Study protocol

Title

Applying telemedicine technologies in a novel model of organizing and implementing comprehensieve cardiac rehabilitation in heart failure patients – TELEREH-HF.

Introduction

Heart failure (HF) epidemic is an aggressively developing phenomenon, stimulated by developing civilization and generating worrying economic and social effects.[1,2] The benefits of cardiac rehabilitation in HF patients are well established.[3] Therefore current guidelines strongly recommend exercise training as an important component of HF management. [1-6] Despite these facts, many HF patients do not undergo the programmes of cardiac rehabilitation.[3] In Poland, cardiac rehabilitation availability is highly unsatisfactory (around 8%) and unacceptably varied (0.5-70%).[7,8] With the existing organization and technical background, improving this situation seems impossible. Therefore we create the project: „To apply telemedicine technologies to implement a novel model of home-based comprehensive cardiac rehabilitation in HF patients".

The project will enable early secondary prevention in the population of people with HF to be implemented. It will be achieved via:

- Novel concept - "From Hospital To Home"
- Novel technology - telemedicine
- Novel method of comprehensive cardiac rehabilitation implementation

Hybrid comprehensive TELEREHabilitation in Heart Failure patients (TELEREH-HF) - a randomized, multi-center, prospective, open-label, parallel group controlled trial .

The TELEREH-HF trial is design to determine if a hybrid model of comprehensive telerehabilitation (TR) in HF patients influences days alive and out of hospital (DAOH) and prognosis when compared with usual care.

Objectives

The primary objective of the TELEREH-HF trial is to determine whether introducing a novel hybrid model of comprehensive TR in HF patients will significantly increase DAOH when compared with usual care.

The secondary objectives are to assess the effects of a hybrid comprehensive TR compared to usual care on all-cause and cardiovascular (CV) mortality and all-cause, CV and HF hospitalization.

The tertiary analyses will include: evaluation of the safety, effectiveness, quality of life (QoL), depression, anxiety, patients acceptance of and adherence to a hybrid comprehensive TR.

Study design

The TELEREH-HF study is a randomized, multicenter, prospective, open-label, parallel group controlled trial introducing a novel hybrid comprehensive TR in HF patients.

The study conduct is guided by good clinical practice, in accordance with the Declaration of Helsinki and the laws and regulations applicable in Poland.

The main investigator and Steering Committee designed the trial and wrote the study protocol. The study was approved by the local Ethics Committee. An independent Data Safety Monitoring Board will review patient data and a Clinical Endpoint Committee, blinded to treatment allocation, is appointed to adjudicate deaths and hospitalisations **(Table 1)**. Each patient is obliged to provide written informed consent.

Table 1. The Principal Investigator, Members of the Steering Committee, The Data Safety Monitoring Board and The Clinical Endpoint Committee

Principal Investigator	Ewa Piotrowicz MD, PhD
Steering Committee	Grzegorz Opolski MD, PhD (Warsaw, Poland; Chair), Maciej Banach MD, PhD Łódź, Poland), Michael Pencina PhD (Durham, NC, USA), Ryszard Piotrowicz (Warsaw, Poland), Wojciech Zaręba (Rochester, NY, USA)
Data Safety Monitoring Board	Tomasz Krauze PhD (Poznań, Poland; Chair), Rafał Dąbrowski MD, PhD (Warsaw, Poland), Marcin Grabowski MD, PhD (Warsaw, Poland)
Clinical Endpoint Committee	Mariusz Pytkowski MD, PhD (Warsaw, Poland; Chair), Paweł Krzesiński MD, PhD (Warsaw, Poland), Mariusz Kruk MD, PhD (Warsaw, Poland)

The study is ongoing in 5 centers in Poland:

- Institute of Cardiology, Warsaw (Coordinating Center),
- Medical University of Gdansk,
- Silesian Center for Heart Diseases in Zabrze,
- Medical University of Lodz,
- Medical University of Warsaw.

Study population, recruitment and randomization

The TELEREH-HF study has a target enrollment of 850 clinically stable HF patients (New York Heart Association [NYHA] class I, II or III and left ventricular ejection fraction [LVEF] ≤ 40%) after a cardiovascular (CV) hospitalization incident within 6 months prior to randomization. The inclusion and exclusion criteria are shown in **Table 1**.

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria
Patients eligible for the trial have to meet the following criteria of randomization, i.e. patients need to: - be of either sex with any aetiology of left ventricular systolic heart failure as defined in the ESC guidelines - have a LVEF ≤ 40% on echocardiography - belong to NYHA class I, II or III - have had a hospitalization incident within 6 months prior to randomization - be stable clinically (a patient does not need intravenous medication or has not had therapy modified for at least 7 days) - have no contraindications to undergo cardiopulmonary exercise test - be able to exercise using the new model of hybrid telerehabilitation

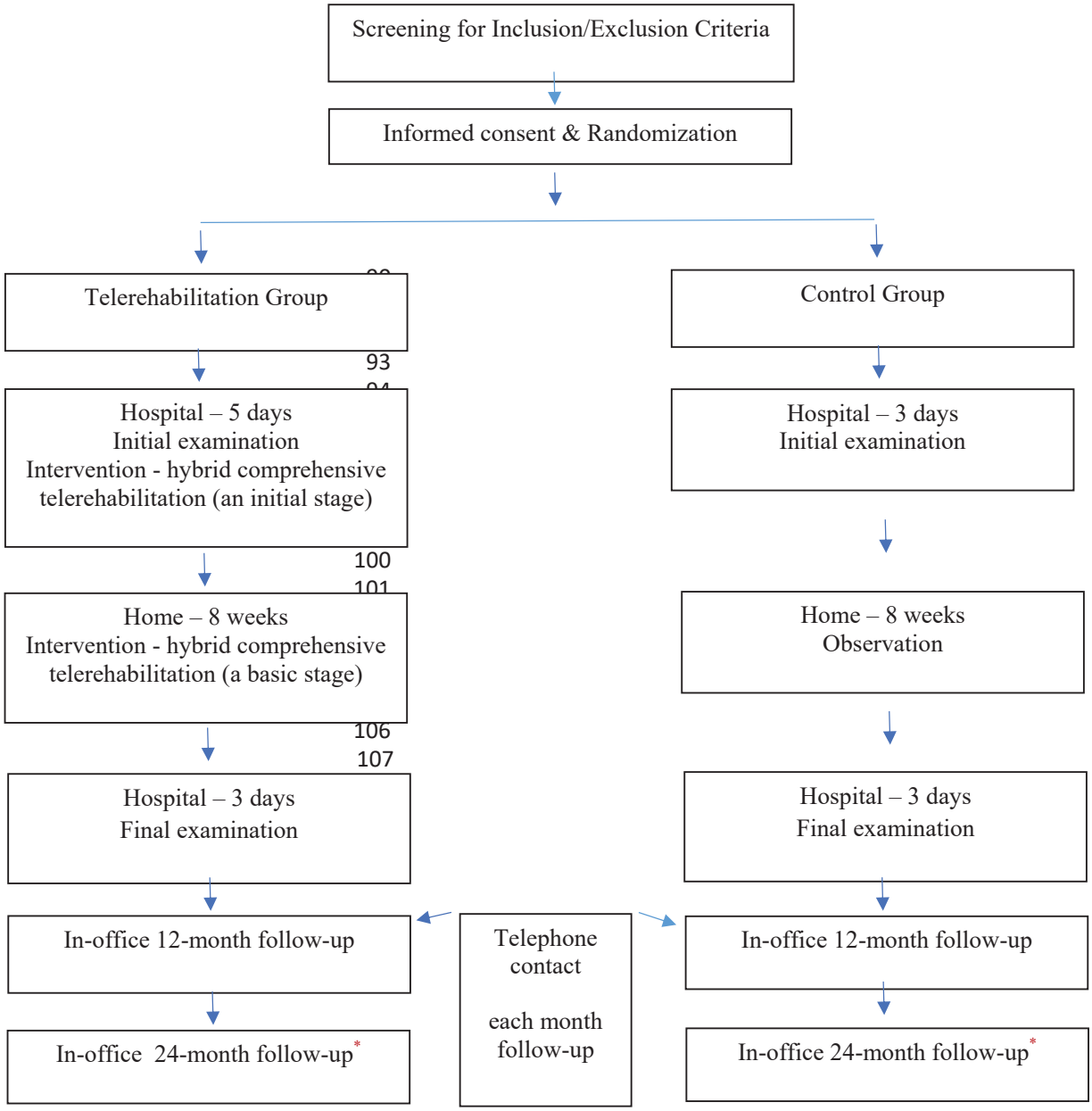
Exclusion Criteria
None of the following conditions may exist at randomisation: - NYHA class IV - unstable angina - unstable clinical status - a history of acute coronary syndrome within the last forty days in patients with LVEF ≤ 35% - percutaneous angioplasty within the last 2 weeks - coronary artery bypass grafting within the last 3 months - implantation/initiation of CRT-P or CRT-D or ICD or PM within the last six weeks - lack of ICD, CRT-P or CRT-D or PM therapy despite the indications for implantation according to ESC guidelines - intracardiac thrombus - rest heart rate >90/min - tachypnoe >20 breaths per minute - symptomatic and/or exercise-induced cardiac arrhythmia or conduction disturbances - acute myocarditis and/or pericarditis - valvular or congenital heart disease requiring surgical treatment - hypertrophic cardiomyopathy - severe pulmonary disease - uncontrolled hypertension - anemia (hemoglobin <11.0 g/dL) - physical disability related to severe musculoskeletal or neurological problems - recent embolism - thrombophlebitis - acute or chronic inflammatory disease - acute or chronic decompensated non-cardiac diseases (thyreotoxicosis, uncontrolled diabetes) - active malignant neoplastic diseases with survival prognosis below 2 – 5 years - orthotropic heart transplant in anamnesis - presence of an implanted left ventricular assist device or biventricular assist device - aortic aneurysm - severe psychiatric disorder - patient's refusal to participate

ESC - European Society of Cardiology, LVEF - left ventricular ejection fraction, NYHA - New York Heart Association, CRT-P - cardiac resynchronization therapy, CRT-D - cardiac resynchronization therapy and implantable cardioverter-defibrilator, ICD - implantable cardioverter-defibrilator, PM - pacemaker

Eligible patients will be randomized in 1:1 ratio to either hybrid TR + usual care (TR group) or to usual care only control group (CG) via a secure web-based randomization system – Research Electronic Data Capture (REDCap) housed in the Coordinating Center.[9] All sites will use the same allocation process to ensure uniform randomization.

The study schedule is shown in **Figure 1**.

Figure 1. The study schedule and follow-up.



* All patients whose 24-month follow up is not later than 31/03/2019 (in accordance with the regulations of the National Center for Research and Development).

Intervention in Telerehabilitation Group

The TR group patients will undergo a 9-week hybrid comprehensive TR program consisting of two stages: an initial stage (1-week) conducted at hospital and a basic stage 8-week home-based TR

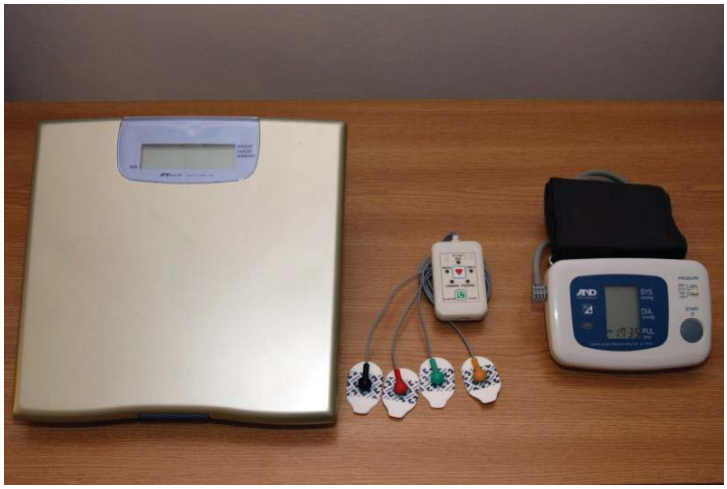
five times weekly. The goals of the initial stage are: a baseline clinical examination, optimization of treatment, education, individual planning of exercise training and performing five monitored educational training sessions. The basic stage, which is conducted at home consisted of two parts, is performed prior to each training session: the first part - the training consent procedure is required for a patient to access each training session, and the second part - the training session.[10-12]

Telemonitoring

Remote monitoring during rehabilitation and training consent procedure.

Telerehabilitation is carried out by a medical team and advanced monitoring systems are used. A TR medical team is composed of: physicians, physiotherapists, nurses and a psychologist. The monitoring system includs: (1) a special remote device for tele-ECG-monitored and supervised exercise training - TR set (manufactured by Pro Plus Company, Poland), which consists of: EHO mini device, blood pressure measuring and weighing machine, (2) data transmission set via a mobile phone, (3) a monitoring centre capable of receiving and storing patients' medical data (specialized hardware and software are necessary).[10-12]

Figure 2. Telerehabilitation set — a weighing machine, the EHO mini device, a manometer.



The TR group patients will receive a TR set and mobile phone. 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. An EHO mini device has training sessions preprogrammed individually for each patient (defined exercise duration, breaks, timing of ECG recording). The moments of automatic ECG registration are preset and coordinated with the exercise training. The planned training sessions are executed with the device indicating what needed to be done with sound and light signals. There are sound signals in the form of bleeps and light signals from color emitting diodes. Bleeps and green diode blinking meant that the patient has to perform exercise. Another set of bleeps and red diode blinking meant "stop exercise". The timing of automatic ECG recordings correspond to peak exercise.

An EHO mini device has a tele-event-Holter ECG feature as well. It enables a patient, whenever a worrying symptom occurs, to register and immediately send the ECG recording via mobile phone network to the telemonitoring center. [10-12]

Before beginning a training session, patients will use the mobile phone to answer a series of questions regarding their present condition, including fatigue, dyspnea, blood pressure, body mass, and medication taken. Patients then will transmit resting ECG data to the monitoring center. Before giving permission to start the training session, the medical staff also will analyze data from the remote monitoring of CIEDs. If no contraindications to training are identified, patients will be given permission to start the training session.[10-12] The system is used to monitor and control the training in any place where the patient will decide to exercise. If the training session is completed uneventfully, the patient will transmit the ECG recording via the mobile phone network to the monitoring center immediately after the end of every training session. The ECG recordings will be analyzed at the monitoring center, and the safety, efficacy, and accuracy of a tailored patient's rehabilitation program will be assessed. Using the data on heart rate (HR) during exercise and the patient's subjective evaluation of the perceived exertion according to Borg scale, consultants will be able to adjust the training workload appropriately or, if necessary, to discontinue the session. Telephone contact is also use for psychological support.[10-12]

Remote monitoring of cardiac implantable electronic devices (CIEDs)

Additionaly, TRG patients with CIEDs (if technical requirements were complied with) will receive the transmitter (Biotronik - CardioMessenger; Medronic transmitter [Home Monitor] of the CareLink™ network; St-Jude – Merlin@home™ wireless transmitter) which allows the automatic transmission of data from the implant to a web-based monitoring platform (Biotronik – Home Monitoring Service Center, Medtronic – CareLink-Network , St-Jude – Merlin.net™Patient Care Network). Remote monitoring will rely on data acquired automatically on a daily basis by the device, with unscheduled transmission of any predefined alerts to the medical staff in each center. These alerts involved device integrity [e.g. battery status- the battery depletion indicators: end of service (EOS), the elective replacement indicator (ERI) lead impedance], programming issues [e.g. disabling of ventricular fibrillation (VF) therapy, antitachycardia pacing (ATP) therapy, insufficient safety margins for sensing or capture], and medical data [e.g. arrhythmias – supraventricular tachycardia (SVT)/atrial fibrillation (AF)/atrial flutter (AFl), ventricular tachycardia (VT)/VF, indication of lung fluid accumulation].

In addition, each patient with CIEDs and a remote monitoring device will have scheduled standard follow-up visits in order to evaluate the device functioning [after four weeks from the beginning of hybrid TR in TRG and usual care in CG and immediately after the intervention (after 9 weeks) in the TG and the observation period in CG]. The following parameters will be evaluated: mean heart rates, patient activity, supraventricular (SVT, AF/AFl) and ventricular [non-sustained VT (nsVT), VT/VF] arrhythmia, impedance, percentage of resynchronization stimulation, intracardiac electrogram (IEGM).

Exercise training

Cardiac rehabilitation is planned according to the published guidelines for HF patients.[1-3] In order to ensure patients safety, the following recommendations will be taken into account: (1) special attention is paid to appropriate patient risk stratification before cardiac rehabilitation; (2) contraindications to exercise training are never overlooked (**Table 3**); (3) in patients with an

implantable cardioverter-defibrilator (ICD), maximal training HR is set at 20 b.p.m. lower than the ICD discharge threshold; and (4) in patients with a pacemaker, cardiac resynchronization therapy (CRT-P), cardiac resynchronization therapy and implantable cardioverter-defibrilator (CRT-D), the rate-response function is switched on, enabling HR adjustment to the physical effort which facilitated reaching the desired training HR.

Table 3. Contraindications to exercise training

Acute worsening of exercise tolerance, dyspnoea or chest pain
Increase of 1.8 kg or more in body mass over the previous 1–3 days
Supine resting heart rate > 90 beat per minute
New-onset cardiac arrhythmias: atrial fibrillation/atrial flutter/supraventricular tachycardia, complex ventricular arrhythmia at rest or appearing with exertion
New-onset advanced atrioventricular block
New-onset of significant ischaemia during low-intensity exercise
Decrease in systolic blood pressure with exercise
Uncontrolled hypertension, resting blood pressure >140/90 mmHg
Recent embolism
Recent thrombophlebitis
Acute systemic illness
New-onset uncontrolled endocrine and metabolic disorders

Exercise trainings will be planned individually for each patient during hospitalization.[3] The telerehabilitation program encompasses three training modalities: endurance aerobic Nordic walking training, respiratory muscle training and light resistance and strength exercises. The details are presented in **Table 4** and **Table 5**.[6.10,11]

Table 4. Exercise training model

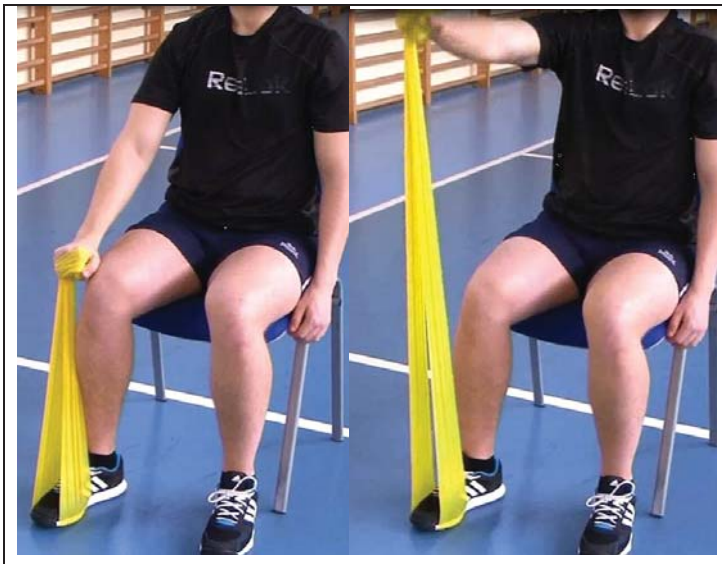
Type of exercise training	Exercise prescription
Aerobic endurance training	**Devices:** Nordic walking poles **Training session** consists of: 1.Warm-up: breathing and light resistance exercises using poles for Nordic walking; duration 5–10 min 2.Nordic walking training **Intensity:** 40-70% of heart rate reserve, perceived exertion level—score of 11-12 on the Borg scale **Duration:** start at 10 min/session/day[a] 15 min/session/day[b] 20 min/session/day[c] gradually increased to 30–45 min/session/day[d] 3.Cool down: relaxation, breathing exercise; duration 5 min **Frequency:** 1 session/day

Respiratory muscle training	**Devices:** Train Air software - during the initial stage at the hospital Threshold Inspiratory Muscle Trainer - during the basic stage at home **Intensity:** start at 30% of the maximal inspiratory mouth pressure (PI_{max}) and readjusted to a maximum of 60% (if possible) **Duration:** minimum 5-10 minutes/day maximum 20-30 minutes/day; **Frequency:** 3-5 times/ throughout the day
Resistance and strength training	**Devices:** Thera Band - yellow color **Intensity:** 5-10 repetitions of each of the seven exercises (see Appendix 2) **Duration:** gradually increased 5-10-15 minutes/day **Frequency:** 1 session/ day

Duration of aerobic endurance training depended on the functional capacity in baseline cardiopulmonary exercise test:
[a]baseline peak VO_2 below 10 mL/kg/min.
[b]baseline peak VO_2 10–18 mL/kg/min.
[c]baseline peak VO_2 over 18 mL/kg/min.

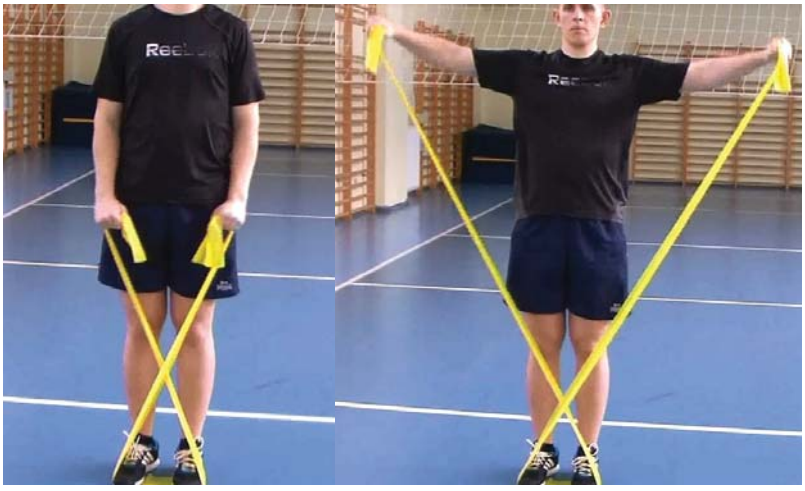
Table 5. Resistance and strengh exercise using Thera band

Upper limbs
Exercise 1. Position: sitting, the center of the band under the right / left foot. We keep the ends of the tape in the right / left hand. Flexing the right / left elbow. 
Exercise 2. Position: sitting, the center of the band under the right / left foot. We keep the ends of the band in the right / left hand. Raise the right / left upper limb to the level of the shoulder.



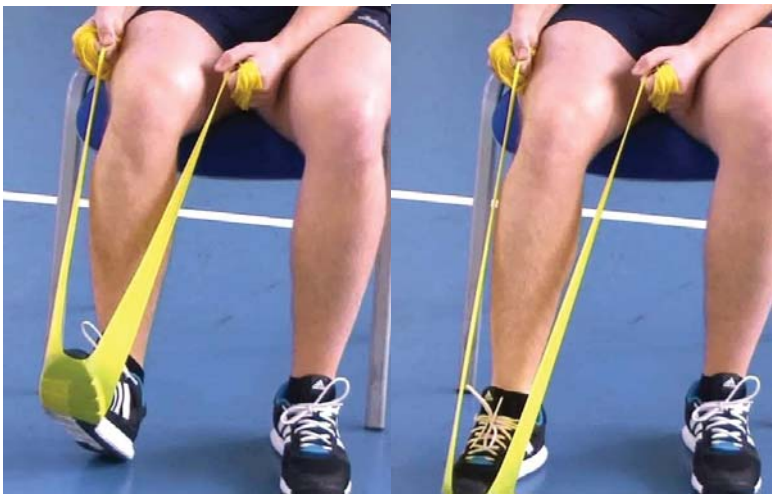
Exercise 3. Position: sitting, band placed on the back. We grab the ends of the band. Upper limbs flex at the elbows at the chest level, hands keep the tape slightly taut. We stretch the tape as far forward as possible, trying to keep the movement horizontally at chest level.

Exercise 4. Position: standing in the middle of the band. The band crossed in front of the body. Abduction of the arms and returning to the starting position.

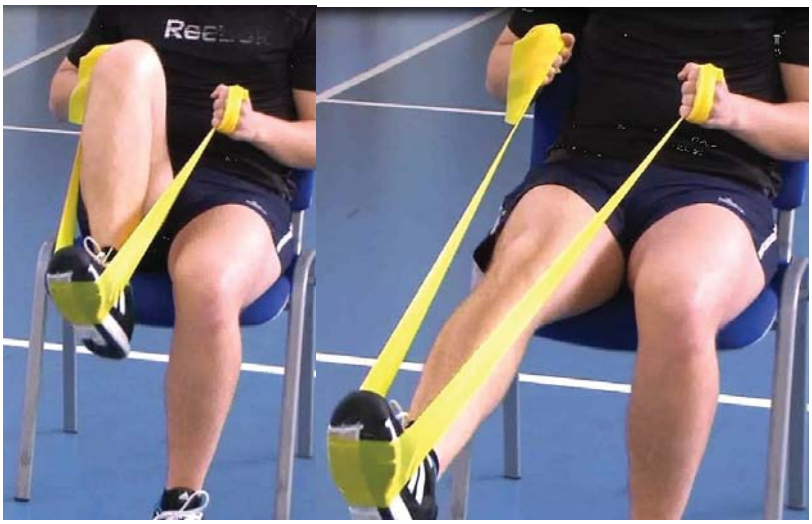


Lower limbs

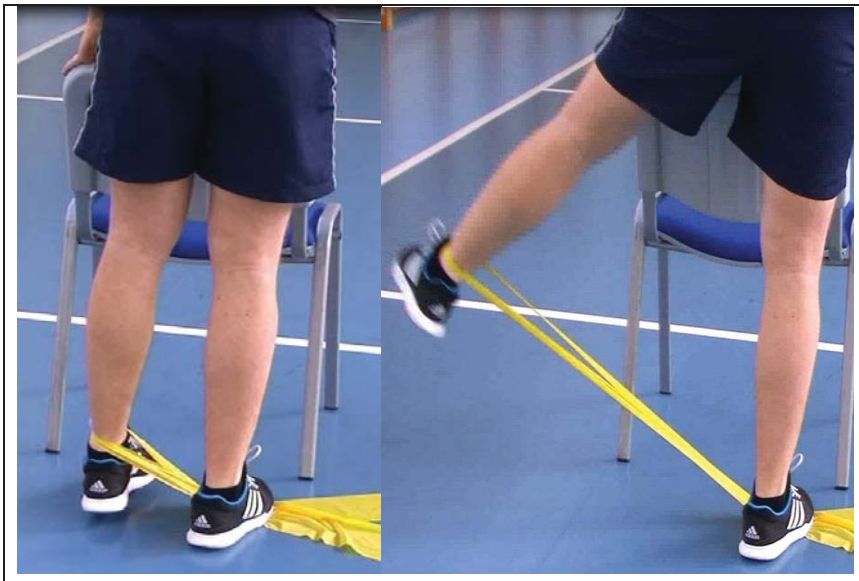
Exercise 5. Position: sitting, the center of the band under the foot, the ankle joint extended (dorsiflexion). The ends of the band are held in the hands at the level of the knee joint. The band tight. Plantar flexion of the ankle.



Exercise 6. Position: sitting, the hip and knee joint bent. Wrap the band wrapped around the foot with both hands. Hands are placed on the chest. Extension in the hip and knee joint.



Exercise 7. Position: Standing in a light stride, place the widely spread band under the foot of the supporting leg and attach it at the height of the ankle joint of the other limb. Abduction of the lower limb.



The chosen workload during Nordic walking is supposed to reflect individual effort tolerance with regard to: (1) perceived exertion according to the Borg scale and (2) the training HR range established individually for each patient based on cardiopulmonary exercise test (CPET) perform before the start of the TR program. In line with the recommendations, the assumption is that patients are not to exceed perceived moderate exertion during exercise training (i.e. a score of 11-12 on the Borg scale). The training HR is calculated using the method known as HR reserve. This method uses a percentage of the difference between the maximum HR and the resting HR rate, and adds this value to the resting HR. The target training HR is 40–70% of the HR reserve. Patients train five times a week.[11]

Education

Education program is designed and run by the TR team. Patients will be taught how to self-evaluate, how to measure HR, blood pressure, body mass, how to performed all modalities of exercise training, how to evaluate the level of perceived exertion according to the Borg scale and how to operate a TR set. Education will also encompass nutritional counselling, lipid management, smoking cessation, vocational and psychosocial support.[6,10-12]

Control Group

Patients randomized to the CG will undergo baseline clinical examinations during a 3-day hospitalisation and then will be under observation until the end of the 9th week and will receive usual care appropriate for their clinical status and standardized within a particular center (some of them can participate in a rehabilitation program and some of them has remote monitoring of CIEDs). After the 9th week patients will undergo final assessments during a 3-day hospitalization.

All patients, regardless of the treatment group, will receive recommendations for suitable lifestyle changes and self-management according to guidelines.[1-10]

Clinical examinations

All 850 patients will undergo the following assessments at entry (during 5 days of hospitalization-TRG, and 3 days of hospitalisation-CG) and after completing the 9-week program (during 3 days hospitalisations – both groups): clinical examination with symptom evaluation (NYHA class), blood testing [blood count, serum creatinine, electrolities (natrium, potassium), glycaemia, N-terminal pro B-type natriuretic peptide (NT-proBNP), aspartate aminotransferase, alanine aminotransferase, thyroid stimulating hormone (TSH), international normalized ratio (INR), urinalysis], ECG, two-dimensional echocardiography, six-minute walk test (6-MWT), CPET, 24 hours holter ECG monitoring, evaluation of CIEDs proper functioning, and psychological assessment: the QoL based on SF-36 Survey; the depression based on Beck inventory; the anxiety based on STAY.[6,10-12]Additionally, after 9 weeks, the TRG will be analyzed for: safety and patients' acceptance of and adherence to hybrid comprehensive TR.

Evaluation of novel model of hybrid comprehensive telerehabilitation in terms of tertiary analyses

<u>Assessment of hybrid comprehensive TR effectiveness.</u>

The effectiveness of TR and the comparison of the two arms will be based on the analysis of changes (between entry and 9 weeks – intervention period in TRG and observation period in CG) of the following parameters: HF functional class according to NYHA, CPET duration, peak oxygen consumption (pVO_2), % of predicted peak VO2 (pVO_2%N), 6-MWT distance, QoL (SF-36) score, depression and anxiety assessment.

Assessment of hybrid comprehensive TR safety.

The safety assessment will include the incidence of: adverse events (ischemic symptoms, dyspnea – tachypnoe > 20/min, syncope or fainting, passing to a higher NYHA class, putting on ≥1.8kg body mass during 1-3 days, symptomatic drop in systolic blood pressure, SVT, AF, nsVT, VT, VF, II and III degree atrio-ventricular block, resting HR ≥100/min, left- and/or right-ventricular insufficiency, need for urgent hospitalization, death) during exercise training, directly following it (up to 1 hour) and adverse events regardless of the training (including data from remote monitoring of CIEDs).

Assessment of the patients' acceptance of hybrid comprehensive TR.

The patients' acceptance of TR will be analyzed based on a 12-item questionnaire filled out by patients at the end of TR, which will include the assessment of: difficulties in operating the TR set, the influence of the TR set of their perceived safety, patients' compliance to the recommendations on pharmacotherapy, nutrition and their lifestyle **(Table6)** .[12]

Table 6. Patients' acceptance of hybrid comprehensive telerehabilitation questionnaire.

Questions	Answers (%)
1.Did you control the device by yourself ?	Yes/No
2.Was operating the device:	Very easy / Easy / Difficult / Very difficult
3.Was accurate placing electrodes on your skin difficult?	Yes/No
4.Did you observe any significant skin reaction to electrodes?	Yes/No
5.When using provided equipment to communicate with monitoring centre, was the sound quality satisfactory?	Yes/No
6.Did you find it difficult to coordinate exercise with the instructions from the device?	Yes/Sometimes/No

7.Was transmitting data (ECG, blood pressure) troublesome?	Yes/Sometimes/No
8.Did you ever miss doing a telerehabilitation session because of technical problems? If Yes, how many times?	Yes/No
9.When did you use the telemedicine equipment?	Only during exercise During exercise and when I felt unwell
10.Did TR stimulate you to do exercise?	Yes/Moderately/No
11.Did you feel safer during TR than when you did exercises at home without supervision?	Yes/No
12.Did TR make you increase your everyday activities? Physical exercises Mental Social Professional Sexual	 Yes/No Yes/No Yes/No Yes/No no applicable Yes/No

ECG - electrocardiogram; TR - telerehabilitation

Assessment of the adherence to hybrid comprehensive TR.

Adherence during TR will be assessed based on the daily telephone contact with the monitoring centre, which is required to obtain the necessary permission for the training and compliance to the exercise training. Adherence is defined as the percentage of patients who carry out the prescribed exercise training. According to the recommendations, in terms of their adherence, the patients will be divided into three groups: the first group are adherent patients, i.e. patients who adhere both to the number of training sessions prescribed and to the duration of the prescribed cycle by at least 80%; the second category consisted of non-adherent patients, who adhere < 20% to the prescribed number of training sessions and their duration. The third group correspond to the partially adherent patients who carry out the prescribed exercise, yet tend to omit some of them or do not carry them out for the prescribed duration (i.e. who adhere ≥ 20% and <80%).[13]

Follow-up

All patients will be followed up for a maximum of 24 months with a maximum of two check-up visits within the 12 and 24 months following the end of the preliminary 9-week training program in TRG and the observational period in CG. Each month follow-up will be also conducted via telephone (conversations with the patient and/or family member) in order to collect data about primary and secondary endpoints. All patients will be followed-up for a maximum of 24 months after the 9-week period.

Primary hypothesis sample size considerations

The primary study hypothesis is that TRG strategy is superior to CG strategy resulting in a larger percent of DAOH. Because possible follow-up varies between patients (12 to 24 months after the 9-week training period), the primary analysis will rely on the percent of DAOH calculated as the ratio of the DAOH divided by total days of follow-up for each patient.

The sample size for this study is 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 for the TRG arm and the CG arm is 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 increases to 842.

Statistical Analyses

Primary Outcome

The primary analysis will be based on the percent of DAOH during the 12-24-month follow-up and analyzed using the Wilcoxon-Mann-Whitney test. DAOH is defined as the number days out of the first 365 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. We plan to conduct two analyses, intent-to-treat (ITT) and modified intent-to-treat (MITT). The follow-up for ITT will start at randomization and extend for a minimum of about 14 months (9 week training period and 12 month follow-up) and a

maximum of 26 months (9 week training period plus 24 months of follow-up). For the MITT analysis, the follow-up will start at the end of the 9-week period.

Missing data

If a patient remained in the study for less than 365 days 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 and multiplied by 365;
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.

Subgroup and Sensitivity Analyses

Subgroup analyses will be conducted to assess treatment heterogeneity by study site, age, sex, baseline NYHA class, peak VO_2 consumption and duration of follow-up. An additional sensitivity analysis will be conducted excluding patients from the control arm if they participated in a rehabilitation program.

Secondary Outcomes Assessed at 12 months.

The following time-to-event outcomes will be illustrated using Kaplan-Meier plots and compared between treatment arms using Cox proportional hazards regression with site and treatment arm as covariates: all-cause mortality, CV mortality, all-cause hospitalizations, CV hospitalizations, HF hospitalization, composite of all-cause mortality or all-cause hospitalization, composite of all-cause mortality or CV hospitalization, composite of all-cause mortality or HF hospitalization and composite of cardiovascular mortality or HF hospitalization. All available follow-up will be used with event rates estimated at 12 months.

Tertiary Outcomes Assessed at 9 weeks.

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 pVO_2 in CPET, change inpVO_2%N in CPET, change in 6-MWT distance, change in QoL measures with the SF-36 instrument as well as change in depression and anxiety scales. NYHA class will be analyzed as ordinal variable using ordinal logistic regression including terms of baseline NYHA class, site and treatment arm.

The summary is included in the **Table 7 and Table 8**.

Table 7. TELEREH-HF Endpoints

Primary end-point: The percent of number of days alive and out of hospital (DAOH) during the12-24 months follow-up
Secondary end-points: **Secondary outcomes assessed at 12-24 months:** - all-cause and CV mortality - all-cause, CV and HF hospitalization **Tertiary analysis - outcomes assessed at 9 weeks - the effectiveness of hybrid TR based on:** - New York Heart Association class - cardiopulmonary exercise treadmill test duration - peak oxygen consumption (pVO_2) - percentage of predicted peak oxygen consumption (pVO_2%N) - six-minute walking test distance - quality of life assessment - depression assessment - anxiety assessment - acceptance of TR - adherence to TR
Composite end-points encompases: - CV mortality and HF hospitalization - CV mortality and CV hospitalization - CV mortality and non CV hospitalization - all-cause mortality and CV hospitalization - all-cause mortality and non CV hospitalization

TRG-telerehabilitation group, CG-control group, CV-cardiovascular, HF-heart failure,TR-telerehabilitation

Table 8. Definitions of Outcomes

Hospitalization
Regarding this trial, hospitalization is defined as hospital admission resulting in an overnight stay where the length of stay is at least 24 hours. In case of emergency room visits that include a date change with an unclear length of stay the (Clinical Endpoint Committee) CEC members are requested to discuss these events at a CEC meeting where the final classification (ambulatory visit versus hospital stay) will be made. All other events leading to an emergency room visit with a length of stay under 24 hours will be not classified as hospitalization.
Primary reason of hospitalization ***I.Non-cardiovascular reason for hospitalization*** For a hospitalization considered as non-cardiovascular the admission reason should be clearly not associated with a deterioration of a cardiovascular condition. Examples are: admission due to a fall, back pain or others. ***II. Cardiovascular reason for hospitalization*** For a hospitalization considered as cardiovascular the admission reason should be clearly associated with a deterioration of a cardiovascular condition or need of intensified diagnostic procederes only feasable in a hospital. Examples could be: newly occurred or recurrent arrhythmia, acute coronary syndrome, myocardial infarction, worsening of heart failure, myocarditis, endocarditis, stroke or pulmonary infarction with the need for intensified diagnostic and therapy. The admission reason should be determined in the evaluation form. Hospitalisation for or with worsening heart failure 1.A cardiovascular hospitalisation will be classified as 'for or with worsening heart failure' if the reason for admission is worsening heart failure. The CEC diagnosis will be made using the criteria described below, irrespective of the investigator and/or discharge diagnosis. The following two criteria must apply to adjudicate 'worsening heart failure': a. Presence of 2 typical heart failure signs or symptoms (including shortness of breath, dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, bendopnea, fatigue, reduced exercise tolerance, pulmonary oedema, jugular vein distensions, pulmonary rales, S3 on cardiac auscultation, hepatojugular reflux, altered haemodynamics, peripheral oedema, and cardiomegaly). OR objective evidence for worsening heart failure (as revealed by echocardiography, chest radiography or measurement of a natriuretic peptide) and an intensification of heart failure therapy). b. Treatment for heart failure started or intensified: To fulfil this criterion, the patient must have an initiation or intensification of therapy for heart failure, including at least one of the following: - Augmentation in oral diuretic therapy - Intravenous diuretic or vasoactive agent (e.g. inotrope, vasopressor or vasodilator) - Mechanical circulatory support or mechanical fluid removal For the avoidance of doubt, if the patient developed worsening heart failure during a hospitalisation (but heart failure was not the reason or a major component of the respective hospital admission), this will not be judged a 'Hospitalisation for or with worsening heart failure', but should be discussed in a CEC meeting.
Death
For this trial, death is defined as death of any cause within a hospital or outside of a hospital. For secondary endpoint, the death will be distinguished in cardiovascular and non-cardiovascular death. If it is not possible to evaluate the cause of death, the CEC members are requested to discuss these

events at a CEC meeting where the final classification will be made.

I Cardiovascular death

A death will be considered 'cardiovascular' when it is due to cardiovascular causes, which includes but is not limited to the following: deterioration of heart failure, acute myocardial infarction, arrhythmia, heart failure, pulmonary embolism, cerebrovascular disease (e.g. stroke), severe bleeding, endocarditis etc. The most applicable cause should be entered by the CEC-member in the evaluation form.

1.Death due to heart failure

Death resulting from mechanical dysfunction of the heart (even if the terminal event was likely an arrhythmia or sudden cardiac death) will be classified as heart failure death when preceded by persistent or frequently recurrent NYHA class IV symptoms, an escalating need for supportive therapy and often by evidence of organ failure (e.g.: renal). Subjects with cardiogenic shock or pulmonary oedema resistant to therapy are included in this category.

2.Sudden cardiac death

Sudden cardiac death is defined as natural death due to cardiac causes, preceded by abrupt loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected. Unwitnessed deaths equally will considered as 'sudden cardiac death'.

As well as a patient was asymptomatic or without evidence of a deteriorating medical condition and seen alive within 24 hours prior to being found dead, this will be considered to be a 'sudden cardiac death'.

II Non-cardiovascular death

Death due to non-cardiovascular causes including, but not limited to the following: death from suicide, violence or accident; death from infection, but non-cardiovascular; death from renal failure, but non-cardiovascular; death from respiratory insufficiency, but non-cardiovascular; death from cancer; death from other non-cardiovascular cause.

III Death from unknown causes

This category applies to death with an unknown cause despite available data, and not attributable to any of the above categories. All attempts will be made to obtain adequate data for classification in an effort to minimize the number of subjects falling into this category.

IV Death from unclassifiable cause due to lack of data

This applies to death where review and classification is not possible because of lack of data. Such cases will be classified as 'Unknown'.

The TELEREH-HF trial will provide data on the effects of the novel model of HF patients management including hybrid comprehensive TR in terms of days alive and out of hospital, hospitalization and mortality rate. In addition, it will become a unique source of data on safety, effectiveness, QoL, depression, anxiety and patients' acceptance of and adherence to this intervention.

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