and sudden cardiac death. Deaths of unknown causes and not clearly cardiovascular or non-cardiovascular should be classified as unknown or undetermined.
5. All-cause mortality.
6. Quality of life. This endpoint will be analysed as the mean difference of the Overall Summary Score of KCCQ between baseline and 12 months of follow-up.
7. The efficiency of patient care in terms of cost-utility. The efficiency will be assessed with an incremental cost-effectiveness ratio.
8. Total number of hospitalization, days of hospitalization and total number of outpatient clinic consultations, defined as, respectively, the number of hospitalization, the mean number of days of hospitalization and the number of outpatient clinic consultations reported between inclusion and 12 months of follow-up.
9. Safety. The safety will be evaluating by the diuretic intolerance, comprising at least one of the following items:
    a. Acute renal failure defined as doubling of the serum creatinine level from baseline, or a decrease of at least 50% in the estimated GFR, or renal-replacement therapy.
    b. Hypokalemia defined as a potassium level < 3 mmol/L.

c. Hypotension defined as a systolic blood pressure < 85 mmHg.

8. Inclusion criteria

- Patients aged ≥18 years old;
- Patients implanted with a cardiac defibrillator for less than 6 months, with or without resynchronization, enabling the HeartLogic™ algorithm;
- Patients with a history of HF (left ventricular ejection fraction ≤40%; or at least one episode of clinical HF with NT-proBNP blood concentration ≥450 ng/L);
- Patients with New York Heart Association Class II or III HF;
- Patients able to comply with the protocol, including Latitude™ transmissions (including adequate connectivity), and study visits;
- Patients with compulsory health insurance.

9. Non-inclusion criteria

- Patients not consenting and non-compliant with remote care directions;
- Patients with invasive remote HF monitoring device (such as CardioMems);
- Patients with a concomitant HF device other than cardiac resynchronization, such as a ventricular assist devices or cardiac contractility modulation devices;
- Patients on heart transplant list, or patients with a heart transplant;
- Patients with a glomerular filtration rate <30 ml/min/m2;
- Participation to a concomitant study evaluating management of HF decompensation, or diuretic titration;
- Patients enable to consent;
- The patient is covered under State Medical Assistance;
- Persons benefiting from a reinforced protection, namely minors, persons deprived of liberty by a judicial or administrative decision, adults under legal protection, and finally patients in emergency situations;
- Pregnant or breastfeeding women, women of childbearing age who do not have effective contraception (Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation : oral, intravaginal, transdermal; Progestogen-only hormonal contraception associated with inhibition of ovulation : oral, injectable, implantable; Intrauterine device; Intrauterine hormone-releasing system; Bilateral tubal occlusion) or permanent sterilization methods (hysterectomy, bilateral salpingectomy, bilateral oophorectomy).

10. Definition of the two compared groups

- Control group: The control group is treated with a usual follow-up. Current guidelines recommend follow-up at intervals no longer than 6 months to check symptoms, heart rate and rhythm, blood pressure, full blood count, electrolytes, and renal function. Patients randomized in the control group will be monitored at baseline, 6 and 12 months after inclusion. During these visits, the patient's general practitioner and cardiologist are free to adjust or prescribe treatments in accordance with the patient's clinical condition.
- Experimental group (HeartLogic group): After enrolment, patients of the intervention arm will be remotely followed up based on an alert-driven strategy by the local research coordinator and the remote monitoring team on the Latitude platform. At the beginning of the study, the following recommendations will be forwarded to the participating center. In case of index value ≥16, the investigator should contact the patient to assess the patient's clinical status: dyspnea, peripheral oedema, fatigue and orthopnea. Moreover, a cause for false alert, such as an active infection, can be sought. If this not the case, a trigger for HF deterioration, such as arrhythmia or a chest pain evoking a coronary syndrome should be ruled out. If there is no obvious reason for a false alert, diuretics should be increased by 50 to 100% during 4 to 5 days, or HF guidelines directed medication therapy will be up titrated, at the discretion of local investigator. Re-

evaluation of clinical status, the HeartLogic index and renal function are recommended after 4 to 5 days of diuretic increase. In case of alert, the reason for non-modification or the details of the treatment adjustment will be collected.

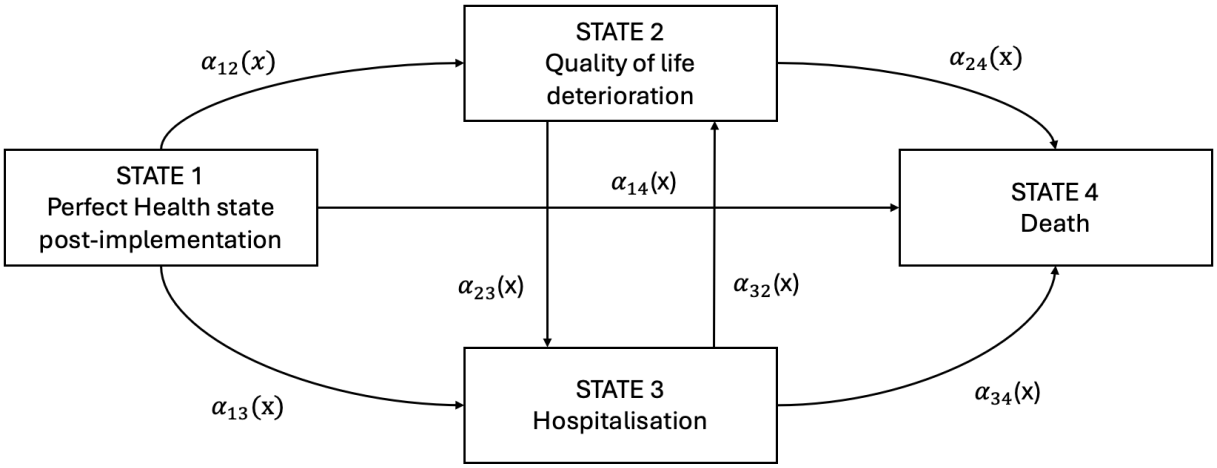
11. Randomization details

The randomization list is established by a methodologist of the platform for methodology, statistics and data-management of the Poitiers University Hospital.
The individual randomization will be stratified on center.

12. Sample size calculation

The primary outcome is the 12-month proportion of alive patients with no unscheduled hospitalization for HF and no quality-of-life deterioration defined as 5 points reduction in Kansas City Cardiomyopathy Questionnaire. Because we had relevant information for each of the three failures (date, hospitalization and death) for a French cohort of patient and the literature, we performed simulation to estimate the 12-month event proportions.

The following figure illustrates the multistate process related to the possible post-randomization failures. Let $\alpha_{ij}(x)$ be the incidence function of the event j assumed constant over the time spent in the state i for patients in the group x (1 for the experimental group and 0 for the control group).



The multistate process describing the possible evolution of the patients.

We considered the data from the French HeartLogic observational cohort study (Study registration: ClinicalTrials.gov ID NCT04619888) in which 310 patients with HF were managed with the HeartLogic™ algorithm during 12 months, allowing pre-emptive treatment of HF exacerbations. Because quality of life (QoL) was not collected at the end of follow up, we considered the data published by Brugts et al. (MONITOR-HF trial). We also considered this trial to extract the hazard ratios to obtain the expected incidences in the future control group. The following tables 1 and 2 detail the assumptions we made.

From these assumptions, we computed to series of simulations. We used the methodology proposed by Beyersmann et al. for several sample sizes from 150 to 350 patients per group (by 10 patients). We generated 10000 data sets per sample size.

Based on this simulation study, one can expect a 12-month percentage of patients alive with no hospitalization for HF and no quality-of-life deterioration equals to 69% in the experimental group versus 55% in the control arm. We estimated that a sample size of 251 patients per arm is required to achieve a 90% power, with a type I error of 0.05. Accounting for a 15% missing data at 12 months, mainly because

no incomplete or missing quality-of-life questionnaires, 289 patients per arm will be included, i.e. a total of **578 patients**.

The expected incidences in the experimental group.

Incidences	Assumptions
$\alpha_{12}(1)$	From MONITOR-HF, the proportion with QoL deterioration at 12 months was 24.2%. Assuming a constant incidence up to 12 months, it corresponded to 0.277 event per patient-year. Because we specifically consider the incidence without hospitalization, which represent a risk factor increasing the incidence, we assumed: $\boldsymbol{\alpha_{12}(1)}$=0.95*0.277 = 0.263 event per patient-year
$\alpha_{13}(1)$	From FC-HF, it was the overall incidence was 0.064 event per patient-year. Because we specifically consider the incidence without QoL deterioration, which represent a risk factor increasing the incidence, we assumed: $\boldsymbol{\alpha_{13}(1)}$=0.95*0.065 = 0.061 event per patient-year
$\alpha_{14}(1)$	From FC-HF, it was the overall incidence was 0.046 event per patient-year. Because we specifically consider the incidence without QoL deterioration, which represent a risk factor increasing the incidence, we assumed: $\boldsymbol{\alpha_{14}(1)}$=0.95*0.046 = 0.044 event per patient-year
$\alpha_{23}(1)$	Because QoL deterioration represents a risk factor increasing the incidence of hospitalization, we assumed: $\boldsymbol{\alpha_{23}(1)}$=1.5*$\boldsymbol{\alpha_{13}(1)}$ = 0.091 event per patient-year
$\alpha_{24}(1)$	Because QoL deterioration represents a risk factor increasing the mortality, we assumed: $\boldsymbol{\alpha_{24}(1)}$=1.5*$\boldsymbol{\alpha_{14}(1)}$ = 0.066 event per patient-year
$\alpha_{34}(1)$	From FC-HF, we estimated $\boldsymbol{\alpha_{34}(1)} = 0.397$ event per patient-year
$\alpha_{32}(1)$	From FC-HF, the relative increase of mortality due to hospitalization was $\alpha_{34}(1)/\alpha_{14}(1) = 9.1$. We assumed the same impact on the QoL deterioration: $\boldsymbol{\alpha_{32}(1)}$=$\boldsymbol{\alpha_{12}(1)}$*9.1=2.388 event per patient-year

The expected incidences in the control group.

Incidences	Assumptions
$\alpha_{12}(0)$	From MONITOR-HF, the proportion with QoL deterioration at 12 months was 39.5%. Assuming a constant incidence up to 12 months, it corresponded to 0.502 event per patient-year. Therefore, the related HR was 0.227/0.502=0.55 $\boldsymbol{\alpha_{12}(0)}$= $\boldsymbol{\alpha_{12}(1)}$/0.55 = 0.477 event per patient-year
$\alpha_{13}(0)$	From MONITOR-HF, the HR was 0.71. We considered that this impact may be smaller for the future trial. We defined two scenarios: Optimist scenario: $\boldsymbol{\alpha_{13}(0)}$= $\boldsymbol{\alpha_{13}(1)}$/0.71 = 0.085 event per patient-year Realistic scenario: $\boldsymbol{\alpha_{13}(0)}$= $\boldsymbol{\alpha_{13}(1)}$/0.85 = 0.071 event per patient-year
$\alpha_{14}(0)$	From MONITOR-HF, the HR was 0.95: $\boldsymbol{\alpha_{14}(0)}$= $\boldsymbol{\alpha_{14}(1)}$/0.95 = 0.046 event per patient-year
$\alpha_{23}(0)$	We assumed the same relative impact of the device in reducing the hospitalization incidence regardless the QoL deterioration, i.e. HR = 0.71 or 0.85: Optimist scenario: $\boldsymbol{\alpha_{23}(0)}$= $\boldsymbol{\alpha_{23}(1)}$/0.71 = 0.128 event per patient-year Realistic scenario: $\boldsymbol{\alpha_{13}(0)}$= $\boldsymbol{\alpha_{13}(1)}$/0.85 = 0.107 event per patient-year
$\alpha_{24}(0)$	We assumed the same relative impact of the device in reducing the mortality regardless the QoL deterioration, i.e. HR = 0.95: $\boldsymbol{\alpha_{24}(0)}$= $\boldsymbol{\alpha_{24}(1)}$/0.95 = 0.069 event per patient-year
$\alpha_{34}(0)$	We assumed the same relative impact of the device in reducing the mortality regardless the hospitalization, i.e. HR = 0.95: $\boldsymbol{\alpha_{34}(0)}$= $\boldsymbol{\alpha_{34}(1)}$/0.95 = 0.418 event per patient-year
$\alpha_{32}(0)$	We assumed the same relative impact of the device in reducing the QoL deterioration regardless the hospitalization i.e. HR = 0.55: $\boldsymbol{\alpha_{32}(0)}$= $\boldsymbol{\alpha_{32}(1)}$/0.55 = 4.331 event per patient-year

13. Interim analysis (timing, person, adjustment of the significance level)

No interim analysis was planned.

14. Guidelines for an early stop of the study

The study may be prematurely suspended in the event of unexpected adverse events. On the same token, in the event of unexpected developments or new information and showing that the objectives of the study or the clinical program are unlikely to be reached, the sponsor may be persuaded to prematurely suspend the study.

No statistical discontinuation criteria have been drawn up.

15. Reporting the representativity of the studied population

A flowchart (**Deliverable #1**) will be decomposed according to the following sets. The effectives and the related differences in-between two consecutive sets will be reported. The causes of the related differences will also be listed.

- **The screened set**. The patients having signed the informed consent.
- **The intention-to-treat (ITT) analysis set.** The patients who were randomized according to treatment assignment, regardless of their adherence to the entry criteria, regardless of the treatment they received, and regardless of subsequent withdrawal from treatment or deviation from the protocol.
- **The full analysis set (FAS)**. The previous ITT population, excluding participants who failed to meet major entry criteria and with no data post-randomization.
- **The per-protocol population**. The previous FAS population, only including those patients who have completed the treatment originally allocated.

16. Withdrawals and follow-up data

Patients may be withdrawn early from the clinical investigation for several reasons, including but not limited to consent withdrawal, lost to follow-up, death. The investigator will document the reasons for premature study discontinuation. The withdrawals will be exhaustively described in the flowchart.

17. Definition of the studied population

All the analyses will be performed based on the full analysis set.

If a patient withdraws consent, he/she will be asked for permission to use data obtained prior to withdrawal and to collect the primary outcome. If this is achieved, the patient will be included in the final analyses. If the patient declines, all data from that patient will be deleted (except for safety data).

18. Level of statistical significance (p-values, confidence intervals, one- or two-sided)

For the primary and secondary objectives, statistical significance will be achieved for p-value < 5% by using two-sided alternative hypothesis and two-sided 95% confidence interval.

19. Plan and rationale for controlling the type I error (multiplicity of tests)

We will not consider the inflation of the type I error. The level of the proof will be the higher for the primary outcome. The statistical analyses related the secondary outcomes will be considered as exploratory results with a risk of false positive.

20. Sub-group analyses and/or tests of interactions

No sub-group analyses or tests of interactions are planned.

21. Description of baseline patient characteristics

Demographic variables and other baseline characteristics will be summarized in a descriptive table (**Deliverable #2**) for the full analysis set.

The means, the standard deviations and the number of missing values will be presented for each arm and marginally for the following continuous variables: age (in years), body mass index (in kg/m^2), systolic blood pressure (mmHg), Nt pro BNP (ng/L), Creatinine (µmol/L), Left ventricular ejection fraction (%).

The sample size, the proportion of patients in each category, and the number of missing values will be reported for each study arm and overall for the following categorical variables.: gender (male/female), New York Heart Association (I/II/III/IV), hypertension (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), history of atrial fibrillation (yes/no), Cardiomyopathy type(Ischemic cardiomyopathy/

hypertrophic cardiomyopathy/ valvular cardiomyopathy/ dilated cardiomyopathy with normal coronary arteries), history of chronic renal failure (yes/no), , type of device (atrial lead, right ventricular lead [no/conventional positioning/left bundle branch pacing], left ventricular lead via the coronary sinus), Beta-blockers (yes/no), ACE-inhibitor/ARB (yes/no), Sacubitril/Valsartan (yes/no), SGLT2 inhibitor (yes/no), Mineralocorticoid receptor antagonists (yes/no), Diuretics (yes/no), Anticoagulants (yes/no), Amiodarone (yes/no).

No p-value will be reported. The balance diagnostics of baseline covariates between the two arms will be achieved by estimating standardized differences (2). Unbalances will be considered for values higher than 10%.

22. Quality of life questionnaire

The KCCQ is a self-administered, 23-item questionnaire developed to provide a description of quality of life in patients with HF.

In details, the KCCQ maps 7 domains: physical limitation; symptom stability; symptom frequency; symptom burden; self-efficacy; quality of life; and social limitations. The symptom frequency and symptom burden domains are merged into a total symptom score, which can be combined with the physical limitation domain to create a clinical summary score. The symptom, physical limitations, social limitations, and quality of life domains can also be combined to create an overall summary score, which will be the measure of interest in the present study. Scoring instructions are available Appendix #1.

23. Analysis of the endpoints

A table will describe the outcomes (**Deliverable #3**). The number and percentage of patients who are alive with no unscheduled hospitalization for HF and no deterioration in quality of life at 12 months will be presented and compared according to the group using a Chi-2 test (or Fisher exact tests if expected numbers of patients are less than 5). The same strategy will be used to analyze the number of patients who have diuretic intolerance. The mean and standard deviation of the number of days of hospitalization will be presented and compared using a Student t-test.

Overall survival will be estimated using the Kaplan–Meier method, and the corresponding survival curves will be plotted. (**Deliverable #4**). The cumulative incidence of unscheduled hospitalization for HF, of HF-related death and of cardiovascular death will be estimated using Aalen-Johansen estimator in competition with all-cause mortality and the curves will be plotted (**Deliverable #5**). The proportions of events estimated at 12 months will be presented in the descriptive table (**Deliverable #3**). The unknown cause of death will be considered related to HF, i.e. the worst case scenario.

For the win ratio, the three following outcomes in this order of priority will be considered: the time-to-death, time-to–first unscheduled hospitalization for HF, and a 5-point difference in the KCCQ score. Each subject in the treatment group will be compared with every subject in the control group. For the three endpoints, the winner will depend on who had the event first. If both patient of a pair had a 5-point or more difference in the overall summary score of the KCCQ at 12 months, they will be considered tied.

24. Health-economics analysis

The proposed health economic analysis is a cost-utility analysis, in line with the recommendations of the Haute Autorité de Santé (3). The analysis adopts the perspective of both the national health insurance system and patients. The economic evaluation will cover the full analysis set. Costs and effects will not be discounted, given the 12-month time horizon.

Healthcare resource use data will be collected retrospectively via the National Health Data System (using deterministic linkage). Direct costs will include follow-up and hospitalization expenses. Follow-up costs will encompass medications, laboratory tests, radiology, consultations, and home nursing care. All lost workdays will be recorded and valued according to the French insurance system.

All reimbursement data will be converted into euros constant euros for the year of analysis.

Utility will be assessed prospectively using the EQ-5D-5L questionnaire (available Appendix #2). Each reported health state will be converted into a utility value using the French population-specific weighting matrix (4). Quality-adjusted life years (QALY) will be calculated by weighting the time spent in each health state by the corresponding utility scores.

Costs and QALYs will be presented for each treatment group as mean cost and mean QALY per patient, with a detailed breakdown of costs by expenditure category.

The incremental cost-utility ratio (ICER) will be estimated by dividing the difference in mean cost by the difference in mean effectiveness, expressed in QALYs. This ratio measures the additional cost or savings required to gain one perfect health year through the intervention.

Uncertainty surrounding cost and QALY estimates will be assessed using non parametric bootstrapping approach (1000 samples). The cost-effectiveness plane will be generated based in these bootstrap replications.

A cost-effectiveness acceptability curve (CEAC) will be generated, representing the probability of the intervention being cost-effective as a function of the willingness-to-pay (WTP) threshold. To do this, we will calculate the net monetary benefit (NMB) for a range of WTP values. For each threshold value, 1,000 bootstrap samples will be generated. The probability of cost-effectiveness will be determined by the proportion of replicates for which the NMB is strictly positive.

Both deterministic and probabilistic (Monte Carlo) sensitivity analyses will be conducted to evaluate the impact of parameter uncertainty on the results. The deterministic analysis will vary key cost items, while the probabilistic analysis will treat each uncertain parameter (cost, QALY) as a random variable following a specified probability distribution.

25. Adjusted comparison

Ignoring stratification factors in the analysis leads to incorrect confidence intervals. More generally, adjusted analyses on the risk factors of the outcome may increase power and give correct type I error rates. We will use the G-computation to estimate the average treatment effect for the main outcome.

Firstly, we will estimate the outcome model. We will consider the following potential risk factors of death, unscheduled hospitalization for HF, or deterioration in quality of life: age, sex, left ventricular ejection fraction, Nt pro BNP, New York Heart Association class, cardiomyopathy type, hemoglobin, glomerular filtration rate,, systolic blood pressure, atrial fibrillation (yes/no). No interaction between the randomization arm and the predictors will be tested. A logistic regression with elastic net regularization will be used. The penalty parameters will by estimated by minimizing the 20-fold cross-validation mean square errors.

Secondly, based on the outcome model, we will predict the primary outcome if all participants were assigned to the intervention arm and then if all participants were assigned to the control arm. The Average Treatment Effect (ATE) will be the difference between the two proportions of the individual predictions.

26. Consideration of missing data

To avoid the exclusion of patients with missing values on the baseline predictors, multivariate imputation by chained equations will be performed *m* times. *m* will be at least equal to the percentage of incomplete cases (5). For each completed dataset, 1,000 bootstrap samples will be generated. Confidence intervals will be estimated non-parametrically from the *m* x 1,000 resulting samples (6). Among the *m* x 1,000 samples, the number and percentage of occurrence of each predictor will be reported to illustrate their relative importance.

For non-health-economics analysis, we will perform complete case analyses, as the percentage of missing data on the outcomes is expected to be very low. For health-economics analysis, the same imputation strategy will be applied to missing EQ-5D-5L questionnaires data (7), except for missing data due to patient death, which will be assigned a value of 0.

27. The assumptions of statistical methods

Missing baseline covariates will be assumed missing at random (MAR). They will be handled using multiple imputation, including treatment assignment and outcome in the imputation models. Treatment is randomized; therefore, confounding adjustment is not required for unbiasedness, but covariate adjustment may improve precision. The primary estimand will be obtained from outcome regression models; hence validity relies on adequate specification of the outcome model. For continuous covariates, linearity on the logit scale will be assessed; if evidence of non-linearity is found, spline terms (B-splines) will be used.

28. References

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Appendix #1: The Kansas City Cardiomyopathy Questionnaire – Scoring Instructions

The Kansas City Cardiomyopathy Questionnaire
Scoring Instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. **Physical Limitation**

   - Code responses to each of Questions 1a-f as follows:

     Extremely limited = 1
     Quite a bit limited = 2
     Moderately limited = 3
     Slightly limited = 4
     Not at all limited = 5
     Limited for other reasons or did not do = *<missing value>*

   - If at least three of Questions 1a-f are not missing, then compute

     Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

     (see footnote at end of this document for explanation of meaning of "actually answered")

2. **Symptom Stability**

   - Code the response to Question 2 as follows:

     Much worse = 1
     Slightly worse = 2
     Not changed = 3
     Slightly better = 4
     Much better = 5
     I've had no symptoms over the last 2 weeks = 3

   - If Question 2 is not missing, then compute

     Symptom Stability Score = 100*[(Question 2) – 1]/4

3. **Symptom Frequency**

   - Code responses to Questions 3, 5, 7 and 9 as follows:

     Question 3
     Every morning = 1
     3 or more times a week but not every day = 2
     1-2 times a week = 3
     Less than once a week = 4
     Never over the past 2 weeks = 5

3. Symptom Frequency (cont.)

Questions 5 and 7
All of the time = 1
Several times a day = 2
At least once a day = 3
3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

  S3 = [(Question 3) – 1]/4
  S5 = [(Question 5) – 1]/6
  S7 = [(Question 7) – 1]/6
  S9 = [(Question 9) – 1]/4

  Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

- Code responses to each of Questions 4, 6 and 8 as follows:

  Extremely bothersome = 1
  Quite a bit bothersome = 2
  Moderately bothersome = 3
  Slightly bothersome = 4
  Not at all bothersome = 5
  I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

  Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

= mean of the following available summary scores:
  Symptom Frequency Score
  Symptom Burden Score

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

  Question 10
  Not at all sure = 1
  Not very sure = 2
  Somewhat sure = 3
  Mostly sure = 4
  Completely sure = 5

  Question 11
  Do not understand at all = 1
  Do not understand very well = 2
  Somewhat understand = 3
  Mostly understand = 4
  Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

  Question 12
  It has extremely limited my enjoyment of life = 1
  It has limited my enjoyment of life quite a bit = 2
  It has moderately limited my enjoyment of life = 3
  It has slightly limited my enjoyment of life = 4
  It has not limited my enjoyment of life at all = 5

  Question 13
  Not at all satisfied = 1
  Mostly dissatisfied = 2
  Somewhat satisfied = 3
  Mostly satisfied = 4
  Completely satisfied = 5

  Question 14
  I felt that way all of the time = 1
  I felt that way most of the time = 2
  I occasionally felt that way = 3
  I rarely felt that way = 4
  I never felt that way = 5

7. Quality of Life (cont.)

- If at least one of Questions 12, 13 and 14 is not missing, then compute

  Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:

  Severely limited = 1
  Limited quite a bit = 2
  Moderately limited = 3
  Slightly limited = 4
  Did not limit at all = 5
  Does not apply or did not do for other reasons = <*missing value*>

- If at least two of Questions 15a-d are not missing, then compute

  Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores:
  Physical Limitation Score
  Total Symptom Score
  Quality of Life Score
  Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores:
  Physical Limitation Score
  Total Symptom Score

Note: references to "**means of questions actually answered**" imply the following.

- If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as
  (sum of the responses to those *n-i* questions) / (*n-i*)
  not
  (sum of the responses to those *n-i* questions) / *n*

If doing these calculations seems like too much trouble, consider using one of our tools – available at www.cvoutcomes.org:

- SAS or SPSS code
- Excel spreadsheets
- Web data services

Appendix #2: The EQ-5D-5L Questionnaire

Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- ☐ 1 I have no problems in walking about
- ☐ 2 I have slight problems in walking about
- ☐ 3 I have moderate problems in walking about
- ☐ 4 I have severe problems in walking about
- ☐ 5 I am unable to walk about

SELF-CARE

- ☐ 1 I have no problems washing or dressing myself
- ☐ 2 I have slight problems washing or dressing myself
- ☐ 3 I have moderate problems washing or dressing myself
- ☐ 4 I have severe problems washing or dressing myself
- ☐ 5 I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- ☐ 1 I have no problems doing my usual activities
- ☐ 2 I have slight problems doing my usual activities
- ☐ 3 I have moderate problems doing my usual activities
- ☐ 4 I have severe problems doing my usual activities
- ☐ 5 I am unable to do my usual activities

PAIN / DISCOMFORT

- ☐ 1 I have no pain or discomfort
- ☐ 2 I have slight pain or discomfort
- ☐ 3 I have moderate pain or discomfort
- ☐ 4 I have severe pain or discomfort
- ☐ 5 I have extreme pain or discomfort

ANXIETY / DEPRESSION

- ☐ 1 I am not anxious or depressed
- ☐ 2 I am slightly anxious or depressed
- ☐ 3 I am moderately anxious or depressed
- ☐ 4 I am severely anxious or depressed
- ☐ 5 I am extremely anxious or depressed

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the below.

YOUR HEALTH TODAY =

