TELEREH-HF

Statistical Analysis Plan 2.0

Prepared by Michael J. Pencina, PhD

May 8, 2019

Amendments

Amended by Michael J. Pencina on 05/08/2019 based on feedback from American Heart Journal reviewer comments on the design manuscript.

1. Clarified definitions of analysis sets and duration of follow-up for analyses.
2. Clarified nomenclature and added table of contents

Table of Contents

1. Introduction

This statistical analysis plan (SAP) contains definitions of analysis populations, derived variables and statistical methods for the final analyses of the TELEREH-HF study. This SAP specifies the pre-planned analyses and serves as the base for the main study analyses.

TELEREH-HF trial is a multi-center, randomized, open-label, parallel, controlled study in patients with heart failure. The study is being conducted in 5 centers in Poland. The study is being performed according to the principles laid out in the Declaration of Helsinki, and approvals have been obtained from Ethics Committees.

1.1 Study Objective

This study is designed to compare the effectiveness and safety of tele-rehabilitation (TELEREH) versus appropriate medical therapy (AMT) in reducing mortality and the number of hospitalizations during 12-24 months of follow-up.

1.2 Study Outcomes

1.2.1 Primary Outcome

The primary study outcome is the number of days alive and out of hospital (DAOH) in the 12-24 months following the end of the preliminary 9-week training program.

1.2.2 Secondary and Tertiary Outcomes

1.2.2.1 Secondary Outcomes assessed throughout the follow-up include:

- all-cause mortality
- cardiovascular mortality,
- all-cause hospitalizations
- cardiovascular hospitalizations
- heart failure hospitalization

- composite of all-cause mortality or all-cause hospitalization
- composite of all-cause mortality or cardiovascular hospitalization
- composite of all-cause mortality or heart failure hospitalization.
- composite of cardiovascular mortality or heart failure hospitalization.
- number of days in the hospital

1.2.2.2 Tertiary Outcomes assessed at 9 weeks include:

- - NYHA class
- - CPET duration
- - peak oxygen consumption (pVO2) in CPET
- - % of predicted peak VO2 (pVO2%N) in CPET
- - 6-minute walk test distance
- - quality of life (QoL) measures with the SF-36 instrument
- - depression and/or anxiety assessment.

1.3 Study Population

This study will enroll adults over the age of 18 who satisfy the following criteria:

(i) any aetiology of left ventricular systolic HF [as defined in the European Society of Cardiology (ESC) guidelines]

(ii) left ventricular ejection fraction ≤40% on echocardiography

(iii) New York Heart Association (NYHA) class I, II or III

(iv) who have had a hospitalization incident and are stable clinically (a patient does not need intravenous medication or has not had therapy modified for at least 7 days);

(v) who have no contraindications to undergo cardiopulmonary exercise test;

(vi) who are able to exercise using the new model of home-based tele-rehabilitation.

The following constitute the exclusion criteria:

(i) NYHA class IV;

(ii) unstable angina;

(iii) unstable clinical status

(iv) a history of acute coronary syndrome within the last forty days in patients with LVEF ≤ 35%;

(v) percutaneous angioplasty (PCI) within the last 2 weeks, coronary artery bypass grafting within the last 3 months, or initiation of cardiac resynchronization therapy (CRT-P, CRT-D) and/or implantable cardioverter-defibrilator (ICD) or pacemaker within the last six weeks;

(vi) lack of ICD, CRT-P or CRT-D therapy despite the indications for implantation according to ESC guidelines;

(vii) intracardiac thrombus (vii) rest heart rate (HR) >90/min,

(viii) tachypnoe >20 breaths per minute

(ix) symptomatic and/or exercise-induced cardiac arrhythmia or conduction disturbances;

(x) acute myocarditis and/or pericarditis

(xi) valvular or congenital heart disease requiring surgical treatment;

(xii) hypertrophic cardiomyopathy;

(xiii) severe pulmonary disease;

(xiv) uncontrolled hypertension;

(xv) anemia (hemoglobin < 11.0 g/dL);

(xvi) physical disability related to severe musculoskeletal or neurological problems;

(xvii) recent embolism;

(xviii) thrombophlebitis;

(xix) acute or chronic inflammatory disease;

(xx) acute or chronic decompensated non-cardiac diseases (thyreotoxicosis, uncontrolled diabetes);

(xxi) active malignant neoplastic diseases with survival prognosis below 2 – 5 years;

(xxii) orthotropic heart transplant in anamnesis;

(xxiii) aortic aneurysm;

(xxiv) severe psychiatric disorder;

(xxv) patient's refusal to participate.

1.4 Study Design

This is a multi-center, randomized, open-label, parallel, controlled study in patients with heart failure conducted in 5 centers in Poland designed to compare the effectiveness and safety of tele-rehabilitation (TELEREH) versus appropriate medical therapy (AMT) in reducing mortality and the number of hospitalizations during 12-24 months of follow-up.

Patients randomized to the control group undergo a 9-week procedure appropriate for their clinical condition/status standardized for a particular center.

Patients randomized to the treatment arm undergo a 9-week program of early hybrid, comprehensive cardiac tele-rehabilitation as detailed in the Study Protocol. Patients will train five times a week. Patients will receive a special remote device for tele-ECG-monitored and supervised exercise training – tele-rehabilitation set, which consists of: EHO mini device, blood pressure measuring and weighing machine. The EHO mini device is able to record ECG data from three pre-cordial leads and transmit them via a mobile phone network to the monitoring center. The mobile phone is also used for voice communication. An EHO mini device has training sessions preprogrammed individually for each patient (defined exercise duration, breaks, timing of ECG recording). Details of tele-monitoring on follow-up are included in the Study Protocol.

Follow-up duration in both study arms will extend for 12-24 months from the end of the initial supervised 9-week training period (modified intent-to-treat) or for 14-26 months (12-24 months + 9 weeks) from randomization (intent-to-treat). Patients will return to their study site for a visit at the end of the 12-month follow-up and for a final visit at the study end (maximum follow-up of 24 months).

1.5 Primary Hypothesis and Sample Size Determination

TELEREH strategy is superior to control AMT strategy resulting in a larger percent of days alive and out of hospital (DAOH) during the follow-up. Because possible follow-up varies between patients, the primary analysis will rely on the percent DAOH calculated as the ratio of the DAOH divided by total days of follow-up for each patient.

The sample size for this study was calculated assuming 1:1 treatment allocation ratio, and an overall two-sided level of significance alpha = 0.05. Mean difference in the number of DAOH between the TELEREH arm and the AMT arm was assumed to be 21 days with a common standard deviation in each arm of 100. The Wilcoxon-Mann-Whitney test with the above assumptions and with a sample size of 400 evaluable subjects per study arm (a total of 800) yields 80% power to declare the observed difference as statistically significant. Accounting for a 5% loss to the follow-up, the total number is increased to at least 842 subjects to be randomized.

2. PLANNED ANALYSES

2.1 Analysis Populations

Intent-to-Treat (ITT) Analysis Set: The ITT set includes all randomized subjects, regardless of whether a patient completed the study or adhered to the randomized treatment regimen. Follow-up will start at randomization.

Modified Intent-to-Treat (MITT) Analysis Set: The MITT set includes all randomized subjects who remained in the study through the 9-week initial period and, if randomized to TELEREH arm, conducted at least 1 training at home. Follow-up will start after the 9-week initial period. This will be the primary analysis set.

2.2 Methods of Analysis

All descriptive statistical analyses will be performed using SAS statistical software (version 9 or higher), unless otherwise noted.

Data collected in this study will be described in summary tables. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group, and two-sided 95% confidence intervals of the mean difference between the treatment groups. Binary variables will be described with frequencies, percentages, and two-sided 95% confidence intervals of the difference in percentages between treatments. For time-to-event data, Kaplan-Meier estimates at the indicated time points will be displayed along with 95% confidence intervals for the difference in the estimates along with the log rank test results. In addition, survival curves will be constructed for all time to event outcomes using Kaplan-Meier methods.

Unless otherwise specified, the following statistical tests will be adopted.

1. Two independent samples t-test or Wilcoxon rank-sum test for continuous variables;

2. Wilcoxon-Mann-Whitney test for ordinal variables;

3. Chi-square test of independence for binary comparisons unless the number of events is less than 5, in which case Fisher's exact test will be used;

4. Cochran Mantel-Haenszel Modified Ridit Scores for non-time-to-event categorical variables with >2 categories

- Nominal variables will be compared using the General Association p-value

- Ordinal variables will be compared using the Row Mean Score p-value

5. Log-rank test for first occurrence of time-to-event variables;

All statistical tests and/or confidence intervals, as appropriate, will be performed at $\alpha=0.05$ (2-sided) unless specified otherwise. All p-values reported will be rounded to three decimal places.

No imputation methods will be used to infer missing values for baseline variables.

2.3 Primary Outcome Analysis

The primary analysis of the primary outcome of DAOH during the 12-24-month follow-up (MITT) or 14-26-month follow-up (ITT) will be analyzed using the Wilcoxon-Mann-Whitney test. DAOH is defined as the number days out of the total days of follow-up that the patient was alive minus the total number of days the patient spent in the hospital (sum of days spent in the hospital for each hospitalization). Fractions of days spent in the hospital will be rounded up to full days. Because possible follow-up varies between patients, the primary analysis will rely on

the percent DAOH calculated as the ratio of the DAOH divided by total days of follow-up for each patient. Total days of follow-up will be calculated as the number of days between randomization (ITT analysis) or end of 9-week initial period (MITT analysis) and 24 months or the end of study date (whichever is smaller).

2.3.1 Missing Data

If a patient remained in the study for less than the full period for reasons other than death, the following imputation methods will be applied:

1. Proportional Fraction. The proportion of DAOH will be calculated for the period the patient was on study;

2. Worst case scenario. Days not on study will be counted as NOT alive/out of hospital;

3. Best case scenario. Days not on study will be counted as alive and out of hospital;

2.3.2 Heterogeneity of treatment effect

2.3.2.1 Effect of Site

Because the study in conducted in several sites, the potential for heterogeneity due to site exists. To account for this potential heterogeneity a stratified form of the Wilcoxon test will be conducted. Furthermore, we will perform stratum specific analyses and visually inspect the type of heterogeneity with particular focus on treatment effects going in the opposite direction between sites.

2.3.2.2 Stratified Analyses

Additional stratified analyses will be conducted to assess treatment heterogeneity by age, sex, baseline NYHA class, peak VO2 consumption and duration of follow-up.

2.3.2.3 Sensitivity Analysis

An additional sensitivity analysis will be conducted excluding patients from the control arm if they participated in a rehabilitation program.

2.4 Secondary and Tertiary Outcomes Analyses

2.4.1 Time-to-event Secondary Outcomes

Kaplan-Meier plots will be created to illustrate survival experience between treatment arms for the following secondary outcomes: all-cause mortality, cardiovascular mortality, all-cause hospitalizations, cardiovascular hospitalizations, heart failure hospitalization, composite of all-cause mortality or all-cause hospitalization, composite of all-cause mortality or cardiovascular hospitalization, composite of all-cause mortality or heart failure hospitalization and composite of cardiovascular mortality or heart failure hospitalization. All available follow-up will be used with event rates estimated at 12 (MITT) or 14 (ITT) months.

The following time-to-event outcomes will be compared between treatment arms using Cox proportional hazards regression with site and treatment arms as covariates: all-cause mortality, cardiovascular mortality, composite of all-cause mortality or all-cause hospitalization, composite of all-cause mortality or cardiovascular hospitalization, composite of all-cause mortality or heart failure hospitalization and composite of cardiovascular mortality or heart failure hospitalization.

2.4.2 Ordinal Secondary Outcomes

Numbers of days in the hospital will be summarized by each treatment arm with corresponding 95% confidence intervals.

2.4.3 Tertiary Outcomes assessed at 9 weeks

2.4.3.1 Continuous Outcomes

The following continuous outcomes will be compared between treatment arms using analysis of variance adjusting for baseline level of the outcome measure and site: change in CPET duration, change in peak oxygen consumption (pVO2) in CPET, change in % of predicted peak VO2 (pVO2%N) in CPET, change in 6-minute walk test distance, change in quality of life (QoL) measures with the SF-36 instrument as well as change in depression and anxiety scales.

2.4.3.2 Ordinal Outcomes

NYHA class will be analyzed as ordinal variable using ordinal logistic regression including terms of baseline NYHA class, site and treatment arm.

2.5 Study Parameters

2.5.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be presented for all patients, including but not limited to:

- Age
- Sex
- NYHA class
- LVEF
- Chronic kidney disease
- COPD
- Diabetes
- Hypertension

- Coronary artery disease
- Blood pressure (systolic and diastolic)
- Medications (ACE inhibitors or ARBs, beta-blockers, diuretics, digoxin, aldosterone-receptor antagonists)
- CPET duration
- peak oxygen consumption (pVO2) in CPET
- % of predicted peak VO2 (pVO2%N) in CPET
- 6-minute walk test distance
- quality of life (QoL) measures with the SF-36 instrument
- depression scale
- anxiety scale

2.5.2 Randomization and Discontinuation

We will present numbers of subjects randomized by each site as well as list all premature discontinuations and identify their reasons.

2.5.3 Safety and Clinical Parameters

2.5.3.1 Adverse Events

An adverse event is defined as any detrimental change in the subject's condition, whether it is related or not to assigned treatment. Adverse events will be monitored throughout the study. Adverse events will be summarized by tabulating the number and percentages of patients with an event.

2.5.3.2 Serious Adverse Events

Serious Adverse Events (SAEs) will be defined as any adverse experience that results in any of the following outcomes: death, a life-threatening adverse experience, in-patient hospitalization, or prolongation of existing hospitalization or a persistent or significant disability/incapacity. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Serious Adverse Events will be presented in the same manner as Adverse Events.

3 TABLES AND FIGURES

Table 1. Baseline Study Characteristic According to Treatment Arm

Characteristic	**Tele Rehabilitation**	**Usual Care**
Age		
Male sex		
NYHA class		
I		
II		
III		
IV		
Left ventricular ejection fraction		
Chronic kidney disease		
COPD		
Diabetes		
Hypertension		
Coronary Artery Disease		
Systolic Blood Pressure		
Diastolic Blood Pressure		
ACE inhibitor or ARB		
Beta-blocker		
Loop diuretic		
Digoxin		
Aldost-receptor antagonist		

Table 2a. Change from baseline to 9 weeks in continuous functional outcomes

Measure	Tele Rehabilitation			Usual Care			p-value
	Baseline	9 weeks	Change	Baseline	9 weeks	Change	
CPET duration							
peak oxygen consumption in CPET							
% predicted peak VO2 in CPET							
6-minute walk test distance							
quality of life (QoL)							
Depression scale							
Anxiety scale							

Table 2b. Change in distribution of NYHA class from baseline to week 9.

NYHA class	Tele Rehabilitation		Usual Care		p-value
	Baseline	9 weeks	Baseline	9 weeks	
I					
II					
III					
IV					

Table 3a-MITT. Primary outcome analysis – percent days alive and out of hospital in 12 months from 9-week initial period

Method of Imputation	Tele Rehabilitation	Usual Care	p-value
Proportional Fraction			
Worst case			
Best case			
Patients with full follow-up			

Table 3b-MITT. Primary outcome analysis – percent days alive and out of hospital in 12 months from 9-week initial period – by site

Method of Imputation	Tele Rehabilitation	Usual Care	p-value for heterogeneity
Proportional Fraction			
Site I			
Site II			
Site III			
Site IV			
Site V			
Worst case			
Site I			
Site II			
Site III			
Site IV			
Site V			
Best case			
Site I			
Site II			
Site III			
Site IV			
Site V			
Patients with full follow-up			
Site I			
Site II			
Site III			
Site IV			
Site V			

Table 3c-MITT. Primary outcome analysis – percent days alive and out of hospital in 12 months from 9-week initial period – by important baseline characteristic

	Tele Rehabilitation	Usual Care	p-value for heterogeneity
Proportional Fraction			
Age > median			
Age ≤ median			
Women			
Men			
NYHA I or II			
NYHA III or IV			
Peak VO2 > median			
Peak VO2 ≤ median			
Follow-up > median			
Follow-up ≤ median			
Worst case			
Age > median			
Age ≤ median			
Women			
Men			
NYHA I or II			
NYHA III or IV			
Peak VO2 > median			
Peak VO2 ≤ median			
Follow-up > median			
Follow-up ≤ median			
Best case			
Age > median			
Age ≤ median			
Women			
Men			
NYHA I or II			
NYHA III or IV			
Peak VO2 > median			
Peak VO2 ≤ median			
Follow-up > median			
Follow-up ≤ median			

Table 4a-MITT. Time-to-event Outcomes from 9-week initial period through end of follow-up

Outcome	Tele Rehabilitation		Usual Care		Hazard ratio	p-value
	N (%)	Event rate at 12m	N (%)	Event rate at 12m		
All-cause mortality						
Cardiovascular mortality						
All-cause hospitalization						
Cardiovascular hospitalization						
Heart failure hospitalization						
All-cause mortality or all-cause hospitalization						
All-cause mortality or heart failure hospitalization						
Cardiovascular mortality or heart failure hospitalization						

Table 4b-MITT. Number of days in the hospital from 9-week initial period

Method of Imputation	Tele Rehabilitation	Usual Care
Proportional Fraction		
Worst case		
Best case		
Patients with full follow-up		

Table 3a-ITT. Primary outcome analysis – percent days alive and out of hospital in 14 months from randomization

Method of Imputation	Tele Rehabilitation	Usual Care	p-value
Proportional Fraction			
Worst case			
Best case			
Patients with full follow-up			

Table 3b-ITT. Primary outcome analysis – percent days alive and out of hospital in 14 months from randomization– by site

Method of Imputation	Tele Rehabilitation	Usual Care	p-value for heterogeneity
Proportional Fraction			
Site I			
Site II			
Site III			
Site IV			
Site V			
Worst case			
Site I			
Site II			
Site III			
Site IV			
Site V			
Best case			
Site I			
Site II			
Site III			
Site IV			
Site V			
Patients with full follow-up			
Site I			
Site II			
Site III			
Site IV			
Site V			

Table 3c-ITT. Primary outcome analysis – percent days alive and out of hospital in 14 months from randomization– by important baseline characteristic

	Tele Rehabilitation	Usual Care	p-value for heterogeneity
Proportional Fraction			
Age > median			
Age ≤ median			
Women			
Men			
NYHA I or II			
NYHA III or IV			
Peak VO2 > median			
Peak VO2 ≤ median			
Follow-up > median			
Follow-up ≤ median			
Worst case			
Age > median			
Age ≤ median			
Women			
Men			
NYHA I or II			
NYHA III or IV			
Peak VO2 > median			
Peak VO2 ≤ median			
Follow-up > median			
Follow-up ≤ median			
Best case			
Age > median			
Age ≤ median			
Women			
Men			
NYHA I or II			
NYHA III or IV			
Peak VO2 > median			
Peak VO2 ≤ median			
Follow-up > median			
Follow-up ≤ median			

Table 4a-ITT. Time-to-event Outcomes from randomization through end of follow-up

Outcome	Tele Rehabilitation		Usual Care		Hazard ratio	p-value
	N (%)	Event rate at 14m	N (%)	Event rate at 14m		
All-cause mortality						
Cardiovascular mortality						
All-cause hospitalization						
Cardiovascular hospitalization						
Heart failure hospitalization						
All-cause mortality or all-cause hospitalization						
All-cause mortality or heart failure hospitalization						
Cardiovascular mortality or heart failure hospitalization						

Table 4b-ITT. Number of days in the hospital from randomization

Method of Imputation	Tele Rehabilitation	Usual Care
Proportional Fraction		
Worst case		
Best case		
Patients with full follow-up		

Table 5a Randomization by site

Site	Tele Rehabilitation	Usual Care
Total		

Table 5b Discontinuations by site

Site	Tele Rehabilitation	Usual Care
Total		

Table 5c Adverse Events

Adverse Event	Tele Rehabilitation	Usual Care	p-value

Table 5d Serious Adverse Events

Serious Adverse Event	Tele Rehabilitation	Usual Care	p-value