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Study design paper

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Optimising exercise training in prevention and treatment of diastolic heart failure (OptimEx-CLIN): rationale and design of a prospective, randomised, controlled trial

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Abstract

Background: Heart failure with preserved left ventricular ejection fraction (HFpEF) currently affects more than seven million Europeans and is the only cardiovascular disease increasing in prevalence and incidence. No pharmacological agent has yet been shown to improve symptoms or prognosis. The most promising way to improve pathophysiology and deprived exercise-tolerance in HFpEF patients seems to be exercise training, but the optimal approach and dose of exercise is still unknown.

Objectives: The major objective of the optimising exercise training in prevention and treatment of diastolic heart failure study (OptimEx-CLIN) is to define the optimal dose of exercise training in patients with HFpEF. In order to optimise adherence, supervision and economic aspects of exercise training a novel telemedical approach will be introduced and investigated.

Study design: In a prospective randomised multi-centre study, 180 patients with stable symptomatic HFpEF will be randomised (1:1:1) to moderate intensity continuous training, high intensity interval training, or a control group. The training intervention includes three months supervised followed by nine months of telemedically monitored home-based training. The primary endpoint is change in exercise capacity, defined as change in peak oxygen uptake (VO_{2peak}) after three months, assessed by cardiopulmonary exercise testing. Secondary endpoints include diastolic filling pressure (E/e′) and further echocardiographic and cardiopulmonary exercise testing (CPX) parameters, biomarkers, quality of life and endothelial function. Training sessions and physical activity will be monitored and documented throughout the study with accelerometers and heart rate monitors developed on a telemedical platform for the OptimEx-CLIN study. Inclusion of patients started in July 2014, first results are expected in 2017.

Keywords

Heart failure, diastolic heart failure, heart failure with preserved ejection fraction, exercise training, interval training, training intensity, telemonitoring, exercise capacity

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Background

More than 14 million Europeans are affected by heart failure (HF) whereof at least 50% are considered to have heart failure with preserved ejection fraction (HFpEF).[1] Besides advanced age and female gender, prevalent modifiable risk factors for HFpEF also include hypertension, diabetes, obesity, and inactive lifestyle.[2,3] The ageing population explains in part why HFpEF is the only cardiovascular disease with increasing prevalence and incidence, affecting 10–20% of the elderly and contributing substantially to hospitalisations of elderly HF patients.

The poor clinical outcome in patients with HFpEF is not explained by age, gender, nor the high prevalence of cardiovascular risk factors and co-morbidities,[4] and the underlying mechanisms and therefore treatment options are incompletely understood. The pharmacological therapy for HFpEF to improve outcome and symptoms has been particularly disappointing. Several large trials, using established pharmacological strategies in HFpEF, such as angiotensin-converting-enzyme inhibitors (PEP-CHF),[5] angiotensin receptor blockers (PARAMOUNT,[6] CHARM-PRESERVED,[7] I-PRESERVE[8]) or spironolactone (Aldo-DHF,[9] TOPCAT[10]) have failed to convincingly demonstrate substantially improved symptoms, morbidity or mortality in HFpEF. Overall, currently no pharmacological agent has shown to improve symptoms, exercise capacity or prognosis in this severely debilitated patient population. Therefore, other approaches have to be explored.

Rationale

A cardinal feature of HFpEF is severely impaired exercise capacity, objectively determined as peak oxygen uptake (VO_{2peak}), which is one of the strongest prognostic markers in chronic HF.[11] Exercise training is a promising way to improve exercise intolerance in HFpEF patients. In addition, exercise training may exert beneficial effects on a number of pathophysiological components in patients with HFpEF. Therefore, the concept of exercise training as a powerful strategy to tackle HFpEF is progressively emerging, but clinical as well as pathophysiological data are still limited. In the largest randomised, controlled exercise training trial ($n = 67$, Ex-DHF-P) in HFpEF patients published so far, three months of combined endurance/resistance training (3×20–40 min, 70% VO_{2peak} plus resistance training 60–65% 1-RM) led to a significant improvement in VO_{2peak}, coinciding with an improvement in diastolic function, reduction in left atrial volume and improvement in quality of life (QoL).[12] However, in this pilot study, mechanistic aspects, long-term effects and the optimal mode and dose of exercise interventions were not studied. Therefore, the optimising exercise training in prevention and treatment of diastolic heart failure study (OptimEx-CLIN) is the first phase IIb, multi-centre randomised controlled trial (RCT) investigating exercise-dose in HFpEF patients.

Study population

The study will include sedentary patients with stable symptomatic HFpEF, diagnosed according to criteria of the European Society of Cardiology.[13] Patients with reduced left ventricular ejection fraction, as well as patients with other causes for HF symptoms such as significant valvular or coronary disease or uncontrolled hypertension or arrhythmias will be excluded. Inclusion and exclusion criteria are listed in Table 1.

Study design

OptimEx-CLIN study is a prospective, randomised, controlled, three-armed, multi-centre trial.

Study objectives

The primary objective of OptimEx-CLIN is to define the optimal exercise dose in terms of improvements in exercise capacity and diastolic function in patients with HFpEF.

Our secondary objective is to determine the optimal exercise dose to reverse the underlying mechanisms involved in exercise intolerance. We will specifically focus on cardiac function and structure, peripheral arterial endothelial function and arterial stiffness, skeletal muscle structure and function (mitochondrial function, capillary density, anabolic/catabolic pathways, modifications and expression of contractile proteins) and blood parameters as microRNAs (miRs), fasting glucose, HbA1c and insulin concentrations.

Further endpoints are the effects of different exercise doses on currently established (e.g. N-terminal prohormone of brain natriuretic peptide (NT-proBNP)) and potential novel pathophysiological markers and therapeutic targets (e.g. collagen markers, protein kinase G, miRs) and QoL. Additionally, the potential impact of exercise training on cost for HFpEF will be calculated.

As an important monitoring tool in OptimEx-CLIN we will develop and test a telemedical platform for accelerometer and heart rate monitoring with individualised feedback for each training session. This platform will automatically record adherence to the training sessions and intensities, and overall physical activity level.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Stable symptomatic heart failure with preserved ejection fraction (diagnosis according to criteria of the European Society of Cardiology (2012)) (a) Signs and symptoms of heart failure failure with associated signs or symptoms e.g. dyspnoea on exertion, orthopnoea, paroxysmal dyspnoea, and peripheral oedema (NYHA II or III) (b) LVEF $\geq$50% (c) Diastolic dysfunction (E/e $'>$15 or E/e $'$8–15 + NT-proBNP $>$220 or BNP $>$80 pg/ml). 2. Sedentary men and women (structured exercise $<2 \times 30$ min/wk) 3. Age $\geq$ 40 years 4. Written informed consent 5. Clinically stable for $\geq$6 weeks 6. Optimal medical treatment for $\geq$6 weeks	1. Non-cardiac causes for heart failure symptoms: • Significant valvular or coronary disease • Uncontrolled hypertension or arrhythmias • Primary cardiomyopathies 2. Significant pulmonary disease (FEV1 $<$ 50% predicted, GOLD III–IV) 3. Inability to exercise or conditions that may interfere with exercise intervention 4. Myocardial infarction in the last 3 months 5. Signs of ischaemia during CPX 6. Comorbidity that may influence one-year prognosis 7. Participation in another clinical trial

CPX: cardiopulmonary exercise testing; E/e': diastolic filling pressure; FEV1: forced expiratory pressure in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; pg: picogram.

Endpoints

The primary endpoint is a *clinical endpoint* of three months change in VO_{2peak}.

Secondary endpoints are:

1. Change in E/e′ after three and 12 months.
2. Change in VO_{2peak} after 12 months.
3. Change in NT-proBNP after three and 12 months.
4. Change in health-related QoL measured by the Kansas City Cardiomyopathy Questionnaire after three and 12 months.
5. Change in left atrial volume index after three and 12 months.
6. Change in e′ medial after three and 12 months.
7. Change in submaximal exercise capacity after three and 12 months. Submaximal exercise capacity is expressed as workload at the first ventilatory threshold (VT1).
8. Change in minute ventilation/carbon dioxide production (VE/VCO_2) slope after three and 12 months.
9. Change in flow-mediated dilation (FMD) after three and 12 months.

Intervention

After informed consent and screening, patients will be randomised (1:1:1) to three groups: group 1: moderate intensity continuous training (MCT); group 2: high intensity interval training (HIIT); and a control group (CG) using an online protocol at the Coordinating Centre (Figure 1).

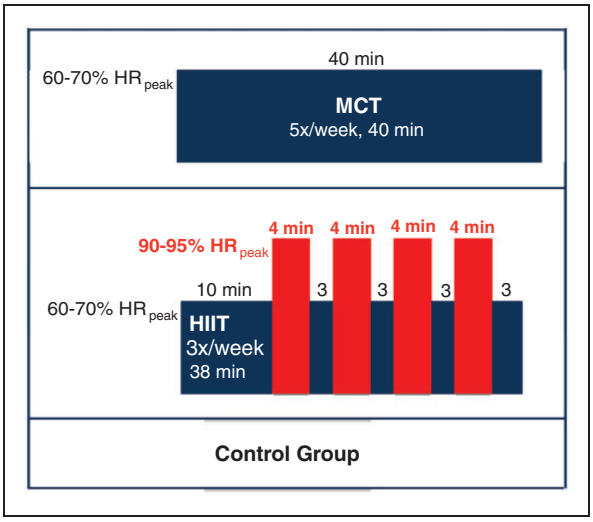

Figure 1. Training protocols of moderate intensity continuous training (MCT), high intensity interval training (HIIT) and control group.
HR_{peak}: peak heart rate.

CG

Patients in the CG will be given standard advice on the general cardiovascular benefit of exercise according to current guidelines (30 min of walking on most days of the week)[14] and to follow their daily leisure physical activity as usual throughout the study. However, normal daily activity is an important co-variable and will therefore be continuously recorded using QoL and activity questionnaires and accelerometry.

Training intervention

Patients in groups 1 and 2 will perform intensity-controlled training on bicycle ergometers. Exercise intensity (relative to peak heart rate; %HRpeak) is determined by maximal cardiopulmonary exercise testing (CPX) at baseline and will be adapted at six weeks, three months, and six months, based on repeated CPX.

MCT. Patients will exercise for 40 min five times per week on cycle ergometers at 50–60% VO_{2peak} (60–70% of peak heart rate).

HIIT. Patients will perform three training sessions per week. Each training session starts with a warm up for 10 min at moderate intensity (corresponding to 50–60% of VO_{2peak}, 60–70% of peak heart rate, 11–13 Borg scale, no shortness of breath) before cycling four 4 min intervals at high intensity (corresponding to 85–90% of VO_{2peak}, 90–95% of peak heart rate, 15–17 Borg scale, shortness of breath). Each interval will be separated by 3 min active pauses, cycling at 50–70% of peak heart rate. The training session will be terminated by 3 min cool-down at moderate intensity. Total exercise time will be 38 min for the HIIT group.

Duration of the intervention. The training intervention is 12 months, divided into three months of supervised clinic-based training followed by nine months telemonitored home-based training (Figure 2).

Supervised training. In the supervised training (months 1–3) the training workload will be individually adapted with the aim of reaching target exercise intensities in less than four weeks. The workload on the

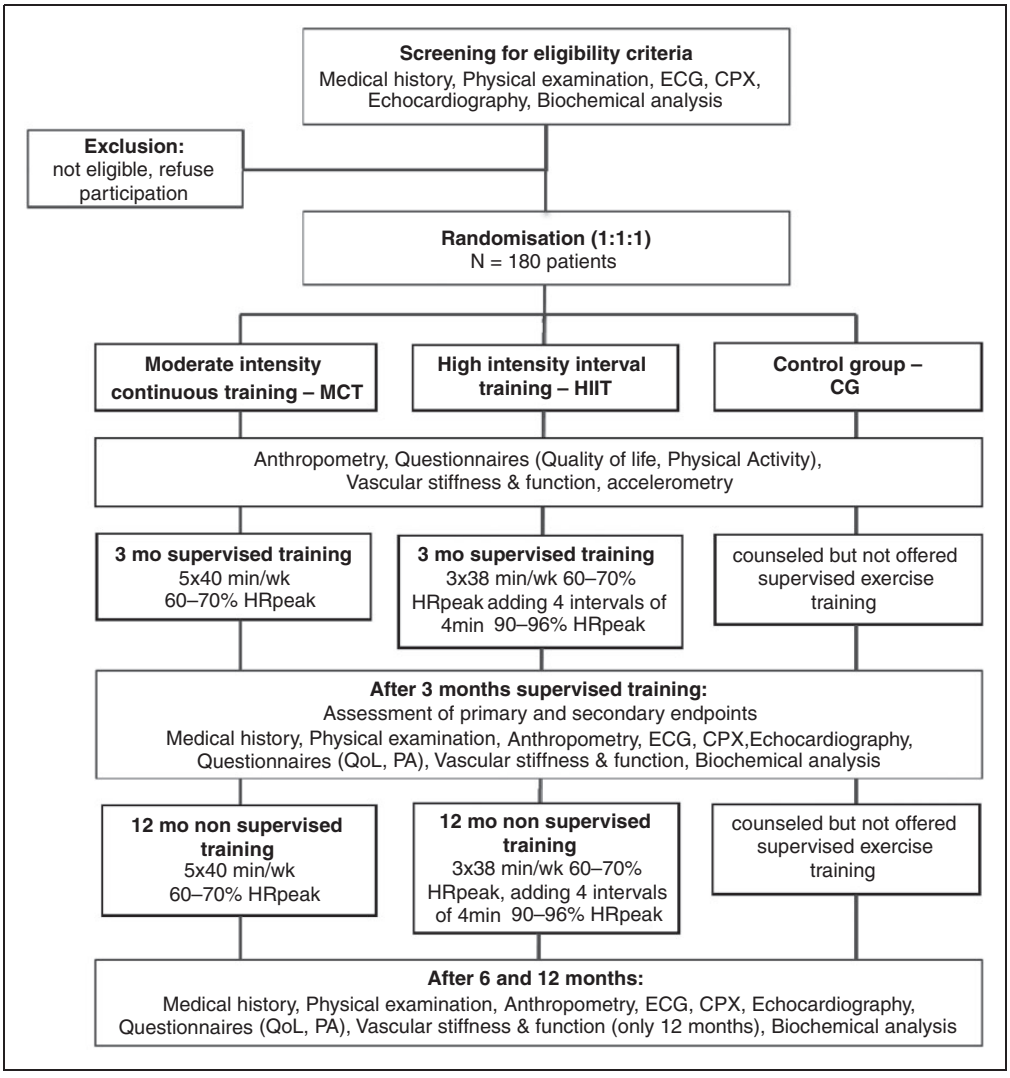

Figure 2. Flow chart for patient inclusion and follow up. Screening, inclusion and exclusion, randomisation and tests at baseline and follow up. CG: control group; CPX: cardiopulmonary exercise testing; ECG: echocardiography; HIIT: high intensity interval training; HRpeak: peak heart rate; MCT: moderate intensity continuous training; QoL: quality of life; PA: physical activity.

bicycle ergometer will be adjusted as necessary, to ensure that training sessions will be carried out at the assigned heart rates.

Home-based training. After performing three months of supervised exercise, participants will be followed for a further nine months in a home-based maintenance programme. In this home-based training period, cycle ergometers will be provided to all patients. Patients will perform supervised exercise at the clinic monthly for monitoring and control of exercise intensity and to have any questions answered. Daily physical activity and adherence to structured exercise will be documented via telemonitoring.

During the home-based phase, patients will be instructed to perform the same exercise protocol as they performed during the supervised phase. Patients will be instructed to immediately stop home-based training if they experience chest pain or discomfort and immediately to contact the emergency ward at the hospital. Exercise training will be terminated at signs of any serious adverse event (SAE), and all adverse events (AE) will be reported to the safety monitoring committee and to the central database within 48 h.

Criteria for non-adherence and prolongation of training. To be considered adherent to exercise training, patients must attend at least 70% of the possible training sessions within the time allotted. Training adherence will be monitored and documented regularly throughout the trial. If due to unforeseen circumstances a patient becomes non-adherent during the supervised intervention phase (months 1–3), supervised training may be prolonged for up to four weeks. If non-adherence occurs during home-based training (months 4–12), patients will be contacted and given individual feedback and advice. No prolongation of the home-based training phase will be possible.

Key measurements and reference evaluation

CPX. The core laboratory for exercise testing acts as blinded reference centre and will certify all trial sites before inclusion of the first patient. Therefore, test personnel at each trial site will perform a cardiopulmonary exercise test with a reference person to ensure accurate test procedure and comparable test values.

CPX will be performed using bicycle ergometer protocols, starting at a workload of 20 W, followed by a stepwise 10 W increment every minute. Standard 12-lead electrocardiography (ECG) will be monitored continuously for heart rate, changes in repolarisation and arrhythmias. Blood pressure will be recorded at rest and every 2 min. Oxygen uptake and CO_2 production will be measured by ventilatory gas exchange. Criteria for discontinuation of the exercise test are defined as recommended by the current guidelines.[15] Patients will be encouraged to exercise to levelling off of VO_2 despite an increase in workload and to respiratory exchange ratio >1.05. Data derived from CPX will be additionally analysed at the core laboratory.

Echocardiography. The Echocardiography Reference Centre will be responsible for all quality aspects in the trial and will train and certify all echocardiographers prior to patient recruitment for the study. A standard echocardiograph will be performed to assess systolic and diastolic function and to rule out other cardiac disease that may influence exercise capacity. Data will be stored digitally and analysed at the core laboratory.

Baseline and follow-up investigations

All patients will be examined at baseline, after three months supervised training, and six months and 12 months after randomisation. Examination will include medical history, physical examination, anthropometry, ECG, CPX, echocardiography, biochemical analysis, physical activity (International Physical Activity Questionnaire (IPAQ)), QoL and depression and personality traits (EuroQol (EQ-5D), Kansas City Cardiomyopathy Questionnaire (KCCQ), Global Mood Scale (GMS-12), Generalized Anxiety Disorder 7-item (GAD-7), Patient Health Questionnaire (PHQ-9), and Type D Scale (DS-14)), as well as endothelial function (flow mediated dilation at the level of the brachial artery). The flow chart is summarised in Figure 2.

Statistics

The null hypothesis of the study is that all study-group means are equal for the primary endpoint. Sample size calculation is based on data from the pilot study by Edelmann et al.[12] and revealed that 45 patients per group would provide 90% power at $p < 0.05$ to detect a statistically significant result for VO_{2peak}, the primary outcome. Considering the three exercise groups and a drop-out-rate of 20% and 10% due to the multi-centre design, a total of 180 participants will be included.

Ethical considerations

The clinical trial will be conducted in accordance with local laws and ICH guidelines for good clinical practice (GCP) issued in June 1996 and CPMP/ICH/135/95 from September 1997,[16] taking into account the Declaration of Helsinki and all its revisions. The study has been approved by the Regional Committees for Medical Research Ethics at each of the partner's institutions. A Data Safety and Monitoring Committee and an Endpoint Committee have been established.

Telemedicine-based monitoring of training adherence and physical activity

Background and rationale

Advances in telecommunication technologies have created new opportunities to provide telemedical care as an adjunct to medical management of patients with HF.[17] To include telemedicine in life-style intervention strategies has been suggested to increase adherence in these programmes.[18] However, telemedicine-based monitoring of and feedback on training adherence has not been tested in HFpEF patients yet. Also, the effects of different exercise training volumes particularly differing in intensity (MCT versus HIIT) on regular daily physical activity have not been tested before.

In OptimEx-CLIN, the inclusion of telemedical strategies is important for assessing the relationship between different types of exercise intervention and adherence as well as their impact on daily activity. This is of particular interest as other large HF trials have failed to reach the previously defined target activity levels.[19]

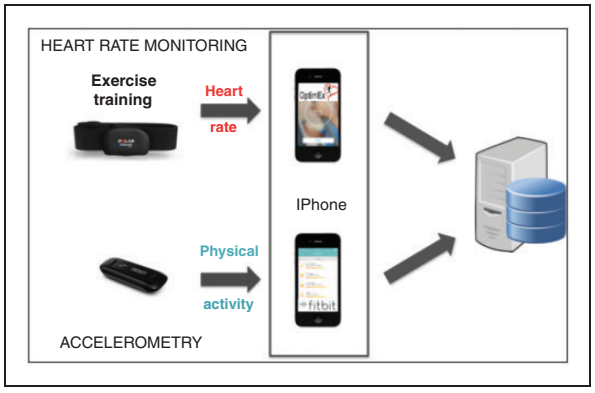

Figure 3. Telemedical approach. Heart rate monitoring: heart rate data of each training session is monitored via chest strap (Polar H7, Polar Electro GmbH, Germany) and pushed to a specially designed mobile application (OptimEx, Vitaliberty, Vitaphone group, Germany) on an iPhone (4 S, Apple Inc., USA) and is recorded in a secured telemedicine database. Accelerometry: daily physical activity is assessed by accelerometers (ONE, Fitbit Inc., USA) and sent via a mobile application (Fitbit, Fitbit Inc., USA) for documentation in the secured telemedicine database.

Objectives

The main objectives of the telemedicine approach in OptimEx-CLIN are:

- To enable continuous monitoring of home-based ergometer exercise sessions.
- To improve adherence by giving automated feedback information to the patient on the training volumes, and individual feedback/advice once adherence drops below 70% of the scheduled exercise training volume.
- To enable continuous monitoring of daily physical activity by accelerometry.

Methods

Heart rate monitoring. For monitoring adherence to structured exercise in OptimEx-CLIN, training sessions, particularly when performed non-supervised (months 4–12), must be recorded. This will be achieved by acquiring heart rate monitor (HRM) data during these sessions yielding duration and intensity of exercise. Patients belonging to the training groups (MCT or HIIT) will receive a chest strap (Polar H7, Polar Electro GmbH, Germany) and will be advised to wear this chest strap at each training session throughout the trial. Each patient will receive an iPhone (4 S, Apple Inc., USA) for the purpose of recording and transferring heart rate and accelerometry data. A mobile application (OptimEx, Vitaliberty, Vitaphone group, Germany) specially designed for this study will continuously document heart rate during each training session. After each training session these data will automatically be sent to a secured telemedicine database, so that local study centres can contact the patient when compliance to exercise sessions drops below 70% or target exercise intensities are not reached (Figure 3).

Accelerometry. To assess daily activity, accelerometers (ONE, Fitbit Inc., USA) will be handed out to all patients at randomisation. All patients are encouraged to wear their accelerometers constantly for the whole period of the trial (12 months). The accelerometers automatically synchronises the activity data to the particular iPhone of the patient. Data will automatically and regularly be transferred to the telemedical web platform for statistical analyses upon conclusion of the study (Figure 3).

Project organisation

The study is conducted at five centres in Europe. The organisation includes the Study Group, which consists of all active investigators, including local coordinators from centres which recruit a significant number of patients, heads of core labs, members of steering and endpoint committees, and other investigators that fulfil Vancouver criteria for authorship, judged by the Steering Committee. The Principal Investigators and Steering Committee have the main responsibility for all aspects of the study protocol and amendments, the execution of the study, as well as for data analysis and

publication of results from the present protocol. Core laboratories are responsible for the distinct examinations: ECG, CPX and exercise training, vascular analyses, biochemical analyses and psychometry analyses. An Endpoint Committee, blinded to the randomisation groups, reviews AEs for evaluation and classification. A Data Safety and Monitoring Committee, independent and unblinded to the randomisation groups, monitor SAEs during the exercise intervention and the closure of the database. Names and affiliations of all participants involved in OptimEx-CLIN are listed in the Appendix.

Conclusion

Exercise training is a promising therapeutic strategy to improve physical capacity, QoL and diastolic function in patients with HFpEF. Before detailed recommendations for exercise in HFpEF can be agreed upon, the impact of exercise and exercise dose on pathophysiology as well as clinical outcomes has to be evaluated in a more comprehensive way in larger human studies. OptimEx-CLIN is a multicentre trial to optimise dose-response relationship to maximally improve objective parameters of exercise intolerance in patients with HFpEF. Overall, the optimal mode, frequency, intensity and duration of exercise for this particular population to improve exercise capacity, reduce symptoms and severity of the disease as well as the underlying mechanisms will be elucidated in OptimEx-CLIN. In addition, adherence to training interventions as well as side effects will be telemonitored by accelerometry and adherence rate optimised by establishing feedback loop information strategies.

Registration. Clinicaltrials.gov NCT02078947. OptimEx-CLIN is part of a multidisciplinary approach, consisting of experimental (animal) and clinical (human) studies, to understand the role of exercise in HFpEF (www.ntnu.edu/optimex).

Acknowledgement

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Conflict of interest

None declared.

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Appendix

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Norway: Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Norway.