



**Rationale and design of the CopenHeartIE – A randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients treated for infective endocarditis**

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4 **Rationale and design of the CopenHeart<sub>IE</sub> – A randomised clinical trial of comprehensive**  
5 **cardiac rehabilitation versus usual care for patients treated for infective endocarditis**  
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## Abstract

### Introduction

Infective endocarditis is among the most serious infectious diseases in the western world. Treatment requires lengthy hospitalisation, high-dosage antibiotic therapy, and possible valve replacement surgery. Despite advances in treatment, the one year mortality remains at 20% to 40%. Studies indicate that patients experience persisting physical symptoms, diminished quality of life, and difficulties returning to work up to a year post-discharge. No studies investigating the effects of rehabilitation have been published. We present the rationale and design of the CopenHeart<sub>IE</sub> trial, which investigates the effect of comprehensive cardiac rehabilitation versus usual care for patients treated for IE.

### Methods and analysis

We will conduct a randomised clinical trial to investigate the effects of comprehensive cardiac rehabilitation versus usual care on the physical and psychosocial functioning of patients treated for infective endocarditis. The trial is a multi-centre, parallel design trial with 1:1 individual randomisation to either the intervention or control group. The intervention consists of five psycho-educational consultations provided by specialised nurses and a twelve-week exercise training programme. The primary outcome is mental health measured by the standardised Short Form 36 (SF-36). The secondary outcome is peak oxygen uptake measured by the bicycle ergospirometry test. Furthermore, a number of exploratory analyses will be performed. Based on sample size calculation, 150 patients treated for left-sided (native or prosthetic valve) or cardiac device endocarditis will be included in the trial. A qualitative and a survey-based complementary study will be undertaken, to investigate post-discharge experiences of the patients. A qualitative post-intervention study will explore rehabilitation participation experiences.

**Ethics and dissemination**

The study complies with the Declaration of Helsinki and was approved by the regional research ethics committee (no H-1-2011-129) and the Danish Data Protection Agency (no 2007-58-0015).

Study findings will be disseminated widely through peer-reviewed publications and conference presentations.

**Registration**

Clinicaltrials.gov identifier: NCT01512615

For peer review only

## Background

Infective endocarditis (IE) is an infection of the heart valves and/or adjacent structures. The bacteria may invade and destroy the tissue, and vegetations can dislodge into circulation and cause harmful and potentially deadly complications. Despite improvements in diagnostic tools, novel antibiotics and changes in treatment regimens, the mortality of IE remains high<sup>1-3</sup>. The incidence of IE in the developed countries is currently between 1.9 and 10.0 per 100,000 people per year<sup>3,4</sup>, and is rising due to the increase in degenerative valvular disease in the elderly, increasing insertions of prosthetic valves and implantable cardiac devices, and exposure to invasive procedures and nosocomial bacteraemia<sup>1,5-7</sup>. In Denmark, the incidence is at least 10 per 100,000 people per year, equivalent to approximately 500 patients per year<sup>4</sup>. The treatment includes a lengthy hospitalisation with intravenous antibiotic therapy, extensive invasive and non-invasive diagnostic procedures and, in about 50% of the patients, valve replacement surgery<sup>4</sup>. The in-hospital mortality rate of patients with IE is 10-25%, between 20-40% at one year post-discharge and up to 50% at 10 years post-discharge<sup>3,8-11</sup>. The causes of post-discharge mortality are still poorly understood.

### *Health and quality of life*

The disease, its treatments and the potential complications can lead to massive deconditioning of the patients<sup>12-15</sup>. The few existing studies on patient experiences after discharge, indicate that patients treated for IE have persisting physical and mental symptoms, such as fatigue in 47% of patients<sup>14</sup>, physical weakness in up to 78% of patients<sup>14,15</sup>, and concentration problems and memory loss in up to 35% of patients<sup>14</sup>. Patients also report diminished health-related quality of life<sup>14</sup>, negatively affected perceived health<sup>12,13</sup>, and up to 55% experience anxiety and depression<sup>15</sup> and 11% showed signs of post-traumatic stress disorder<sup>14</sup>. Furthermore, 35% of previously employed patients had not returned to work after 12 months<sup>14</sup>.

## Rehabilitation

Studies exploring the effects of rehabilitation of patients treated for IE are lacking. As there is no evidence of the effectiveness, the provided rehabilitation is often suboptimal or totally lacking. Lessons, however, might be learned from rehabilitation studies in patients with related cardiac conditions. The positive effects of cardiac rehabilitation have been well documented, particularly in patients with coronary artery disease and heart failure, where rehabilitation has been proven to reduce hospital re-admissions and mortality in a cost-effective way<sup>16-19</sup>. More specifically, studies on the effect of exercise training have demonstrated an increase in exercise capacity of up to 38% in patients after valve replacement surgery<sup>20</sup> and an increase in peak VO<sub>2</sub> of 2.3±2.2 (SD) ml/kg per minute in the intervention group compared with -0.3±2.1 (SD) ml/kg per minute in the control group as well as a significant change in quality of life in older patients with heart failure<sup>21</sup>.

Traditional cardiac rehabilitation has focused on physical training. Although a positive effect of this approach has been proven, studies suggest that interventions designed to improve both physical and psychological symptoms may provide the best method for optimising functioning and enhancing quality of life<sup>22,23</sup>. More evidence in patients with IE, however, is needed. Based on the effects of rehabilitation in other cardiac conditions, we hypothesise that patients treated for IE can benefit from participating in a rehabilitation programme. Therefore, we have designed the CopenHeart<sub>IE</sub> trial.

## Study objectives

The aim of the trial is to test a comprehensive cardiac rehabilitation programme for patients treated for IE versus usual care. The programme consists of a psycho-educational component and an exercise-training component. The primary hypothesis is that comprehensive cardiac rehabilitation improves mental health, measured by the mental component scale (MSC) of the Short Form 36 (SF-36) questionnaire, in patients treated for IE with 6 points (13%) in the intervention group compared

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4 with the control group after the completed intervention. The estimated 13% increase in primary  
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6 outcome is based on a study on ICD recipients with a comparable complex rehabilitation  
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8 intervention which found a similar increase (unpublished data from the COPE-ICD trial <sup>24</sup>). The  
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10 secondary hypothesis is that physical capacity, measured as peak oxygen uptake (VO<sub>2</sub> peak) by the  
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12 bicycle ergospirometry test, will be 3 ml/kg per minute (20%) higher in the intervention group  
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14 compared with the control group after 12 weeks of exercise training. Since no data on physical  
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16 capacity exists on patients treated for IE, this hypothesis is based on rehabilitation studies including  
17  
18 patients after heart valve surgery <sup>25,26</sup>. Exploratory analyses will test the hypotheses that  
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20 comprehensive cardiac rehabilitation improves self-rated health, quality of life, nutritional status,  
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22 sleep quality, and body-image and reduces anxiety, depression and fatigue after 6, 12 and 24  
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24 months. Furthermore, we intend to assess whether comprehensive cardiac rehabilitation can reduce  
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26 health care utilisation, work cessation and mortality and increase cost-effectiveness after 24 months.  
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### 31 **Design**

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33 The CopenHeart<sub>IE</sub> trial is part of the overall CopenHeart project, which is designed to develop  
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35 evidence-based knowledge on rehabilitation among patients with complex cardiac conditions <sup>27</sup>.

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37 The CopenHeart<sub>IE</sub> trial is a multi-centre, multidisciplinary, randomised clinical trial designed to  
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39 examine the effects of a comprehensive cardiac rehabilitation programme compared with usual care  
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41 for patients treated for IE. In addition to this, the CopenHeart<sub>IE</sub> trial includes two complementary  
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43 studies, aimed at investigating the post-discharge experiences and rehabilitation needs of patients  
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45 treated for IE, and a qualitative post-intervention study to explore the meaning of the CopenHeart<sub>IE</sub>  
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47 rehabilitation programme from the patient's perspective. Accordingly, the trial combines  
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49 quantitative and qualitative research methods. The methods are integrated by applying the mixed  
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51 method embedded experimental design (see Figure 1) <sup>28,29</sup>. The rationale for this approach is that  
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53 the quantitative findings provide a general understanding of the research problem through statistical  
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4 results, and qualitative findings refine and explain the results by exploring participants' views in  
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6 greater detail. This paper presents the study protocol for the CopenHeart<sub>IE</sub> randomised clinical trial.  
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9 The complementary studies are briefly described in a separate section.

### 10 11 ***Study population and eligibility criteria***

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14 Consecutive patients treated for left-sided (native or prosthetic valve) or cardiac device endocarditis  
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16 at the tertiary referral heart centres in Copenhagen, Denmark (Rigshospitalet and Gentofte Hospital)  
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18 will be screened for inclusion and approached for study participation. Patients aged 18 years or  
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20 older, having completed treatment for IE based on the Duke Criteria <sup>30</sup>, speaking and understanding  
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22 Danish, and providing written informed consent will be considered eligible for participation.  
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24 Patients unable to understand study instructions, with a cardiac ischemic event within the past 6  
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26 months, who are pregnant or breastfeeding, with reduced ability to follow the planned programme  
27  
28 due to, e.g., substance abuse problems or other somatic illness, with considerable illness in the  
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30 musculoskeletal system or with physical disability which complicates exercise training or patients  
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32 whose physician advise against participation, will be excluded.  
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### 37 ***Study procedure, randomisation and follow-up***

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39 Patients will be approached for participation during the expected last week of their treatment for IE.  
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41 When the informed consent form is signed, baseline data will be collected including the baseline  
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43 questionnaire package, demographic variables, and clinical characteristics. The enrolling research  
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45 assistant will call the trial coordinating centre (Copenhagen Trial Unit) for randomised allocation.  
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47 The allocation sequence will be computer-generated with varying block-sizes, blinded to  
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49 investigators, randomising patients 1:1 to either the experimental intervention versus standard  
50  
51 follow-up. Patients will be stratified according to sex and the treating heart centre. For both groups,  
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53 the follow-up assessment will take place at 1 month (T<sub>1</sub>), 4 months (T<sub>4</sub>), 6 months (T<sub>6</sub>), and 12  
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months (T<sub>12</sub>) post-discharge and a register-based follow-up assessment will be conducted at 24 months (T<sub>24</sub>) (see Figure 2).

### *The experimental intervention group*

Patients in the intervention group will follow the integrated rehabilitation programme, consisting of a psycho-educational component and an exercise training component as well as usual care (see below). The intervention has been developed and tested in two clinical trials; the DANREHAB trial including patients with ischemic heart disease and heart failure<sup>31</sup>, and the COPE-ICD trial including patients with an implantable cardioverter defibrillator<sup>24</sup>. The blood work and clinical control described for the control group (see below) are incorporated in the follow-up of the intervention group.

### The psycho-educational component

The aim of the psycho-educational intervention is to provide emotional support and improve coping skills and illness appraisal in order for the patient to respond appropriately to physical and psychological symptoms. Education and information about the disease prepare the patient for expected symptoms and sensations. Dialogue and shared reflection facilitate strategies for coping with symptoms and experiences associated with the condition, e.g., anxiety and fear. Cardiac care nurses with specific training will perform the psycho-educational intervention. The most commonly reported concerns of patients treated for IE, such as fatigue, gastrointestinal function, and concerns about work life, are outlined in an inspiration guide for the nurses to address when and if relevant (see Table 1).

**Table 1. Inspiration guide for nursing consultations/psycho-educational intervention.**

	1	2	3	4	5
<b>How have you been? What has happened since you were here last time?</b>	x	x	x	x	x
<b>Discuss the events leading up to the diagnosis of IE. Experiences before and during hospital admission.</b>	x				

<b>Address present thoughts and questions.</b>	X	X	X	X	X
<b>How did you having IE affect your life? Are there things/activities you avoid or feel you can't do after having IE?</b>	X				
<b>Have you initiated exercise training? How is training going?</b>	X	X	X	X	X
<b>Discuss social network/family. How do they handle the situation? Has anything changed in your social relationships?</b>	X				
<b>Has you having IE affected your work situation? /had financial consequences?</b>		X			
<b>Have you had a changed view/perception of your body and its functions?</b>		X			
<b>How is your health in relation to e.g. fatigue, dyspnoea, pain, appetite, gastrointestinal function, sleep, sexual functioning, other?</b>			X	X	X
<b>Information/recommendations in relation to discussed issues/problems.</b>	X	X	X	X	X

The consultations focus on managing life after IE by establishing a joint approach to disease management and coping strategies, using a holistic view. The psycho-educational intervention is inspired by R.R. Parse's Human Becoming Practice Methodologies three dimensions<sup>32</sup>. These are interpreted as: 1) discuss and give meaning to the past, present and future, 2) explore and discuss events and possibilities and 3) move along with envisioned possibilities. According to this theory, there are three ways of changing health: creative imaging, that is to see, hear and feel what a situation might be like if lived in a different way, affirming personal patterns and value priorities, and shedding light on paradoxes, that is, looking at the incongruence in a situation and changing the view held of something. The nurse is truly present in the process through discussions, silent immersion and reflection. The consultations take place in a quiet setting at the out-patient clinic and will last for approximately one hour. The nurse is able to facilitate contact with or seek advice from a physician if needed. The first consultation will be approximately one week after discharge, and then once every four to six weeks, with a total of five consultations. Consultations can be done by telephone, according to the patient's wishes. The primary investigator will attend the consultations regularly to ensure protocol compliance.

The physical exercise training component

The main objective of the exercise training is to improve the patient's physical capacity and facilitate lifestyle/behavioural changes, which will subsequently result in physical and

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4 psychological health-benefits for the patient. However, the exercise training programme is also  
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6 targeted at relieving the fear and uncertainty that the patient may feel in relation to physical activity.  
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8 The intervention is based on the European guidelines for physical training in cardiac rehabilitation<sup>33</sup>  
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10 and complies with the recommendations on physical activity of the Danish National Board of  
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12 Health<sup>34</sup>. The intervention consists of three components: 1) individual planning of the exercise  
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14 training, 2) twelve weeks of high intensity exercise training, and 3) continuous moderate daily  
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16 physical exercise.  
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### 20 21 1) Individually planned physical exercise by a specialised cardiac rehabilitation physiotherapist

22 Integrating detailed information regarding the specific type of IE, co-morbidities, hospitalisation,  
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24 activities of daily living (ADL) and level of physical activity prior to IE, the physiotherapist  
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26 conducts a patient consultation of up to 30 minutes taking into consideration the patients'  
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28 preferences with regard to training at a CopenHeart certified training facility at the local hospital, in  
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30 a municipal setting or as home based training. The consultation is based on the initial testing of the  
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32 patient, including the cardiopulmonary exercise testing, described in the outcome measures section,  
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34 a 6 minute walk test and a 'sit to stand' test. For all patients an individual training diary is prepared,  
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36 and all patients are instructed in the use of a heart rate monitor integrated into Polar watches,  
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38 provided by Rigshospitalet. The heart rate monitor is essential to ensure CopenHeart training  
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40 protocol compliance throughout the study period.  
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### 45 46 2) High intensity physical exercise

47 The initial training sessions take place in a physiotherapist supervised setting at the primary  
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49 investigating hospital, Rigshospitalet, to ensure the quality, intensity, and safety of training.  
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51 Training is started four weeks post-discharge to ensure optimum post-surgery healing after heart  
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53 valve surgery or cardiac device implantation. Using wireless electrodes integrated into t-shirts  
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(Corus-Fit, CardioCardio and Corus Exercise Assistant, CEA, vs. 2.0.16, Finland) potential cardiac arrhythmias, electrocardiographic abnormalities such as ST-depression, ST-elevation, Q-or T-wave altering, atrial fibrillation and ventricular arrhythmias, and training intensity level are monitored.

The physical exercise training continues for 12 weeks, comprising 3 sessions weekly of 60 minutes, with a total of 36 sessions. The training protocol consists of aerobic and anaerobic exercise to accommodate endurance and muscle strength. Long-term effects on the cardiovascular system are expected such as; reduction of cardiac after-load, decrease in systemic blood pressure at rest and maximum exhaustion, and improvement in left ventricle systolic, and diastolic function is expected for individuals with decreased left ventricular ejection fraction (LVEF).

A high intensity exercise training session consists of 10 minutes warm up, 20 minutes of bicycling, 20 minutes of resistance training, and 10 minutes stretching and cool-down period. Using the measured maximum heart rate from the cardiopulmonary exercise test performed prior to the initial training session, the aerobic exercise is performed at 50% to 80% of the maximum heart rate. The anaerobic resistance training is at 30% to 40 % of 1 repetition maximum (RM) for the upper body, and 40% to 50 % of 1 RM for the lower body, with an increasing work load during the training sessions. To achieve cardiovascular adjustment and reduce the risk of malignant cardiac arrhythmias and ischemia, the training session is initiated and terminated with a warm up and a cool down period to gradually increase and decrease training intensity and heart rate. This cardiovascular adjustment has been proven to reduce the risk of ischemia and arrhythmia in relation to exercise training<sup>35,36</sup>. Training is predominantly performed in the upright position to reduce left ventricle preload (diastolic volume) and the risk of ischemia and arrhythmias due to heart failure<sup>36</sup>.

### 3) Continuous moderate daily physical exercise

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4 Participants are instructed to perform moderate physical exercise at least 30 minutes a day during  
5 the intervention period, e.g., bicycling, walking, gardening, jogging or recreational sports. Daily  
6 moderate physical exercise is encouraged to be continued throughout life.  
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### 10 11 *The usual care control group*

12 Patients in the control group will follow standard follow-up for patients treated for IE, with 1 to 2  
13 visits within the first month post-discharge, including blood work and clinical assessment.  
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16 Haemoglobin level, infection variables, kidney function, and, on indication, liver status is assessed,  
17 and blood cultures are drawn on suspicion of IE relapse. Blood pressure, pulse and temperature  
18 parameters are obtained. If results give cause for concern, the patient will see a specialist physician  
19 during the follow-up visit. A transthoracic echocardiogram will be performed within the first year  
20 post-discharge, typically between 1 and 6 months post-discharge and again at 12 months, depending  
21 on whether the individual patient has had heart valve surgery and on the status of the native or  
22 replaced valve. These patients will be contacted at 1, 4, 6, 12, and 24 months for outcome  
23 assessment including functional test, questionnaires and clinical data collection (see figure 2).  
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### 37 *Outcomes and data collection*

38 Numerous data will be collected to evaluate the effect and meaning of the intervention. The primary  
39 and the secondary outcome reflect the primary modifiable factors of the intervention. Since almost  
40 no evidence exists, a number of explorative outcomes will also be collected.  
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47 *Primary outcome:* Mental health will be measured by the Mental Component Subscale (MCS) of  
48 the Medical Outcome Study Short Form 36 (SF-36) questionnaire<sup>37</sup> after 1 month (T<sub>1</sub>), 4 months  
49 (T<sub>4</sub>), 6 months (T<sub>6</sub>), 12 months (T<sub>12</sub>) and 24 months (T<sub>24</sub>). The SF-36 questionnaire is a measure of  
50 self-rated health. It is a validated multipurpose health survey comprised of 36 items that address the  
51 following 8 dimensions: physical functioning (PF), role physical (RP), bodily pain (BP), general  
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4 health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH).  
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6 The first four scales (PF, RP, BP, GH) are then combined into a physical component scale and the  
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8 latter four (VT, SF, RE, MH) into a mental component scale<sup>37</sup>. The instrument was chosen for its  
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10 ability to detect changes in self-rated health within domains that could potentially be influenced by  
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12 the CopenHeart<sub>IE</sub> intervention. Mental health was chosen as the primary outcome as other studies  
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14 have shown that mental health is affected in patients with IE compared to healthy controls<sup>13, 14</sup> and  
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16 the rehabilitation intervention focuses on this modifiable factor.  
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21 *Secondary outcome:* Physical capacity will be measured by peak VO<sub>2</sub> using cardiopulmonary  
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23 exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland) by investigators blinded to the  
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25 intervention group. The test will be performed according to current guidelines for ergospirometry  
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27 testing<sup>38-40</sup>, using an ergometer-bicycle with spirometry, monitoring heart-rhythm, blood pressure,  
28  
29 electrocardiogram (ECG), and measuring gas-exchange during workload and in the following  
30  
31 recovery period. Average test duration will be 10-15 minutes including pre- and post- test phase  
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33 without work load. Before each session calibration will be performed to address changes in room  
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35 temperature, humidity and air O<sub>2</sub> content. A standardised ramp-protocol will be used with an initial  
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37 work load of 25 or 50 watts, increasing gradually by 25 watts every second minute until peak  
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39 exhaustion, aiming to reach respiratory exchange ratio (RER)  $\geq 1.10$  and obtain anaerobic  
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41 threshold. In order to encourage patients equally, independent of the tester, a standardised guide has  
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43 been developed. During the test, clinical manifestations, ECG abnormalities (ST depression, ST  
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45 elevation, q-and t-wave changes, supraventricular or ventricular arrhythmias), blood pressure  
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47 response and several physiological parameters will be observed and documented. The test will be  
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49 performed prior to the exercise training programme (T<sub>1</sub>), after 12 weeks of exercise training (T<sub>4</sub>)  
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51 and at 12 months follow-up (T<sub>12</sub>). Physical capacity was chosen as the secondary outcome measure,  
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as studies indicate that patients treated for IE are physically deconditioned after long-term illness and hospitalisation<sup>14</sup>.

*Exploratory outcomes:* A more extensive evaluation of the physical and psychological status of the patients over time will be performed, exploring demographic, clinical, paraclinical and imaging variables, as well as additional physical capacity tests and additional questionnaires exploring for example fatigue, sleep quality and anxiety and depression (see Table 2).

**Table 2. CopenHeart<sub>IE</sub> – Exploratory quantities subjected to post-hoc analysis**

Quantity	Time of measure	Type of quantity
<b>Demographic</b>		
Sex	Baseline	Binary (M/F)
Age, height, weight,	Baseline	Continuous
Marital, occupational, educational status	Baseline	Categorical
<b>Clinical</b>		
NYHA- classification	Baseline, 1, 4, 12	Continuous
Previous heart disease, diabetes mellitus, kidney disease, pulmonary disease (COLD), co-morbidities, hypertension, dyslipidaemia, smoking	Baseline	Binary (Y/N)
Medication	Baseline, 1, 4, 12	Binary (Y/N)
BMI, Nutritional screening	Baseline, 1, 4, 12	Continuous
Endocarditis specific data:		
Valve-/device affected, type of surgery due to IE	Baseline	Categorical
Cerebral insult +, hemodialysis +	Baseline	Binary (Y/N)
Length of hospitalisation (days), weight loss related to IE (kilograms)	Baseline	Continuous
<b>Paraclinical and imaging</b>		
Blood work (Haemoglobin, infection-, kidney- liver and selected nutritional parameters, electrolytes, cholesterol- and thyroid status, ProBNP)	Baseline, 1, 4, 12	Continuous
Echocardiogram	Baseline, 4, 12	Continuous
<b>Physical function</b>		
6 minute walking test <sup>73</sup>	Baseline, 1, 4, 12	Continuous
Sit to stand test <sup>74</sup>	1, 4, 12	Continuous
<b>Questionnaires</b>		
Physical activity level <sup>75</sup>	BL, 1, 4, 6, 12, 24	Binary (Y/N)

SF-36 <sup>37</sup> HADS <sup>61</sup> , QoL-CV <sup>76</sup>	BL, 1, 4, 6, 12, 24	Continuous
Emotions and Health <sup>77</sup>	BL	Continuous
Rehabilitation <sup>78</sup>	12	Continuous
HeartQoL R <sup>65</sup> , EQ-5D <sup>51</sup>	BL, 6, 12, 24	Continuous
IPAQ <sup>67</sup>	1, 4, 12, 24	Continuous
MFI-20 <sup>63</sup>	BL, 1, 4, 12	Continuous
PSQI <sup>79</sup>	1, 6	Continuous
BIQOL <sup>80</sup>	BL, 6	Continuous

Data collected from official national registers regarding mortality, hospitalisation, emergency room visits, outpatient visits, medication, employment status, and payment of welfare benefits (sick leave payment and early retirement pension) will be collected at 24 months to assess the long term effects of the intervention. The Danish official national registers are well-functioning with a small percentage of lost data<sup>41</sup>. Consequently, the method is well suited as an outcome measure in small patient populations. Data will be collected from the Danish National Patient Register<sup>42</sup>, the Danish National Health Service Register<sup>43</sup>, the Danish National Prescription Registry<sup>44</sup>, the Danish National Causes of Death Register<sup>45</sup>, and registers on transfer payments and labour market affiliation<sup>46,47</sup>.

### ***Economic evaluation***

An economic evaluation will be conducted alongside the trial to assess the cost-utility of comprehensive cardiac rehabilitation compared with usual care in the study population. The economic evaluation will compare the costs to QALYs (quality adjusted life years) and take a societal perspective as recommended nationally. QALYs and costs will be assessed at the end of the intervention, 6 months from randomisation and later after 24 months from randomisation using register-based follow-up.

QALYs will be estimated using the self-completed EQ-5D instrument, which is a standardised instrument assessing 5 dimensions of self-reported health status (mobility, self-care, usual activities,



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4 pain/discomfort and anxiety/ depression)<sup>48,49</sup>. The estimated calculations will be evaluated using  
5  
6 Danish preference weights<sup>50</sup>. Information on costs will only include costs that are expected to differ  
7  
8 between the intervention and usual care group<sup>51</sup>. Included costs in the evaluation are health costs  
9  
10 associated with the rehabilitation programme, other health care costs (health care utilisation apart  
11  
12 from rehabilitation), patient costs and costs of productivity losses. Information on costs will be  
13  
14 collected by a mixture of activity-based costing, surveys, patient diaries and by the use of registers.  
15  
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17  
18 Results from the analysis will be reported as an incremental cost-effectiveness analysis (ICER).  
19  
20 Sensitivity-analysis will be conducted to express uncertainty in the estimates<sup>52</sup>. The reporting of  
21  
22 ICER is presented using Bayesian methods, including bootstrapping and presented as cost-  
23  
24 effectiveness acceptability curves<sup>53</sup>.  
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### 28 ***Sample size, power calculations and interim analysis***

29  
30 We will perform a randomised trial with a continuous response variable from independent control  
31  
32 and intervention group participants with one control per intervention group participant. A previous  
33  
34 study on an IE population found that the mental component scale was normally distributed with a  
35  
36 standard deviation of 13<sup>13</sup>. If the true difference between the intervention and control group means  
37  
38 is 6 points, we will need to include 75 participants in each study group (a total of 150 participants)  
39  
40 to be able to reject the null hypothesis, stating that the mean in the intervention and the control  
41  
42 groups are the same with a power of 80%. The type I error probability associated with this test of  
43  
44 this null hypothesis is 5%.  
45  
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47

48  
49 For the secondary outcome, VO<sub>2</sub>, we will be able to reject the null hypothesis that the population  
50  
51 means of the experimental and control groups are equal with a probability (power) of 75.4%,  
52  
53 assuming the VO<sub>2</sub> is normally distributed with a standard deviation of 6.9<sup>25,26</sup>, and the true  
54  
55 difference in the experimental and control means is 3 ml/kg per minute.  
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4 A data monitoring and safety committee will be informed, every nine months, of all serious adverse  
5 events occurring in the two study groups. An interim analysis meeting will be held by the data  
6 monitoring and safety committee to review data relating to intervention efficacy, participant safety,  
7 and quality of trial conduct. The committee will evaluate data on the primary and secondary  
8 outcome measures; mental health (SF-36) / peak VO<sub>2</sub> (efficacy) and all serious adverse events  
9 (safety/tolerability). After the interim analysis meeting, the committee will make a recommendation  
10 to the steering committee whether to continue, hold or terminate the trial. This recommendation will  
11 be based primarily on safety and efficacy considerations and will be guided by statistical monitoring  
12 guidelines defined by the trial safety charter.  
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### 24 *Statistical analysis*

25  
26 Data will be pseudo- anonymised and analysed, blinded by a trial-independent statistician using  
27 intention-to-treat analyses and a mixed model with repeated measures (MMRM) for continuous  
28 outcome measures<sup>54</sup>. Using MMRM ensures that missing data values (in the case of the primary  
29 and secondary outcome) will not create bias as long as the missing values are random. Two sided  
30 tests will be performed. The level of significance is set at 5%. Dealing with multiplicity, gate  
31 keeping will be used to adjust the observed P values for primary and secondary outcomes<sup>55</sup>. Both  
32 original and adjusted P values will be reported.  
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43 For the primary and secondary outcomes, we will conduct sensitivity analysis to assess the potential  
44 impact of non-random missing values. For each intervention group (A and B) some quantities  
45 (imputing quantities) will be computed to be used to impute missing values in a group (A or B) as  
46 explained below. A comparison between group A and group B where missing values in group A are  
47 imputed using imputing quantities obtained from group A and missing values from group B are  
48 imputed using imputing quantities obtained from group B is referred to as a best case analysis. If  
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missing values in group A are imputed using imputing quantities obtained from group B and vice versa the comparison is called a worst case analysis. The imputed quantities for the primary outcome would be the group mean at T1 ( $X1\text{-bar}$ ), the group mean at T4 ( $X4\text{-bar}$ ), the group mean at T6 ( $X6\text{-bar}$ ), the mean difference between the value measured at T4 and that measured at T1 ( $\delta 1$ ), and the mean difference between the value measured at T6 and that measured at T4 ( $\delta 2$ ). Table 3 explains how the quantities will be used to impute missing values in a group (either the same group or the other intervention group).

### Table 3. Statistical appendix

The use of imputed quantities derived from observed values in a group (group A) to impute missing values in a group (group B).

Observed pattern in group B at the times (T1, T4, T6)	Imputed value in group B at T1	Imputed value in group B at T4	Imputed value in group B at T6
mis <sup>A</sup> , mis, mis	$X1\text{-bar}^B$	$X4\text{-bar}^C$	$X6\text{-bar}^D$
mis, mis, Y3 <sup>E</sup>	$Y3 - (\delta 1^F + \delta 2^G)^H$	$Y3 - \delta 2$	
mis, Y2, mis	$Y2 - \delta 1$		$Y2 + \delta 2$
Y1, mis, mis		$Y1 + \delta 1$	$Y1 + \delta 1 + \delta 2$
Y1, Y2, mis			$Y2 + \delta 2$
Y1, mis, Y3		$(Y1 + \delta 1 + Y3 - \delta 2)/2$	
mis, Y2, Y3	$Y2 - \delta 1$		

A) The value at T <sub>4</sub> is missing in group B
B) Mean of values observed in group A at time T <sub>1</sub>
C) Mean of values observed in group A at time T <sub>4</sub>
D) Mean of values observed in group A at time T <sub>6</sub>
E) Observed value in group B at time T <sub>6</sub>
F) The mean of difference between value observed at time T <sub>4</sub> and observed at time T <sub>1</sub> in group A
G) The mean of difference between value observed at time T <sub>6</sub> and observed at time T <sub>1</sub> in group A
H) If an imputed value is < 0 it is set equal to 0

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4 If the standard error (SE) of a parameter estimate calculated using imputed data is smaller than that  
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6 of the corresponding parameter calculated using complete case data it will be replaced by the latter  
7  
8 SE when the p value is calculated.  
9

10  
11 Long term register-based outcomes will be analysed by two different models: non-negative count  
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13 outcomes (e.g., number of contacts to hospital or number of visits to general practitioners) will be  
14  
15 analysed by a Poisson model or a zero-inflated Poisson model if the number of zeros are large, and  
16  
17 time-to-event data (e.g., cause-specific mortality and leaving the labour market) will be analysed  
18  
19 with survival methods (Kaplan-Meier estimator and Cox regression model). Especially for socio-  
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21 economic outcomes, competing risk due to mortality will be considered if a large proportion of  
22  
23 patients die during follow-up.  
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28 Explorative data will be analysed using appropriate statistical methods according to type of data  
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30 (see Table 2). SPSS version 19.0 and SAS version 9.3 will be used.  
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### 33 **Complementary studies**

#### 34 *Qualitative study on post discharge experiences*

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36 The post-discharge experiences of patients treated for IE will be explored through semi-structured  
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38 qualitative interviews, which take a phenomenological-hermeneutic approach. The data derived  
39  
40 from this study will be used to address relevant issues designing the rehabilitation intervention.  
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42 Patients treated for IE, 3-6 months post-discharge will be identified through hospital admission lists.  
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44 A sample sufficient to achieve data saturation will be included. The study aims to answer the  
45  
46 following thematic research questions: What are the experiences of returning home after treatment  
47  
48 for IE? What are the new experiences, if any, in daily living? Which health problems, if any, have  
49  
50 patients experienced? What are the concerns, if any, for the future? The data-analysis is inspired by  
51  
52 Ricoeur's theory of interpretation and consists of three levels: naive reading, structured analysis and  
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critical interpretation and discussion. Qualified interviewees will be chosen, ensuring a representative sample in relation to sex, age and surgery/non-surgery.

### *Survey-based study*

The post-discharge status of the patients treated for IE will be explored through a national survey. The standardised questionnaires Short Form-36 (SF-36)<sup>37, 56-60</sup>, Hospital Anxiety and Depression Scale (HADS)<sup>61</sup>, Multidimensional Fatigue Inventory (MFI-20)<sup>62, 63</sup>, EuroQoL - EQ-5D<sup>51, 64</sup>, Heart Related Quality of Life (HeartQoL R)<sup>65</sup>, International Physical Activity Questionnaire (IPAQ)<sup>66, 67</sup> and a questionnaire developed by the Danish Heart Foundation on the extent and quality of rehabilitation offered will be sent out to patients who have undergone treatment for IE, 6-12 months post-discharge. The instruments are all validated and have good reliability and responsiveness<sup>61, 63-65, 67, 68</sup>. The data will provide knowledge on patients' self-rated health, quality of life, fatigue, anxiety and depression, body image and extent and quality of the rehabilitation currently received. Patients will be identified through the National Patient Register<sup>42</sup> and questionnaires will be sent out to 210 of them. We aim to achieve a response rate of 70%, using repeat mailing strategies and/or telephone reminders to maximize response if necessary<sup>69</sup>. This should result in an estimated 150 questionnaire respondents. Data will be anonymised and analysed by relevant descriptive statistical methods.

### *Qualitative study on rehabilitation participation experiences*

After the intervention, an interview study, including 10% of the intervention population or until data saturation has been reached, will be conducted, in order to explore the experiences and processes behind the potential effect of the intervention. The study aims to answer the following thematic research questions: What are the experiences of participating in the integrated rehabilitation programme? Which components of the programme are meaningful? In what way? Participant

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4 selection and applied methods in this study are consistent with that of the qualitative study on post-  
5 discharge experiences.  
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### 8 9 **Ethics**

10 The trial has been approved by the Regional Research Ethics Committee (no H-1-2011-129) and the  
11 Danish Data Protection Agency (no 2007-58-0015). All eligible patients will be informed about the  
12 trial verbally and in writing, and the patients are included after written informed consent is  
13 obtained. All data will be handled confidentially and patients are ensured anonymity. The study  
14 complies with the latest Declaration of Helsinki and is registered at ClinicalTrials.gov  
15 (NCT01512615). An independent safety committee comprised by an international group of experts  
16 is monitoring the trial; ensuring good clinical practice standards are being upheld. No serious risks  
17 are anticipated to receiving rehabilitation. No risks have previously been reported in relation to  
18 psycho-educational consultations. The physical exercise training and the cardiopulmonary exercise  
19 testing will be supervised by competent health care professionals and will be in accordance with  
20 current guidelines on safety when testing and training cardiac patients<sup>70, 71</sup>. Efforts will be made to  
21 avoid arrhythmias during workload testing and exercise training by protocol with a cool-down  
22 period, which positively affects serious complications. Staff members will be trained according to  
23 guidelines to handle cardiac arrest or other disease- or device-specific emergencies. All serious and  
24 moderate adverse events will be registered and reported according to protocol.  
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### 45 **Discussion**

46 This randomised clinical trial is the first to examine physical functioning by cardiopulmonary  
47 exercise testing and to test a comprehensive rehabilitation programme on a large heterogeneous  
48 population of patients treated for IE. CopenHeart<sub>IE</sub> will provide much needed evidence and insight  
49 on the post-discharge status and rehabilitation needs of patients treated for IE for health care  
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4 professionals and policymakers to make qualified, evidence-based decisions in everyday clinical  
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6 practice and as a foundation for national and international guidelines. With increased physical and  
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8 psychological well-being of patients, lower morbidity and health care utilisation expected in case of  
9  
10 a positive outcome, patients and society are anticipated to benefit greatly. Whether it produces  
11  
12 neutral, negative or positive results, the CopenHeart<sub>IE</sub> trial will have implications for clinical  
13  
14 practice in follow-up care of patients treated for IE in the western world.  
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17  
18 Patients may decline participation due to an unwillingness to return to hospital after a lengthy  
19  
20 illness and hospitalisation. We will attempt to avoid this problem by informing patients of the  
21  
22 potential benefits of participation, e.g., the security we provide by following them closely after post-  
23  
24 discharge and the value to science of their participation for future patients. Furthermore, it is  
25  
26 documented that a substantial number of patients in rehabilitation studies control group perform  
27  
28 self-initiated physical exercise training, possibly motivated by the study information during the  
29  
30 recruitment process<sup>31</sup>. Hence we will abstain from giving extensive information about the training  
31  
32 programme, or elaborate on the health benefits of physical training before knowing to which group  
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34 the patient is randomised.  
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39 The study has been designed to meet the criteria for high quality in non-pharmacological  
40  
41 randomised clinical trials<sup>72</sup> with central randomisation, multi-centre participation, blinded  
42  
43 assessment of the exercise outcome, blinded analysis by study independent statisticians and  
44  
45 furthermore, detailed information on the intervention received and usual care will be collected,  
46  
47 including information on self-initiated exercise training during the trial period. For the primary  
48  
49 outcome, the mental-health component subscale, we are aware of the subjective nature of the data  
50  
51 collected. Accordingly, we will interpret the findings conservatively.  
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## 55 56 **Dissemination plan** 57 58 59 60

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4 The results of the trial and complementary studies will be published in relevant international peer-  
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6 reviewed journals. Authorship will be determined according to the guidelines of the International  
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8 Committee of Medical Journal Editors. Due to the comprehensiveness of the outcome measures the  
9  
10 results will be presented in more than one scientific paper as relevant. Economic and long term  
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12 follow up will be reported as data becomes accessible.  
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### 15 16 **Trajectory**

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18 Inclusion was initiated in December 2011 and is expected to be completed at the end of 2013.  
19  
20 Results from the complementary studies are expected during 2012, and from the clinical trial in  
21  
22 2014.  
23  
24

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39  
40 Research.  
41  
42

### 43 44 **Competing interests**

45  
46 The authors declare that they have no competing interests.  
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**Figure 1. The CopenHeart<sub>IE</sub> study. Mixed method - Embedded Experimental Model.**

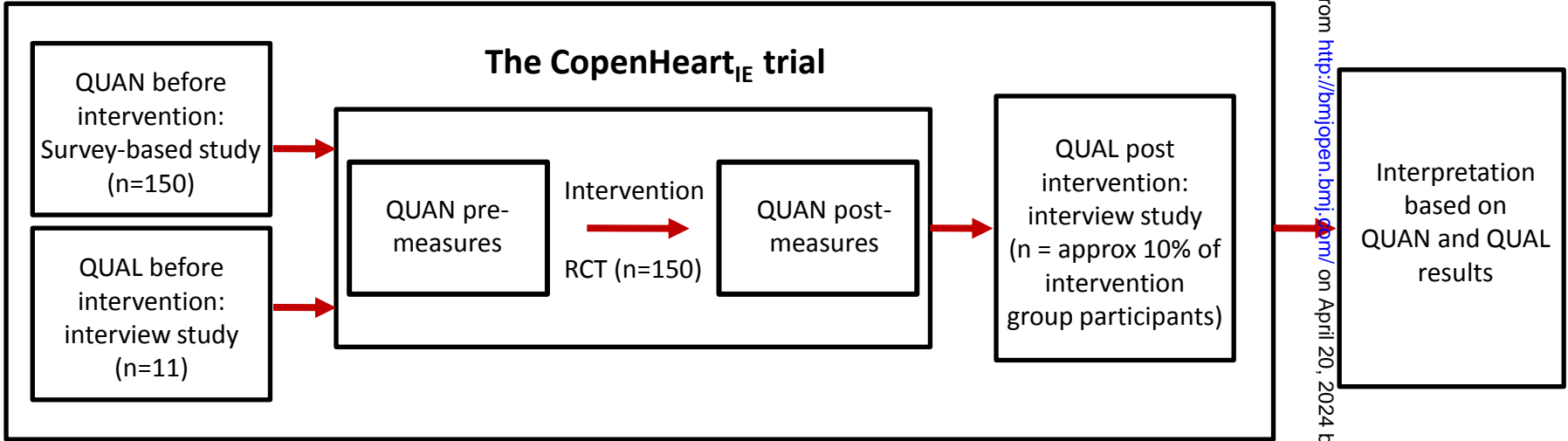
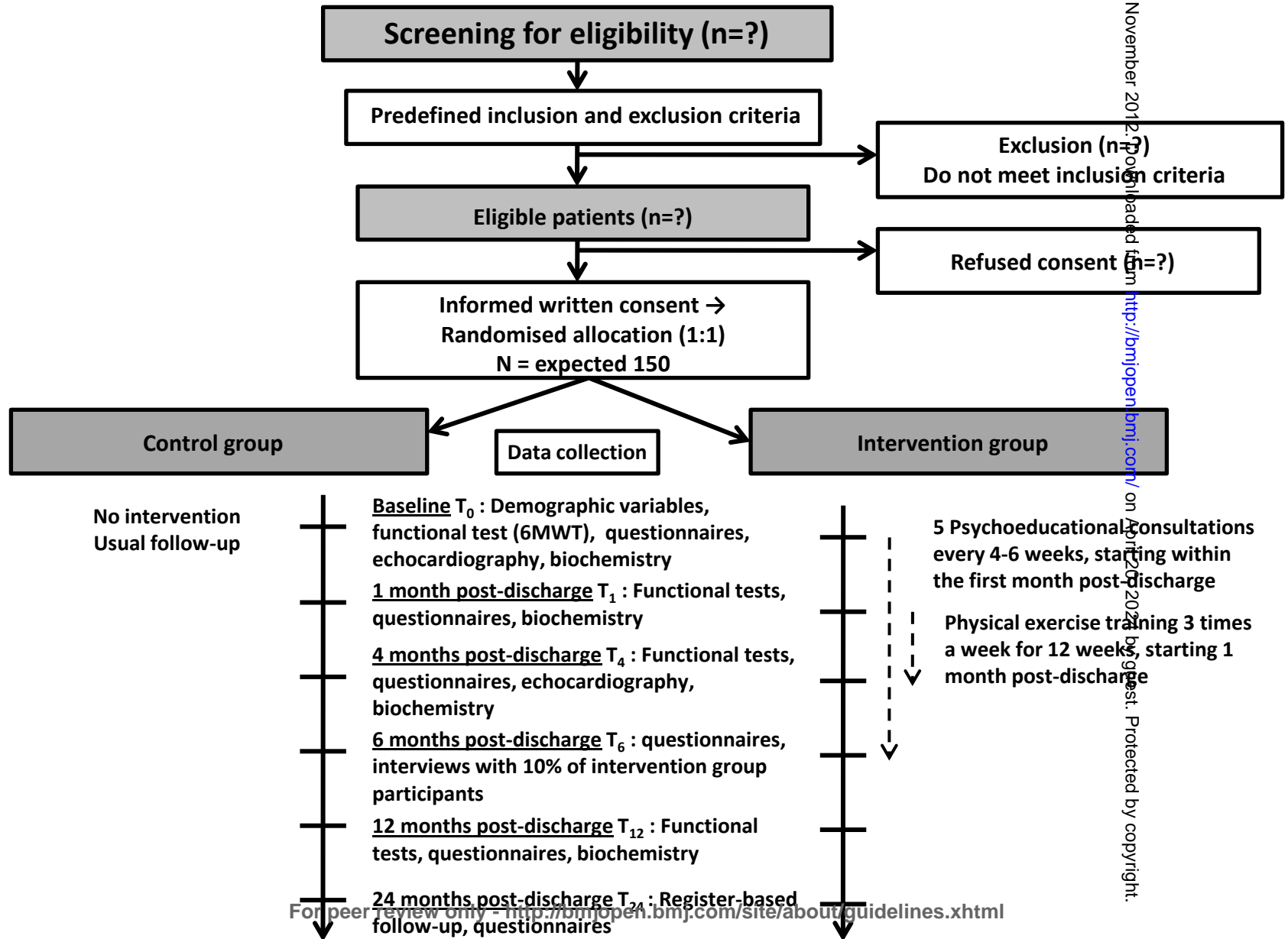


Figure 2. Patient flow.



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## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
<b>Introduction</b>	2a	Scientific background and explanation of rationale	4-5
Background and objectives	2b	Specific objectives or hypotheses	5-6
<b>Methods</b>	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-7
Trial design	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12-16
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	16
	7b	When applicable, explanation of any interim analyses and stopping guidelines	17
Randomisation:	8a	Method used to generate the random allocation sequence	7
Sequence generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7-13

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	assessing outcomes) and how	
11b	If relevant, description of the similarity of interventions	(7 + 13)
12a	Statistical methods used to compare groups for primary and secondary outcomes	N/A
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	17-19
	<i>complementary studies</i>	19-21
<b>Results</b>		
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
14a	Dates defining the periods of recruitment and follow-up	N/A
14b	Why the trial ended or was stopped	N/A
15	A table showing baseline demographic and clinical characteristics for each group	N/A
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
<b>Discussion</b>		
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	21-22
21	Generalisability (external validity, applicability) of the trial findings	21-22
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
<b>Other information</b>		
23	Registration number and name of trial registry	21
24	Where the full trial protocol can be accessed, if available	N/A
25	Sources of funding and other support (such as supply of drugs), role of funders	23

\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).



**A randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients treated for Infective Endocarditis - the CopenHeart IE trial protocol**

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<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Infective Endocarditis, RCT, Mixed Method

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**A randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients treated for Infective Endocarditis - the CopenHeart<sub>IE</sub> trial protocol.**

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Keywords: Rehabilitation, Endocarditis, Cardiovascular diseases, Randomised controlled trial

## Article summary

### Article focus

- The CopenHeart<sub>IE</sub> trial is a randomised clinical trial investigating the effects of comprehensive cardiac rehabilitation versus usual care for patients treated for IE.
- The hypothesis is that comprehensive cardiac rehabilitation improves mental health and physical capacity.
- Using a mixed method approach, a broad range of outcome measures is collected to evaluate the intervention.

### Key messages

- Infective endocarditis is a life threatening disease. Patients experience severe deconditioning and diminished quality of life post-discharge.
- Studies exploring the effects of rehabilitation of patients treated for IE have not been published.
- This trial is the first to examine physical functioning and to test a comprehensive rehabilitation programme on a large population of patients treated for IE. CopenHeart<sub>IE</sub> will provide much needed evidence and insight on the post-discharge status and rehabilitation needs of patients treated for IE.

### Strengths and limitations of this study

- The study has been designed to meet the criteria for high quality in non-pharmacological randomised clinical trials with central randomisation, multi-centre participation, blinded assessment and analysis.
- We are aware of the subjective nature of the mental-health component subscale (primary outcome). Accordingly, we will interpret the findings conservatively.

## Abstract

### Introduction

Infective endocarditis (IE) is among the most serious infectious diseases in the western world. Treatment requires lengthy hospitalisation, high-dosage antibiotic therapy, and possible valve replacement surgery. Despite advances in treatment, the one year mortality remains at 20% to 40%. Studies indicate that patients experience persisting physical symptoms, diminished quality of life, and difficulties returning to work up to a year post-discharge. No studies investigating the effects of rehabilitation have been published. We present the rationale and design of the CopenHeart<sub>IE</sub> trial, which investigates the effect of comprehensive cardiac rehabilitation versus usual care for patients treated for IE.

### Methods and analysis

We will conduct a randomised clinical trial to investigate the effects of comprehensive cardiac rehabilitation versus usual care on the physical and psychosocial functioning of patients treated for infective endocarditis. The trial is a multi-centre, parallel design trial with 1:1 individual randomisation to either the intervention or control group. The intervention consists of five psycho-educational consultations provided by specialised nurses and a twelve-week exercise training programme. The primary outcome is mental health measured by the standardised Short Form 36 (SF-36). The secondary outcome is peak oxygen uptake measured by the bicycle ergospirometry test. Furthermore, a number of exploratory analyses will be performed. Based on sample size calculation, 150 patients treated for left-sided (native or prosthetic valve) or cardiac device endocarditis will be included in the trial. A qualitative and a survey-based complementary study will be undertaken, to investigate post-discharge experiences of the patients. A qualitative post-intervention study will explore rehabilitation participation experiences.

### Ethics and dissemination

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4 The study complies with the Declaration of Helsinki and was approved by the regional research  
5 ethics committee (no H-1-2011-129) and the Danish Data Protection Agency (no 2007-58-0015).  
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9 Study findings will be disseminated widely through peer-reviewed publications and conference  
10 presentations.  
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### 12 **Registration**

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15 Clinicaltrials.gov identifier: NCT01512615  
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## Background

Infective endocarditis (IE) is an infection of the heart valves and/or adjacent structures. The bacteria may invade and destroy the tissue, and vegetations can dislodge into circulation and cause harmful and potentially deadly complications. Despite improvements in diagnostic tools, novel antibiotics and changes in treatment regimens, the mortality of IE remains high<sup>1-3</sup>. The incidence of IE in the developed countries is currently between 1.9 and 10.0 per 100,000 people per year<sup>3,4</sup>, and is rising due to the increase in degenerative valvular disease in the elderly, increasing insertions of prosthetic valves and implantable cardiac devices, and exposure to invasive procedures and nosocomial bacteraemia<sup>1,5-7</sup>. In Denmark, the incidence is at least 10 per 100,000 people per year, equivalent to approximately 500 patients per year<sup>4</sup>. The treatment includes a lengthy hospitalisation with intravenous antibiotic therapy, extensive invasive and non-invasive diagnostic procedures and, in about 50% of the patients, valve replacement surgery<sup>4</sup>. The in-hospital mortality rate of patients with IE is 10-25%, between 20-40% at one year post-discharge and up to 50% at 10 years post-discharge<sup>3,8-11</sup>. The causes of post-discharge mortality are still poorly understood.

### *Health and quality of life*

The disease, its treatments and the potential complications can lead to massive deconditioning of the patients<sup>12-15</sup>. The few existing studies on patient experiences after discharge, indicate that patients treated for IE have persisting physical and mental symptoms, such as fatigue in 47% of patients<sup>14</sup>, physical weakness in up to 78% of patients<sup>14,15</sup>, and concentration problems and memory loss in up to 35% of patients<sup>14</sup>. Patients also report diminished health-related quality of life<sup>14</sup>, negatively affected perceived health<sup>12,13</sup>, and up to 55% experience anxiety and depression<sup>15</sup> and 11% showed signs of post-traumatic stress disorder<sup>14</sup>. Furthermore, 35% of previously employed patients had not returned to work after 12 months<sup>14</sup>.

### *Rehabilitation*

Secondary prevention initiatives including cardiac rehabilitation, is widely recommended by the European society of cardiology (ESC) <sup>16</sup>. Although evidence of the efficacy is strong, cardiac rehabilitation is still poorly implemented and often only on selected populations, and thus the development of full comprehensive preventive programmes, according to the ESC, is warranted <sup>17</sup>. Studies exploring the effects of rehabilitation of patients treated for IE are lacking. As there is no evidence of the efficacy, the provided rehabilitation is presumably often suboptimal or totally lacking. Lessons, however, might be learned from rehabilitation studies in patients with related cardiac conditions. The positive effects of cardiac rehabilitation have been well documented, particularly in patients with coronary heart disease (CHD) and heart failure (HF), where rehabilitation has been proven to reduce hospital re-admissions and mortality in a cost-effective way <sup>18, 19</sup>, as well as improve quality of life <sup>20</sup>. More specifically, studies on the effect of exercise training have demonstrated an increase in exercise capacity of up to 38% in patients after valve replacement surgery <sup>21</sup> and an increase in peak VO<sub>2</sub> of 2.3±2.2 (SD) ml/kg per minute in the intervention group compared with -0.3±2.1 (SD) ml/kg per minute in the control group as well as a significant change in quality of life in older patients with heart failure <sup>22</sup>. Traditional cardiac rehabilitation has focused on physical training and standardized programmes, but studies indicate that individualized content and supervised exercise components are key design characteristics for improving outcomes <sup>23</sup>. In addition to exercise training, evidence support interventions including patient education, which in patients with CHD has been shown to improve health related quality of life and decrease healthcare costs <sup>24</sup> and psychological support, which has been shown to improve psychological symptoms in patients with CHD, such as depression and anxiety <sup>25</sup>. Evidence on the efficacy of comprehensive interventions for patients treated for IE, however, is needed. Based on the effects of rehabilitation in other cardiac conditions, we hypothesise that patients treated for IE

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4 can benefit from participating in a rehabilitation programme, consisting of an individualized  
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6 exercise training programme and a psycho-educational intervention. Therefore, we have designed  
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8 the CopenHeart<sub>IE</sub> trial.  
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### 10 11 **Study objectives**

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14 The aim of the trial is to test a comprehensive cardiac rehabilitation programme for patients treated  
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16 for IE versus usual care. The programme consists of a psycho-educational component and an  
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18 exercise-training component. The primary hypothesis is that comprehensive cardiac rehabilitation  
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20 improves mental health, measured by the mental component scale (MSC) of the Short Form 36 (SF-  
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22 36) questionnaire, in patients treated for IE with 6 points (13%) in the intervention group compared  
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24 with the control group after the completed intervention. The estimated 13% increase in primary  
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26 outcome is based on a study on ICD recipients with a comparable complex rehabilitation  
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28 intervention which found a similar increase (unpublished data from the COPE-ICD trial<sup>26</sup>). The  
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30 secondary hypothesis is that physical capacity, measured as peak oxygen uptake (VO<sub>2</sub> peak) by the  
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32 bicycle ergospirometry test, will be 3 ml/kg per minute (20%) higher in the intervention group  
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34 compared with the control group after 12 weeks of exercise training. Since no data on physical  
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36 capacity exists on patients treated for IE, this hypothesis is based on rehabilitation studies including  
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38 patients after heart valve surgery<sup>27,28</sup>. Exploratory analyses will test the hypotheses that  
39  
40 comprehensive cardiac rehabilitation improves self-rated health, quality of life, nutritional status,  
41  
42 sleep quality, and body-image and reduces anxiety, depression and fatigue after 6, 12 and 24  
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44 months. Furthermore, we intend to assess whether comprehensive cardiac rehabilitation can reduce  
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46 health care utilisation, work cessation and mortality and increase cost-effectiveness after 24 months.  
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### 51 52 **Design**

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4 The CopenHeart<sub>IE</sub> trial is part of the overall CopenHeart project, which is designed to develop  
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6 evidence-based knowledge on rehabilitation among patients with complex cardiac conditions <sup>29</sup>.  
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9 The CopenHeart<sub>IE</sub> trial is a multi-centre, multidisciplinary, randomised clinical trial designed to  
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11 examine the effects of a comprehensive cardiac rehabilitation programme compared with usual care  
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13 for patients treated for IE. In addition to this, the CopenHeart<sub>IE</sub> trial includes two complementary  
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15 studies, aimed at investigating the post-discharge experiences and rehabilitation needs of patients  
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17 treated for IE, and a qualitative post-intervention study to explore the meaning of the CopenHeart<sub>IE</sub>  
18  
19 rehabilitation programme from the patient's perspective. Accordingly, the trial combines  
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21 quantitative and qualitative research methods. The premise of mixed methods research is, that the  
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23 use of qualitative and quantitative approaches in combination provides a better understanding of the  
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25 research problems than either approach alone, because different types of questions require different  
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27 types of data and that mixed methods research provides strengths that offset the weaknesses of both  
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29 qualitative and quantitative research <sup>30</sup>. The methods are integrated by applying the mixed method  
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31 embedded experimental design and include qualitative data to develop the intervention and to  
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33 examine the process of the intervention and the results of the trial (see Figure 1) <sup>30,31</sup>. The rationale  
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35 for this approach is that the quantitative findings provide a general understanding of the research  
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37 problem through statistical results, and qualitative findings refine and explain the results by  
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39 exploring participants' views in greater detail. Evaluation using qualitative research methods is  
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41 increasingly promoted in evidence-based rehabilitation <sup>32-35</sup>. Qualitative research alongside  
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43 randomised controlled trials can contribute in several ways to the development and evaluation of  
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45 complex healthcare interventions and may be particularly useful in evaluating interventions that  
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47 involve social and behavioral processes, that are difficult to explore or capture using quantitative  
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49 methods alone <sup>36</sup>. As patient participation is paramount to the efficacy of the rehabilitation <sup>37</sup>, we  
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51 find it highly valuable to include the patients' perspective in the development and evaluation of the  
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4 intervention. This paper presents the study protocol for the CopenHeart<sub>IE</sub> randomised clinical trial.

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6 The complementary studies are briefly described in a separate section.  
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### 9 10 ***Study population and eligibility criteria***

11 Consecutive patients treated for left-sided (native or prosthetic valve) or cardiac device endocarditis  
12 at the tertiary referral heart centres in Copenhagen, Denmark (Rigshospitalet and Gentofte Hospital)  
13 will be screened for inclusion and approached for study participation. Patients aged 18 years or  
14 older, having completed treatment for IE based on the Duke Criteria <sup>38</sup>, speaking and understanding  
15 Danish, and providing written informed consent will be considered eligible for participation.  
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18 Patients unable to understand study instructions, with a cardiac ischemic event within the past 6  
19 months, who are pregnant or breastfeeding, with reduced ability to follow the planned programme  
20 due to, e.g., substance abuse problems or other somatic illness, with considerable illness in the  
21 musculoskeletal system or with physical disability which complicates exercise training or patients  
22 whose physician advise against participation, will be excluded.  
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### 33 34 35 ***Study procedure, randomisation and follow-up***

36 Patients eligible for participation will be approached by a nurse or a physician from the research  
37 group during the expected last week of their treatment for IE. A brief oral introduction is initially  
38 given together with written information describing the study and implications for the patient in  
39 detail. The patient is given ample time to read the information and if necessary involve a relative in  
40 the decision making. The enrolling nurse or physician will return within 2-3 days or at a planned  
41 time to answer any questions the patient or their relative might have. The patient should  
42 subsequently be able to provide informed consent or reject participation. When the informed  
43 consent form is signed attained, baseline data will be collected including the baseline questionnaire  
44 package, demographic variables, and clinical characteristics. After baseline data collection, central  
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4 randomisation is conducted by telephoning the trial coordinating centre, Copenhagen Trial Unit  
5 (<http://www.ctu.dk/>), for randomised allocation. The allocation sequence will be computer-  
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8 generated with varying block-sizes, blinded to investigators, randomising patients 1:1 to either the  
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10 experimental intervention versus usual care. Thus, neither investigators nor patients or relatives can  
11  
12 influence to which group the patients are allocated. Patients will be stratified according to sex and  
13  
14 the treating heart centre. For both groups, the follow-up assessment will take place at 1 month (T<sub>1</sub>),  
15  
16 4 months (T<sub>4</sub>), 6 months (T<sub>6</sub>), and 12 months (T<sub>12</sub>) post-discharge and a register-based follow-up  
17  
18 assessment will be conducted at 24 months (T<sub>24</sub>) (see Figure 2). In the event of complications  
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20 arising after study enrolment, cases will be handled individually (see section on intervention  
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22 deviation).  
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27 The patients answer questionnaires independently of the researchers, and before randomisation. All  
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29 questionnaires are distributed electronically, thus data management is handled independently from  
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31 the researchers that interpret data. All data entry is double and stored electronically in a coded  
32  
33 database, and in an independent spread sheet, only accessible for the CopenHeart group.  
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37 Personal information about potential and enrolled patients will be collected electronically and  
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39 shared in a database only accessible to those within the project group responsible for patient  
40  
41 recruitment, in order to protect confidentiality before, during and after the trial.  
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#### 44 *The experimental intervention group*

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46 Patients in the intervention group will follow the integrated rehabilitation programme, consisting of  
47  
48 a psycho-educational component and an exercise training component as well as usual care (see  
49  
50 below). The intervention has been developed and tested in two clinical trials; the DANREHAB trial  
51  
52 including patients with ischemic heart disease and heart failure<sup>39</sup>, and the COPE-ICD trial  
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54 including patients with an implantable cardioverter defibrillator<sup>26</sup>. The blood work and clinical  
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4 control described for the control group (see below) are incorporated in the follow-up of the  
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6 intervention group.  
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10 The psycho-educational component

11 The aim of the psycho-educational intervention is to provide emotional support and improve coping  
12 skills and illness appraisal in order for the patient to respond appropriately to physical and  
13 psychological symptoms. Education and information about the disease prepare the patient for  
14 expected symptoms and sensations. Dialogue and shared reflection facilitate strategies for coping  
15 with symptoms and experiences associated with the condition, e.g., anxiety and fear. Cardiac care  
16 nurses with specific training will perform the psycho-educational intervention. Some of the most  
17 commonly reported concerns of patients treated for IE, such as fatigue, gastrointestinal function,  
18 and concerns about work life, are outlined in an inspiration guide for the nurses to address when and  
19 if relevant (see Table 1). Information given will also be based on national guidelines and standard  
20 treatment of patients with infective endocarditis, and on the findings of the qualitative study on post  
21 discharge experiences described in the complementary studies section of this paper. The  
22 consultations focus on managing life after IE by establishing a joint approach to disease  
23 management and coping strategies, using a holistic view. The psycho-educational intervention is  
24 inspired by R.R. Parse's Human Becoming Practice Methodologies three dimensions<sup>40</sup>. These are  
25 interpreted as: 1) discuss and give meaning to the past, present and future, 2) explore and discuss  
26 events and possibilities and 3) move along with envisioned possibilities. According to this theory,  
27 there are three ways of changing health: creative imaging, that is to see, hear and feel what a  
28 situation might be like if lived in a different way, affirming personal patterns and value priorities,  
29 and shedding light on paradoxes, that is, looking at the incongruence in a situation and changing the  
30 view held of something. The nurse is truly present in the process through discussions, silent  
31 immersion and reflection. The human becoming practice methodology was chosen to apply a  
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holistic patient approach, focussing on the coping and transformation process of the individual person. Furthermore, the method is extensively used in the outpatient heart clinics at the heart centre at Rigshospitalet, such as for patients with inherited heart diseases and adults with congenital heart disease, and finally documented in the COPE-ICD trial<sup>26,41</sup>. The consultations take place in a quiet setting at the out-patient clinic and will last for approximately one hour. The nurse is able to facilitate contact with or seek advice from a physician if needed. The first consultation will be approximately one week after discharge, and then once every four to six weeks, with a total of five consultations. Consultations can be done by telephone, according to the patient's wishes. The primary investigator will attend the consultations regularly to ensure protocol compliance.

**Table 1. Inspiration guide for nursing consultations/psycho-educational intervention.**

	1	2	3	4	5
<b>How have you been? What has happened since you were here last time?</b>	x	x	x	x	x
<b>Discuss the events leading up to the diagnosis of IE. Experiences before and during hospital admission.</b>					
<b>Address present thoughts and questions.</b>	x				
<b>How did you having IE affect your life? Are there things/activities you avoid or feel you can't do after having IE?</b>	x				
<b>Have you initiated exercise training? How is training going?</b>		x	x	x	x
<b>Discuss social network/family. How do they handle the situation? Has anything changed in your social relationships?</b>			x		
<b>Has you having IE affected your work situation? /had financial consequences?</b>				x	
<b>Have you had a changed view/perception of your body and its functions?</b>				x	
<b>How is your health in relation to e.g. fatigue, dyspnoea, pain, appetite, gastrointestinal function, sleep, sexual functioning, other?</b>				x	x
<b>Information/recommendations in relation to discussed issues/problems.</b>	x	x	x	x	x

The physical exercise training component

The main objective of the exercise training is to improve the patient's physical capacity and facilitate lifestyle/behavioural changes, which will subsequently result in physical and psychological health-benefits for the patient. However, the exercise training programme is also targeted at relieving the fear and uncertainty that the patient may feel in relation to physical activity.

The intervention is based on the European guidelines for physical training in cardiac rehabilitation<sup>16</sup>

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4 and complies with the recommendations on physical activity of the Danish National Board of  
5 Health <sup>42</sup>. The intervention consists of three components: 1) individual planning of the exercise  
6 training, 2) twelve weeks of high intensity exercise training, and 3) continuous moderate daily  
7 physical exercise.  
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#### 14 1) Individually planned physical exercise by a specialised cardiac rehabilitation physiotherapist

15 Integrating detailed information regarding the specific type of IE, co-morbidities, hospitalisation,  
16 activities of daily living (ADL) and level of physical activity prior to IE, the physiotherapist  
17 conducts a patient consultation of up to 30 minutes. The consultation is based on the initial testing  
18 of the patient, including the cardiopulmonary exercise testing, described in the outcome measures  
19 section, a 6 minute walk test and a ‘sit to stand’ test. For all patients an individual training diary is  
20 prepared, and all patients are instructed in the use of a heart rate monitor integrated into Polar  
21 watches, provided by Rigshospitalet. The heart rate monitor and diary is essential to ensure  
22 CopenHeart training protocol compliance and are returned for data collection at the end of the  
23 exercise training intervention.  
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#### 37 2) Intensive exercise training programme

38 The initial training sessions take place in a physiotherapist supervised setting at the primary  
39 investigating hospital, Rigshospitalet, to ensure the quality, intensity, and safety of training.  
40 Training is started four weeks post-discharge to ensure optimum post-surgery healing after heart  
41 valve surgery or cardiac device implantation. Using wireless electrodes integrated into t-shirts  
42 (Corus-Fit, CardioCardio and Corus Exercise Assistant, CEA, vs. 2.0.16, Finland) potential cardiac  
43 arrhythmias, electrocardiographic abnormalities such as ST-depression, ST-elevation, Q-or T-wave  
44 altering, atrial fibrillation and ventricular arrhythmias, and training intensity level are monitored.  
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54 After 1-3 exercise training sessions at Rigshospitalet, the patient continues the programme at a local  
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4 CopenHeart certified training facility supervised by physiotherapists or as supervised home-based  
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6 training. Supervised home-based exercise training has shown similar results as hospital-based  
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8 exercise training<sup>43</sup>, and has been confirmed in a Danish setting<sup>44</sup>.  
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11 The physical exercise training continues for 12 weeks, comprising 3 sessions weekly of 60 minutes,  
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13 with a total of 36 sessions. The training protocol consists of aerobic and anaerobic exercise to  
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15 accommodate endurance and muscle strength.  
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19 An exercise training session consists of 10 minutes warm up, 20 minutes of bicycling, 20 minutes of  
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21 resistance training, and 10 minutes stretching and cool-down period. Using the results from the  
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23 cardiopulmonary exercise test performed prior to the initial training session, in combination with  
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25 the Borg scale measuring subjective exhaustion, the aerobic exercise is performed with a gradually  
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27 increasing intensity throughout the exercise intervention period, corresponding to 13 to 17 at the  
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29 Borg Scale and 50% to 80% of the maximum heart rate. The anaerobic resistance training is  
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31 initiated at 30% to 40 % of 1 repetition maximum (RM) for the upper body, and 40% to 50 % of 1  
32  
33 RM for the lower body, with an increasing work load during the training sessions. To achieve  
34  
35 cardiovascular adjustment and reduce the risk of malignant cardiac arrhythmias and ischemia, the  
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37 training session is initiated and terminated with a warm up and a cool down period to gradually  
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39 increase and decrease training intensity and heart rate. This cardiovascular adjustment has been  
40  
41 proven to reduce the risk of ischemia and arrhythmia in relation to exercise training<sup>45, 46</sup>. Training  
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43 is predominantly performed in the upright position to reduce left ventricle preload (diastolic  
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45 volume) and the risk of ischemia and arrhythmias due to heart failure<sup>46</sup>.  
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### 50 51 3) Sustained moderate daily physical exercise 52 53 54 55 56 57 58 59 60

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4 Participants are instructed to perform moderate physical exercise at least 30 minutes a day during  
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6 the intervention period, e.g., bicycling, walking, gardening, jogging or recreational sports. Daily  
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8 moderate physical exercise is encouraged to be continued throughout life.  
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#### 10 11 Intervention deviations

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13 Both components of the intervention will be supervised regularly by the primary investigator to  
14  
15 ensure protocol compliance. Modification of the allocated intervention due to surgery  
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17 complications, rehospitalisation or emerging co morbidities (e.g. pneumonia, pericardial exudation,  
18  
19 musculoskeletal problems) will be individually assessed, and the time of the primary outcome  
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21 assessment at four months (described in section below) will be corrected in accordance with  
22  
23 changes in the intervention.  
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#### 27 28 *The usual care control group*

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30 Patients in the control group will follow standard follow-up for patients treated for IE, with 1 to 2  
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32 visits within the first month post-discharge, including blood work and clinical assessment.  
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34 Haemoglobin level, infection variables, kidney function, and, on indication, liver status is assessed,  
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36 and blood cultures are drawn on suspicion of IE relapse. Blood pressure, pulse and temperature  
37  
38 parameters are obtained. If results give cause for concern, the patient will see a specialist physician  
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40 during the follow-up visit. A transthoracic echocardiogram will be performed within the first year  
41  
42 post-discharge, typically between 1 and 6 months post-discharge and again at 12 months, depending  
43  
44 on whether the individual patient has had heart valve surgery and on the status of the native or  
45  
46 replaced valve. These patients will be contacted at 1, 4, 6, 12, and 24 months for outcome  
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48 assessment including functional test, questionnaires and clinical data collection (see figure 2).  
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#### 52 53 *Outcomes and data collection*

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4 Numerous data will be collected to evaluate the effect and meaning of the intervention. The primary  
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6 and the secondary outcome reflect the primary modifiable factors of the intervention. Since almost  
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8 no evidence exists, a number of explorative outcomes will also be collected.  
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11 *Primary outcome:* Mental health will be measured by the Mental Component Subscale (MCS) of  
12 the Medical Outcome Study Short Form 36 (SF-36) questionnaire<sup>47</sup> after 1 month (T<sub>1</sub>), 4 months  
13 (T<sub>4</sub>), 6 months (T<sub>6</sub>), 12 months (T<sub>12</sub>) and 24 months (T<sub>24</sub>). The SF-36 questionnaire is a measure of  
14 self-rated health. It is a validated multipurpose health survey comprised of 36 items that address the  
15 following 8 dimensions: physical functioning (PF), role physical (RP), bodily pain (BP), general  
16 health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH).  
17  
18 The first four scales (PF, RP, BP, GH) are then combined into a physical component scale and the  
19 latter four (VT, SF, RE, MH) into a mental component scale<sup>47</sup>. The instrument was chosen for its  
20 ability to detect changes in self-rated health within domains that could potentially be influenced by  
21 the CopenHeart<sub>IE</sub> intervention. Mental health was chosen as the primary outcome as other studies  
22 have shown that mental health is affected in patients with IE compared to healthy controls<sup>13, 14</sup> and  
23 the rehabilitation intervention focuses on this modifiable factor.  
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39 *Secondary outcome:* Physical capacity will be measured by peak VO<sub>2</sub> using cardiopulmonary  
40 exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland) by investigators blinded to the  
41 intervention group. The test will be performed according to current guidelines for ergospirometry  
42 testing<sup>48-50</sup>, using an ergometer-bicycle with spirometry, monitoring heart-rhythm, blood pressure,  
43 electrocardiogram (ECG), and measuring gas-exchange during workload and in the following  
44 recovery period. Average test duration is 10-15 minutes including pre- and post- test phase without  
45 work load. Before each session calibration will be performed to address changes in room  
46 temperature, humidity and air O<sub>2</sub> content. A standardised ramp-protocol will be used with an initial  
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work load of 25 or 50 watts, increasing gradually by 12,5 watts/minute until peak exhaustion. Peak exhaustion is evaluated by a respiratory exchange ratio (RER)  $\geq 1.10$  or subjective exhaustion of the patient. In order to encourage patients equally, independent of the tester, a standardised guide has been developed. During the test, clinical manifestations, ECG abnormalities (ST depression, ST elevation, q-and t-wave changes, supraventricular or ventricular arrhythmias), blood pressure response and several physiological parameters will be observed and documented. The test will be performed by either a cardiac care nurse or a physician. For safety reasons preset criteria for initiation and/or termination of the test has been defined. The test will be performed prior to the exercise training programme (T<sub>1</sub>), after 12 weeks of exercise training (T<sub>4</sub>) and at 12 months follow-up (T<sub>12</sub>). Physical capacity was chosen as the secondary outcome measure, as studies indicate that patients treated for IE are physically deconditioned after long-term illness and hospitalisation<sup>14</sup>.

*Exploratory outcomes:* A more extensive evaluation of the physical and psychological status of the patients over time will be performed, exploring demographic, clinical, paraclinical and imaging variables, as well as additional physical capacity tests and additional questionnaires exploring for example fatigue, sleep quality and anxiety and depression (see Table 2).

**Table 2. CopenHeart<sub>IE</sub> – Exploratory quantities subjected to post-hoc analysis**

Quantity	Time of measure	Type of quantity
<b>Demographic</b>		
Sex	Baseline	Binary (M/F)
Age, height, weight,	Baseline	Continuous
Marital, occupational, educational status	Baseline	Categorical
<b>Clinical</b>		
NYHA- classification	Baseline, 1, 4, 12	Continuous
Previous heart disease, diabetes mellitus, kidney disease, pulmonary disease (COLD), co-morbidities, hypertension, dyslipidaemia, smoking	Baseline	Binary (Y/N)
Medication	Baseline, 1, 4, 12	Binary (Y/N)

BMI, Nutritional screening	Baseline, 1, 4, 12	Continuous
Endocarditis specific data:		
Valve-/device affected, type of surgery due to IE	Baseline	Categorical
Cerebral insult +, hemodialysis +	Baseline	Binary (Y/N)
Length of hospitalisation (days), weight loss related to IE (kilograms)	Baseline	Continuous
<b>Paraclinical and imaging</b>		
Blood work (Haemoglobin, infection-, kidney- liver and selected nutritional parameters, electrolytes, cholesterol- and thyroid status, ProBNP)	Baseline, 1, 4, 12	Continuous
Echocardiogram	Baseline, 4, 12	Continuous
<b>Physical function</b>		
6 minute walking test <sup>51</sup>	Baseline, 1, 4, 12	Continuous
Sit to stand test <sup>52</sup>	1, 4, 12	Continuous
<b>Questionnaires</b>		
Physical activity level <sup>53</sup>	BL, 1, 4, 6, 12, 24	Binary (Y/N)
SF-36 <sup>47</sup> HADS <sup>54</sup> , QoL-CV <sup>55</sup>	BL, 1, 4, 6, 12, 24	Continuous
Emotions and Health <sup>56</sup>	BL	Continuous
Rehabilitation <sup>57</sup>	12	Continuous
HeartQoL R <sup>58</sup> , EQ-5D <sup>59</sup>	BL, 6, 12, 24	Continuous
IPAQ <sup>60</sup>	1, 4, 12, 24	Continuous
MFI-20 <sup>61</sup>	BL, 1, 4, 12	Continuous
PSQI <sup>62</sup>	1, 6	Continuous
BIQOL <sup>63</sup>	BL, 6	Continuous

Data collected from official national registers regarding mortality, hospitalisation, emergency room visits, outpatient visits, medication, employment status, and payment of welfare benefits (sick leave payment and early retirement pension) will be collected at 24 months to assess the long term effects of the intervention. The Danish official national registers are well-functioning with a small percentage of lost data <sup>64</sup>. Consequently, the method is well suited as an outcome measure in small patient populations. Data will be collected from the Danish National Patient Register <sup>65</sup>, the Danish National Health Service Register <sup>66</sup>, the Danish National Prescription Registry <sup>67</sup>, the Danish National Causes of Death Register <sup>68</sup>, and registers on transfer payments and labour market affiliation <sup>69, 70</sup>.

### ***Economic evaluation***

An economic evaluation will be conducted alongside the trial to assess the cost-utility of comprehensive cardiac rehabilitation compared with usual care in the study population. The economic evaluation will compare the costs to QALYs (quality adjusted life years) and take a societal perspective as recommended nationally. QALYs and costs will be assessed at the end of the intervention, 6 months from randomisation and later after 24 months from randomisation using register-based follow-up.

QALYs will be estimated using the self-completed EQ-5D instrument, which is a standardised instrument assessing 5 dimensions of self-reported health status (mobility, self-care, usual activities, pain/discomfort and anxiety/ depression)<sup>71,72</sup>. The estimated calculations will be evaluated using Danish preference weights<sup>73</sup>. Information on costs will only include costs that are expected to differ between the intervention and usual care group<sup>59</sup>. Included costs in the evaluation are health costs associated with the rehabilitation programme, other health care costs (health care utilisation apart from rehabilitation), patient costs and costs of productivity losses. Information on costs will be collected by a mixture of activity-based costing, surveys, patient diaries and by the use of registers.

Results from the analysis will be reported as an incremental cost-effectiveness analysis (ICER).

Sensitivity-analysis will be conducted to express uncertainty in the estimates<sup>74</sup>. The reporting of ICER is presented using Bayesian methods, including bootstrapping and presented as cost-effectiveness acceptability curves<sup>75</sup>.

### ***Sample size, power calculations and interim analysis***

We will perform a randomised trial with a continuous response variable from independent control and intervention group participants with one control per intervention group participant. A previous study on an IE population found that the mental component scale was normally distributed with a

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4 standard deviation of 13<sup>13</sup>. If the true difference between the intervention and control group means  
5 is 6 points, we will need to include 75 participants in each study group (a total of 150 participants)  
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7  
8 to be able to reject the null hypothesis, stating that the mean in the intervention and the control  
9  
10 groups are the same with a power of 80%. The type I error probability associated with this test of  
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12 this null hypothesis is 5%.

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16 For the secondary outcome, VO<sub>2</sub>, we will be able to reject the null hypothesis that the population  
17  
18 means of the experimental and control groups are equal with a probability (power) of 75.4%,  
19  
20 assuming the VO<sub>2</sub> is normally distributed with a standard deviation of 6.9<sup>27,28</sup>, and the true  
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22 difference in the experimental and control means is 3 ml/kg per minute.

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26 A data monitoring and safety committee will be informed, every nine months, of all serious adverse  
27  
28 events occurring in the two study groups. An interim analysis meeting will be held by the data  
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30 monitoring and safety committee to review data relating to intervention efficacy, participant safety,  
31  
32 and quality of trial conduct. The committee will evaluate data on the primary and secondary  
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34 outcome measures; mental health (SF-36) / peak VO<sub>2</sub> (efficacy) and all serious adverse events  
35  
36 (safety/tolerability). After the interim analysis meeting, the committee will make a recommendation  
37  
38 to the steering committee whether to continue, hold or terminate the trial. This recommendation will  
39  
40 be based primarily on safety and efficacy considerations and will be guided by statistical monitoring  
41  
42 guidelines defined by the trial safety charter.

### 43 44 45 46 47 ***Statistical analysis***

48  
49 Data will be pseudo- anonymised and analysed, blinded by a trial-independent statistician using  
50  
51 intention-to-treat analyses and a mixed model with repeated measures (MMRM) for continuous  
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53 outcome measures<sup>76</sup>. Using MMRM ensures that missing data values (in the case of the primary  
54  
55 and secondary outcome) will not create bias as long as the missing values are random. Two sided  
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tests will be performed. The level of significance is set at 5%. Dealing with multiplicity, gate keeping will be used to adjust the observed P values for primary and secondary outcomes<sup>77</sup>. Both original and adjusted P values will be reported.

For the primary and secondary outcomes, we will conduct sensitivity analysis to assess the potential impact of non-random missing values. For each intervention group (A and B) some quantities (imputing quantities) will be computed to be used to impute missing values in a group (A or B) as explained below. A comparison between group A and group B where missing values in group A are imputed using imputing quantities obtained from group A and missing values from group B are imputed using imputing quantities obtained from group B is referred to as a best case analysis. If missing values in group A are imputed using imputing quantities obtained from group B and vice versa the comparison is called a worst case analysis. The imputed quantities for the primary outcome would be the group mean at T1 ( $X1\text{-bar}$ ), the group mean at T4 ( $X4\text{-bar}$ ), the group mean at T6 ( $X6\text{-bar}$ ), the mean difference between the value measured at T4 and that measured at T1 ( $\Delta 1$ ), and the mean difference between the value measured at T6 and that measured at T4 ( $\Delta 2$ ). Table 3 explains how the quantities will be used to impute missing values in a group (either the same group or the other intervention group).

### Table 3. Statistical appendix

The use of imputed quantities derived from observed values in a group (group A) to impute missing values in a group (group B).

Observed pattern in group B at the times (T1, T4, T6)	Imputed value in group B at T1	Imputed value in group B at T4	Imputed value in group B at T6
mis <sup>A</sup> , mis, mis	$X1\text{-bar}^B$	$X4\text{-bar}^C$	$X6\text{-bar}^D$
mis, mis, Y3 <sup>E</sup>	$Y3 - (\Delta 1^F + \Delta 2^{G,H})$	$Y3 - \Delta 2$	
mis, Y2, mis	$Y2 - \Delta 1$		$Y2 + \Delta 2$
Y1, mis, mis		$Y1 + \Delta 1$	$Y1 + \Delta 1 + \Delta 2$

Y1, Y2, mis			Y2 + delta2
Y1, mis, Y3		$(Y1 + \text{delta}1 + Y3 - \text{delta}2)/2$	
mis, Y2, Y3	Y2 – delta1		

A) The value at T <sub>4</sub> is missing in group B
B) Mean of values observed in group A at time T <sub>1</sub>
C) Mean of values observed in group A at time T <sub>4</sub>
D) Mean of values observed in group A at time T <sub>6</sub>
E) Observed value in group B at time T <sub>6</sub>
F) The mean of difference between value observed at time T <sub>4</sub> and observed at time T <sub>1</sub> in group A
G) The mean of difference between value observed at time T <sub>6</sub> and observed at time T <sub>1</sub> in group A
H) If an inputted value is < 0 it is set equal to 0

If the standard error (SE) of a parameter estimate calculated using imputed data is smaller than that of the corresponding parameter calculated using complete case data it will be replaced by the latter SE when the p value is calculated.

Long term register-based outcomes will be analysed by two different models: non-negative count outcomes (e.g., number of contacts to hospital or number of visits to general practitioners) will be analysed by a Poisson model or a zero-inflated Poisson model if the number of zeros are large, and time-to-event data (e.g., cause-specific mortality and leaving the labour market) will be analysed with survival methods (Kaplan-Meier estimator and Cox regression model). Especially for socio-economic outcomes, competing risk due to mortality will be considered if a large proportion of patients die during follow-up.

Explorative data will be analysed using appropriate statistical methods according to type of data (see Table 2). SPSS version 19.0 and SAS version 9.3 will be used.

### Complementary studies

*Qualitative study on post discharge experiences*

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4 The post-discharge experiences of patients treated for IE will be explored through semi-structured  
5 qualitative interviews, which take a phenomenological-hermeneutic approach. The data derived  
6 from this study will be used to address relevant issues designing the rehabilitation intervention.  
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10 Patients treated for IE, 3-6 months post-discharge will be identified through hospital admission lists.  
11  
12 A sample sufficient to achieve data saturation will be included. The study aims to answer the  
13 following thematic research questions: What are the experiences of returning home after treatment  
14 for IE? What are the new experiences, if any, in daily living? Which health problems, if any, have  
15 patients experienced? What are the concerns, if any, for the future? The data-analysis is inspired by  
16 Ricoeur's theory of interpretation and consists of three levels: naive reading, structured analysis and  
17 critical interpretation and discussion. Qualified interviewees will be chosen, ensuring a  
18 representative sample in relation to sex, age and surgery/non-surgery.  
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### 29 *Survey-based study*

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31 The post-discharge status of the patients treated for IE will be explored through a national survey.  
32  
33 The standardised questionnaires Short Form-36 (SF-36)<sup>47, 78-82</sup>, Hospital Anxiety and Depression  
34 Scale (HADS)<sup>54</sup>, Multidimensional Fatigue Inventory (MFI-20)<sup>61, 83</sup>, EuroQoL - EQ-5D<sup>59, 84</sup>,  
35 Heart Related Quality of Life (HeartQoL R)<sup>58</sup>, International Physical Activity Questionnaire  
36 (IPAQ)<sup>60, 85</sup> and a questionnaire developed by the Danish Heart Foundation on the extent and  
37 quality of rehabilitation offered will be sent out to patients who have undergone treatment for IE, 6-  
38 12 months post-discharge. The instruments are all validated and have good reliability and  
39 responsiveness<sup>54, 58, 60, 61, 84, 86</sup>. The data will provide knowledge on patients' self-rated health,  
40 quality of life, fatigue, anxiety and depression, body image and extent and quality of the  
41 rehabilitation currently received. Patients will be identified through the National Patient Register<sup>65</sup>  
42 and questionnaires will be sent out to 210 of them. We aim to achieve a response rate of 70%, using  
43 repeat mailing strategies and/or telephone reminders to maximize response if necessary<sup>87</sup>. This  
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4 should result in an estimated 150 questionnaire respondents. Data will be anonymised and analysed  
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6 by relevant descriptive statistical methods.  
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### 9 10 *Qualitative study on rehabilitation participation experiences*

11 After the intervention, an interview study, including 10% of the intervention population or until data  
12 saturation has been reached, will be conducted, in order to explore the experiences and processes  
13 behind the potential effect of the intervention. The study aims to answer the following thematic  
14 research questions: What are the experiences of participating in the integrated rehabilitation  
15 programme? Which components of the programme are meaningful? In what way? Participant  
16 selection and applied methods in this study are consistent with that of the qualitative study on post-  
17 discharge experiences.  
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### 28 **Ethics**

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30 The trial has been approved by the Regional Research Ethics Committee (no H-1-2011-129) and the  
31 Danish Data Protection Agency (no 2007-58-0015). All eligible patients will be informed about the  
32 trial verbally and in writing, and the patients are included after written informed consent is  
33 obtained. All data will be handled confidentially and patients are ensured anonymity. The study  
34 complies with the latest Declaration of Helsinki and is registered at ClinicalTrials.gov  
35 (NCT01512615). An independent safety committee comprised by an international group of experts  
36 is monitoring the trial; ensuring good clinical practice standards are being upheld. No serious risks  
37 are anticipated to receiving rehabilitation. No risks have previously been reported in relation to  
38 psycho-educational consultations. The physical exercise training and the cardiopulmonary exercise  
39 testing will be supervised by competent health care professionals and will be in accordance with  
40 current guidelines on safety when testing and training cardiac patients<sup>88,89</sup>. Efforts will be made to  
41 avoid arrhythmias during workload testing and exercise training by protocol with a cool-down  
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4 period, which positively affects serious complications. Staff members will be trained according to  
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6 guidelines to handle cardiac arrest or other disease- or device-specific emergencies. All serious and  
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8 moderate adverse events will be registered and reported according to protocol.  
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10  
11 Not providing rehabilitation to the control group can be ethically justified, as current national and  
12  
13 international guidelines give no specific recommendations on cardiac rehabilitation for patients  
14  
15 treated for infective endocarditis. The scope and quality of rehabilitation offered to this population  
16  
17 is unknown, but suspicions are, that often no or suboptimal rehabilitation is provided. The survey  
18  
19 based complementary study, described previously in this paper, will hopefully provide more insight.  
20  
21 In screening patients for participation, the enrolling nurse or physician will exclude patients with a  
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23 compelling rehabilitation need, for instance after a cerebral embolic event. Furthermore patients are  
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25 informed of the study design before giving their consent, and are free to decline participation.  
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### 30 **Discussion**

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32 This randomised clinical trial is the first to examine physical functioning by cardiopulmonary  
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34 exercise testing and to test a comprehensive rehabilitation programme on a large heterogeneous  
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36 population of patients treated for IE. CopenHeart<sub>IE</sub> will provide much needed evidence and insight  
37  
38 on the post-discharge status and rehabilitation needs of patients treated for IE for health care  
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40 professionals and policymakers to make qualified, evidence-based decisions in everyday clinical  
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42 practice and as a foundation for national and international guidelines. With increased physical and  
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44 psychological well-being of patients, lower morbidity and health care utilisation expected in case of  
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46 a positive outcome, patients and society are anticipated to benefit greatly. Whether it produces  
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48 neutral, negative or positive results, the CopenHeart<sub>IE</sub> trial will have implications for clinical  
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50 practice in follow-up care of patients treated for IE in the western world.  
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4 Patients may decline participation due to an unwillingness to return to hospital after a lengthy  
5 illness and hospitalisation. We will attempt to avoid this problem by informing patients of the  
6 potential benefits of participation, e.g., the security we provide by following them closely after post-  
7 discharge and the value to science of their participation for future patients. Furthermore, it is  
8 documented that a substantial number of patients in rehabilitation studies control group perform  
9 self-initiated physical exercise training, possibly motivated by the study information during the  
10 recruitment process<sup>39</sup>. Hence we will abstain from giving extensive information about the training  
11 programme, or elaborate on the health benefits of physical training before knowing to which group  
12 the patient is randomised.  
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25 The study has been designed to meet the criteria for high quality in non-pharmacological  
26 randomised clinical trials<sup>90</sup> with central randomisation, multi-centre participation, blinded  
27 assessment of the exercise outcome, blinded analysis by study independent statisticians and  
28 furthermore, detailed information on the intervention received and usual care will be collected,  
29 including information on self-initiated exercise training during the trial period. For the primary  
30 outcome, the mental-health component subscale, we are aware of the subjective nature of the data  
31 collected. Accordingly, we will interpret the findings conservatively.  
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#### 41 Safety aspects and Data Monitoring Safety Committee (DMSC)

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44 In supervised exercise training and testing of other cardiac patient groups than patients after  
45 infective endocarditis, the risk of adverse effects is low (e.g. ischaemic heart disease, chronic heart  
46 failure), however, no current national safety instructions exist. Patient safety is given highest  
47 priority, and exercise training after heart valve surgery is considered safe based on results from  
48 exercise testing and training with heart failure patients<sup>88, 89</sup>. Any serious adverse events will be  
49 registered as part of the data collection.  
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4 The DMSC works independently from the funder and has no competing interests, and consists of  
5  
6 two clinicians and a statistician. The committee is responsible for safeguarding the interests of trial  
7  
8 participants, assessing the safety and efficacy of the interventions during the trial, and for  
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10 monitoring the overall conduct of the clinical trial. The steering committee and the DMSC  
11  
12 communicate regularly and at least every nine month the overall number of all serious adverse  
13  
14 events are reported.  
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### 17 18 **Dissemination plan**

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20 The results of the trial and complementary studies will be published in relevant international peer-  
21  
22 reviewed journals. Authorship will be determined according to the guidelines of the International  
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24 Committee of Medical Journal Editors. Due to the comprehensiveness of the outcome measures the  
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26 results will be presented in more than one scientific paper as relevant. Economic and long term  
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28 follow up will be reported as data becomes accessible.  
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### 32 33 **Trajectory**

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35 Inclusion was initiated in December 2011 and is expected to be completed at the end of 2013.  
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37 Results from two of the complementary studies are expected during 2012, and from the clinical trial  
38  
39 in 2014. To achieve adequate participant enrolment, patients are recruited from two independent  
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41 heart centres, and another heart centre, already in partnership of the trial, will be invited for  
42  
43 inclusion if enrolment rate declines. The inclusion rate is carefully monitored weekly. Patients in  
44  
45 doubt are contacted several times during hospitalisation, and if necessary after hospital discharge by  
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47 phone.  
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### 50 51 **Acknowledgements**

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12  
13  
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15  
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17  
18 interpretation of data.  
19

### 20 21 **Competing interests**

22  
23  
24 The authors declare that they have no competing interests.  
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### 28 29 **Contributorship**

30 SKB, ADO, TBR, HB, CG and JLH, in collaboration with PM and TMN, designed the study and  
31 developed the protocol. PW and LCT specifically designed the statistical analysis plan. TBR,  
32 SKB, ADO, SSR and KLS drafted the manuscript. SKB, ADO, HB, CG, JLH, PW, LCT, PM,  
33 TMN, SSR and KLS all revised the manuscript critically. All authors have given their final  
34 approval of the version to be published.  
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**Rationale and design of the CopenHeart<sub>IE</sub>—A randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients treated for Infective Endocarditis - the CopenHeart<sub>IE</sub> trial protocol.**

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## Article summary

### Article focus

- The CopenHeart<sub>IE</sub> trial is a randomised clinical trial investigating the effects of comprehensive cardiac rehabilitation versus usual care for patients treated for IE.
- The hypothesis is that comprehensive cardiac rehabilitation improves mental health and physical capacity.
- Using a mixed method approach, a broad range of outcome measures is collected to evaluate the intervention.

### Key messages

- Infective endocarditis is a life threatening disease. Patients experience severe deconditioning and diminished quality of life post-discharge.
- Studies exploring the effects of rehabilitation of patients treated for IE have not been published.
- This trial is the first to examine physical functioning and to test a comprehensive rehabilitation programme on a large population of patients treated for IE. CopenHeart<sub>IE</sub> will provide much needed evidence and insight on the post-discharge status and rehabilitation needs of patients treated for IE.

### Strengths and limitations of this study

- The study has been designed to meet the criteria for high quality in non-pharmacological randomised clinical trials with central randomisation, multi-centre participation, blinded assessment and analysis.
- We are aware of the subjective nature of the mental-health component subscale (primary outcome). Accordingly, we will interpret the findings conservatively.

## Abstract

### Introduction

Infective endocarditis (IE) is among the most serious infectious diseases in the western world. Treatment requires lengthy hospitalisation, high-dosage antibiotic therapy, and possible valve replacement surgery. Despite advances in treatment, the one year mortality remains at 20% to 40%. Studies indicate that patients experience persisting physical symptoms, diminished quality of life, and difficulties returning to work up to a year post-discharge. No studies investigating the effects of rehabilitation have been published. We present the rationale and design of the CopenHeart<sub>IE</sub> trial, which investigates the effect of comprehensive cardiac rehabilitation versus usual care for patients treated for IE.

### Methods and analysis

We will conduct a randomised clinical trial to investigate the effects of comprehensive cardiac rehabilitation versus usual care on the physical and psychosocial functioning of patients treated for infective endocarditis. The trial is a multi-centre, parallel design trial with 1:1 individual randomisation to either the intervention or control group. The intervention consists of five psycho-educational consultations provided by specialised nurses and a twelve-week exercise training programme. The primary outcome is mental health measured by the standardised Short Form 36 (SF-36). The secondary outcome is peak oxygen uptake measured by the bicycle ergospirometry test. Furthermore, a number of exploratory analyses will be performed. Based on sample size calculation, 150 patients treated for left-sided (native or prosthetic valve) or cardiac device endocarditis will be included in the trial. A qualitative and a survey-based complementary study will be undertaken, to investigate post-discharge experiences of the patients. A qualitative post-intervention study will explore rehabilitation participation experiences.

### Ethics and dissemination

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4 The study complies with the Declaration of Helsinki and was approved by the regional research  
5 ethics committee (no H-1-2011-129) and the Danish Data Protection Agency (no 2007-58-0015).  
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9 Study findings will be disseminated widely through peer-reviewed publications and conference  
10 presentations.  
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### 12 **Registration**

13 Clinicaltrials.gov identifier: NCT01512615  
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## Background

Infective endocarditis (IE) is an infection of the heart valves and/or adjacent structures. The bacteria may invade and destroy the tissue, and vegetations can dislodge into circulation and cause harmful and potentially deadly complications. Despite improvements in diagnostic tools, novel antibiotics and changes in treatment regimens, the mortality of IE remains high<sup>1-3</sup>. The incidence of IE in the developed countries is currently between 1.9 and 10.0 per 100,000 people per year<sup>3,4</sup>, and is rising due to the increase in degenerative valvular disease in the elderly, increasing insertions of prosthetic valves and implantable cardiac devices, and exposure to invasive procedures and nosocomial bacteraemia<sup>1,5-7</sup>. In Denmark, the incidence is at least 10 per 100,000 people per year, equivalent to approximately 500 patients per year<sup>4</sup>. The treatment includes a lengthy hospitalisation with intravenous antibiotic therapy, extensive invasive and non-invasive diagnostic procedures and, in about 50% of the patients, valve replacement surgery<sup>4</sup>. The in-hospital mortality rate of patients with IE is 10-25%, between 20-40% at one year post-discharge and up to 50% at 10 years post-discharge<sup>3,8-11</sup>. The causes of post-discharge mortality are still poorly understood.

### *Health and quality of life*

The disease, its treatments and the potential complications can lead to massive deconditioning of the patients<sup>12-15</sup>. The few existing studies on patient experiences after discharge, indicate that patients treated for IE have persisting physical and mental symptoms, such as fatigue in 47% of patients<sup>14</sup>, physical weakness in up to 78% of patients<sup>14,15</sup>, and concentration problems and memory loss in up to 35% of patients<sup>14</sup>. Patients also report diminished health-related quality of life<sup>14</sup>, negatively affected perceived health<sup>12,13</sup>, and up to 55% experience anxiety and depression<sup>15</sup> and 11% showed signs of post-traumatic stress disorder<sup>14</sup>. Furthermore, 35% of previously employed patients had not returned to work after 12 months<sup>14</sup>.



## Rehabilitation

Secondary prevention initiatives including cardiac rehabilitation, is widely recommended by the European society of cardiology (ESC) <sup>16</sup>. Although evidence of the efficacy is strong, cardiac rehabilitation is still poorly implemented and often only on selected populations, and thus the development of full comprehensive preventive programmes, according to the ESC, is warranted <sup>17</sup>.

Studies exploring the effects of rehabilitation of patients treated for IE are lacking. As there is no evidence of the ~~effectiveness~~efficacy, the provided rehabilitation is presumably often suboptimal or totally lacking. Lessons, however, might be learned from rehabilitation studies in patients with related cardiac conditions. The positive effects of cardiac rehabilitation have been well documented, particularly in patients with coronary heart disease (CHD) and heart failure (HF), where rehabilitation has been proven to reduce hospital re-admissions and mortality in a cost-effective way <sup>18, 19</sup>, as well as improve quality of life <sup>20</sup>. More specifically, studies on the effect of exercise training have demonstrated an increase in exercise capacity of up to 38% in patients after valve replacement surgery <sup>21</sup> and an increase in peak VO<sub>2</sub> of 2.3±2.2 (SD) ml/kg per minute in the intervention group compared with -0.3±2.1 (SD) ml/kg per minute in the control group as well as a significant change in quality of life in older patients with heart failure <sup>22</sup>. Traditional cardiac rehabilitation has focused on physical training and standardized programmes, but studies indicate that individualized content and supervised exercise components are key design characteristics for improving outcomes <sup>23</sup>. In addition to exercise training, evidence support interventions including patient education, which in patients with CHD has been shown to improve health related quality of life and decrease healthcare costs <sup>24</sup> and psychological support, which has been shown to improve psychological symptoms in patients with CHD, such as depression and anxiety <sup>25</sup>. ~~interventions designed to improve both physical and psycho-educational deficits may provide the best method for optimising functioning and enhancing quality of life. More eEvidence on the efficacy of~~

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4 comprehensive interventions for in-patients treated for with IE, however, is needed. Based on the  
5 effects of rehabilitation in other cardiac conditions, we hypothesise that patients treated for IE can  
6 benefit from participating in a rehabilitation programme, consisting of an individualized exercise  
7 training programme and a psycho-educational intervention. Therefore, we have designed the  
8 CopenHeart<sub>IE</sub> trial.  
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### 14 **Study objectives**

15  
16 The aim of the trial is to test a comprehensive cardiac rehabilitation programme for patients treated  
17 for IE versus usual care. The programme consists of a psycho-educational component and an  
18 exercise-training component. The primary hypothesis is that comprehensive cardiac rehabilitation  
19 improves mental health, measured by the mental component scale (MSC) of the Short Form 36 (SF-  
20 36) questionnaire, in patients treated for IE with 6 points (13%) in the intervention group compared  
21 with the control group after the completed intervention. The estimated 13% increase in primary  
22 outcome is based on a study on ICD recipients with a comparable complex rehabilitation  
23 intervention which found a similar increase (unpublished data from the COPE-ICD trial<sup>26</sup>). The  
24 secondary hypothesis is that physical capacity, measured as peak oxygen uptake (VO<sub>2</sub> peak) by the  
25 bicycle ergospirometry test, will be 3 ml/kg per minute (20%) higher in the intervention group  
26 compared with the control group after 12 weeks of exercise training. Since no data on physical  
27 capacity exists on patients treated for IE, this hypothesis is based on rehabilitation studies including  
28 patients after heart valve surgery<sup>27,28</sup>. Exploratory analyses will test the hypotheses that  
29 comprehensive cardiac rehabilitation improves self-rated health, quality of life, nutritional status,  
30 sleep quality, and body-image and reduces anxiety, depression and fatigue after 6, 12 and 24  
31 months. Furthermore, we intend to assess whether comprehensive cardiac rehabilitation can reduce  
32 health care utilisation, work cessation and mortality and increase cost-effectiveness after 24 months.  
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## Design

The CopenHeart<sub>IE</sub> trial is part of the overall CopenHeart project, which is designed to develop evidence-based knowledge on rehabilitation among patients with complex cardiac conditions<sup>29</sup>.

The CopenHeart<sub>IE</sub> trial is a multi-centre, multidisciplinary, randomised clinical trial designed to examine the effects of a comprehensive cardiac rehabilitation programme compared with usual care for patients treated for IE. In addition to this, the CopenHeart<sub>IE</sub> trial includes two complementary studies, aimed at investigating the post-discharge experiences and rehabilitation needs of patients treated for IE, and a qualitative post-intervention study to explore the meaning of the CopenHeart<sub>IE</sub> rehabilitation programme from the patient's perspective. Accordingly, the trial combines

quantitative and qualitative research methods. The premise of mixed methods research is, that the use of qualitative and quantitative approaches in combination provides a better understanding of the research problems than either approach alone, because different types of questions require different types of data and that mixed methods research provides strengths that offset the weaknesses of both qualitative and quantitative research<sup>30</sup>. The methods are integrated by applying the mixed method embedded experimental design and include qualitative data to develop the intervention and to examine the process of the intervention and the results of the trial (see Figure 1)<sup>30,31</sup>. The rationale for this approach is that the quantitative findings provide a general understanding of the research problem through statistical results, and qualitative findings refine and explain the results by exploring participants' views in greater detail. Evaluation using qualitative research methods is increasingly promoted in evidence-based rehabilitation<sup>32-35</sup>. Qualitative research alongside randomised controlled trials can contribute in several ways to the development and evaluation of complex healthcare interventions and may be particularly useful in evaluating interventions that involve social and behavioral processes, that are difficult to explore or capture using quantitative methods alone<sup>36</sup>. As patient participation is paramount to the efficacy of the rehabilitation<sup>37</sup>, we

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4 find it highly valuable to include the patients' perspective in the development and evaluation of the  
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6 intervention. This paper presents the study protocol for the CopenHeart<sub>IE</sub> randomised clinical trial.  
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9 The complementary studies are briefly described in a separate section.

### 10 11 ***Study population and eligibility criteria***

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14 Consecutive patients treated for left-sided (native or prosthetic valve) or cardiac device endocarditis  
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16 at the tertiary referral heart centres in Copenhagen, Denmark (Rigshospitalet and Gentofte Hospital)  
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18 will be screened for inclusion and approached for study participation. Patients aged 18 years or  
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20 older, having completed treatment for IE based on the Duke Criteria <sup>38</sup>, speaking and understanding  
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22 Danish, and providing written informed consent will be considered eligible for participation.  
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25 Patients unable to understand study instructions, with a cardiac ischemic event within the past 6  
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27 months, who are pregnant or breastfeeding, with reduced ability to follow the planned programme  
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29 due to, e.g., substance abuse problems or other somatic illness, with considerable illness in the  
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31 musculoskeletal system or with physical disability which complicates exercise training or patients  
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33 whose physician advise against participation, will be excluded.  
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### 36 37 ***Study procedure, randomisation and follow-up***

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39 Patients eligible for participation will be approached by a nurse or a physician from the research  
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41 group for participation during the expected last week of their treatment for IE. A brief oral  
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43 introduction is initially given together with written information describing the study and  
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45 implications for the patient in detail. The patient is given ample time to read the information and if  
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47 necessary involve a relative in the decision making. The enrolling nurse or physician will return  
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49 within 2-3 days or at a planned time to answer any questions the patient or their relative might have.  
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51 The patient should subsequently be able to provide informed consent or reject participation. When  
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55 the informed consent form is signed attained, baseline data will be collected including the baseline  
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questionnaire package, demographic variables, and clinical characteristics. After baseline data collection, central randomisation is conducted by telephoning The enrolling research assistant will call the trial coordinating centre, Copenhagen Trial Unit (<http://www.ctu.dk/>), for randomised allocation. The allocation sequence will be computer-generated with varying block-sizes, blinded to investigators, randomising patients 1:1 to either the experimental intervention versus usual care.

Thus, neither investigators nor patients or relatives can influence to which group the patients are allocated. Patients will be stratified according to sex and the treating heart centre. For both groups, the follow-up assessment will take place at 1 month (T<sub>1</sub>), 4 months (T<sub>4</sub>), 6 months (T<sub>6</sub>), and 12 months (T<sub>12</sub>) post-discharge and a register-based follow-up assessment will be conducted at 24 months (T<sub>24</sub>) (see Figure 2). In the event of complications arising after study enrolment, cases will be handled individually (see section on intervention deviation).

The patients answer questionnaires independently of the researchers, and before randomisation. All questionnaires are distributed electronically, thus data management is handled independently from the researchers that interpret data. All data entry is double and stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart group.

Personal information about potential and enrolled patients will be collected electronically and shared in a database only accessible to those within the project group responsible for patient recruitment, in order to protect confidentiality before, during and after the trial.

#### *The experimental intervention group*

Patients in the intervention group will follow the integrated rehabilitation programme, consisting of a psycho-educational component and an exercise training component as well as usual care (see below). The intervention has been developed and tested in two clinical trials; the DANREHAB trial including patients with ischemic heart disease and heart failure<sup>39</sup>, and the COPE-ICD trial

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2  
3  
4 including patients with an implantable cardioverter defibrillator<sup>26</sup>. The blood work and clinical  
5  
6 control described for the control group (see below) are incorporated in the follow-up of the  
7  
8 intervention group.  
9

10  
11 The psycho-educational component

12  
13 The aim of the psycho-educational intervention is to provide emotional support and improve coping  
14  
15 skills and illness appraisal in order for the patient to respond appropriately to physical and  
16  
17 psychological symptoms. Education and information about the disease prepare the patient for  
18  
19 expected symptoms and sensations. Dialogue and shared reflection facilitate strategies for coping  
20  
21 with symptoms and experiences associated with the condition, e.g., anxiety and fear. Cardiac care  
22  
23 nurses with specific training will perform the psycho-educational intervention. Some of the most  
24  
25 commonly reported concerns of patients treated for IE, such as fatigue, gastrointestinal function,  
26  
27 and concerns about work life, are outlined in an inspiration guide for the nurses to address when and  
28  
29 if relevant (see Table 1). Information given will also be based on national guidelines and standard  
30  
31 treatment of patients with infective endocarditis, and on the findings of the qualitative study on post  
32  
33 discharge experiences described in the complementary studies section of this paper. The  
34  
35 consultations focus on managing life after IE by establishing a joint approach to disease  
36  
37 management and coping strategies, using a holistic view. The psycho-educational intervention is  
38  
39 inspired by R.R. Parse's Human Becoming Practice Methodologies three dimensions<sup>40</sup>. These are  
40  
41 interpreted as: 1) discuss and give meaning to the past, present and future, 2) explore and discuss  
42  
43 events and possibilities and 3) move along with envisioned possibilities. According to this theory,  
44  
45 there are three ways of changing health: creative imaging, that is to see, hear and feel what a  
46  
47 situation might be like if lived in a different way, affirming personal patterns and value priorities,  
48  
49 and shedding light on paradoxes, that is, looking at the incongruence in a situation and changing the  
50  
51 view held of something. The nurse is truly present in the process through discussions, silent  
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immersion and reflection. The human becoming practice methodology was chosen to apply a holistic patient approach, focussing on the coping and transformation process of the individual person. Furthermore, the method is extensively used in the outpatient heart clinics at the heart centre at Rigshospitalet, such as for patients with inherited heart diseases and adults with congenital heart disease, and finally documented in the COPE-ICD trial<sup>26, 41</sup>. The consultations take place in a quiet setting at the out-patient clinic and will last for approximately one hour. The nurse is able to facilitate contact with or seek advice from a physician if needed. The first consultation will be approximately one week after discharge, and then once every four to six weeks, with a total of five consultations. Consultations can be done by telephone, according to the patient's wishes. The primary investigator will attend the consultations regularly to ensure protocol compliance.

**Table 1. Inspiration guide for nursing consultations/psycho-educational intervention.**

	1	2	3	4	5
How have you been? What has happened since you were here last time?	x	x	x	x	x
Discuss the events leading up to the diagnosis of IE. Experiences before and during hospital admission.		x			
Address present thoughts and questions.	x	x	x	x	x
How did you having IE affect your life? Are there things/activities you avoid or feel you can't do after having IE?		x			
Have you initiated exercise training? How is training going?			x	x	x
Discuss social network/family. How do they handle the situation? Has anything changed in your social relationships?			x		
Has you having IE affected your work situation? /had financial consequences?				x	
Have you had a changed view/perception of your body and its functions?				x	
How is your health in relation to e.g. fatigue, dyspnoea, pain, appetite, gastrointestinal function, sleep, sexual functioning, other?				x	x
Information/recommendations in relation to discussed issues/problems.	x	x	x	x	x

The physical exercise training component

The main objective of the exercise training is to improve the patient's physical capacity and facilitate lifestyle/behavioural changes, which will subsequently result in physical and psychological health-benefits for the patient. However, the exercise training programme is also targeted at relieving the fear and uncertainty that the patient may feel in relation to physical activity.

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4 The intervention is based on the European guidelines for physical training in cardiac rehabilitation<sup>16</sup>  
5  
6 and complies with the recommendations on physical activity of the Danish National Board of  
7  
8 Health<sup>42</sup>. The intervention consists of three components: 1) individual planning of the exercise  
9  
10 training, 2) twelve weeks of high intensity exercise training, and 3) continuous moderate daily  
11  
12 physical exercise.  
13

#### 14 15 16 1) Individually planned physical exercise by a specialised cardiac rehabilitation physiotherapist

17 Integrating detailed information regarding the specific type of IE, co-morbidities, hospitalisation,  
18  
19 activities of daily living (ADL) and level of physical activity prior to IE, the physiotherapist  
20  
21 conducts a patient consultation of up to 30 minutes. ~~taking into consideration the patients'  
22  
23 preferences with regard to training at a CopenHeart certified training facility at the local hospital, in  
24  
25 a municipal setting or as home based training.~~ The consultation is based on the initial testing of the  
26  
27 patient, including the cardiopulmonary exercise testing, described in the outcome measures section,  
28  
29 a 6 minute walk test and a 'sit to stand' test. **For all patients an individual training diary is prepared,**  
30  
31 **and all patients are instructed in the use of a heart rate monitor integrated into Polar watches,**  
32  
33 **provided by Rigshospitalet. The heart rate monitor and diary is essential to ensure CopenHeart**  
34  
35 **training protocol compliance throughout the study period and are returned for data collection at the**  
36  
37 **end of the exercise training intervention.**  
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#### 44 2) High intensity Intensive physical exercise training programme

45  
46 The initial training sessions take place in a physiotherapist supervised setting at the primary  
47  
48 investigating hospital, Rigshospitalet, to ensure the quality, intensity, and safety of training.  
49  
50 Training is started four weeks post-discharge to ensure optimum post-surgery healing after heart  
51  
52 valve surgery or cardiac device implantation. Using wireless electrodes integrated into t-shirts  
53  
54 (Corus-Fit, CardioCardio and Corus Exercise Assistant, CEA, vs. 2.0.16, Finland) potential cardiac  
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arrhythmias, electrocardiographic abnormalities such as ST-depression, ST-elevation, Q-or T-wave altering, atrial fibrillation and ventricular arrhythmias, and training intensity level are monitored.

After 1-3 exercise training sessions at Rigshospitalet, the patient continues the programme at a local CopenHeart certified training facility supervised by physiotherapists or as supervised home-based training. Supervised home-based exercise training has shown similar results as hospital-based exercise training<sup>43</sup>, and has been confirmed in a Danish setting<sup>44</sup>.

The physical exercise training continues for 12 weeks, comprising 3 sessions weekly of 60 minutes, with a total of 36 sessions. The training protocol consists of aerobic and anaerobic exercise to accommodate endurance and muscle strength. ~~Long-term effects on the cardiovascular system are expected such as; reduction of cardiac after load, decrease in systemic blood pressure at rest and maximum exhaustion, and improvement in left ventricle systolic, and diastolic function is expected for individuals with decreased left ventricular ejection fraction (LVEF).~~

~~An high intensity~~ exercise training session consists of 10 minutes warm up, 20 minutes of bicycling, 20 minutes of resistance training, and 10 minutes stretching and cool-down period. Using the ~~measured maximum heart rate results~~ from the cardiopulmonary exercise test performed prior to the initial training session, in combination with the Borg scale measuring subjective exhaustion, the aerobic exercise is performed with a gradually increasing intensity throughout the exercise intervention period, corresponding to 13 to 17 at the Borg Scale and at 50% to 80% of the maximum heart rate. The anaerobic resistance training is initiated at 30% to 40 % of 1 repetition maximum (RM) for the upper body, and 40% to 50 % of 1 RM for the lower body, with an increasing work load during the training sessions. To achieve cardiovascular adjustment and reduce the risk of malignant cardiac arrhythmias and ischemia, the training session is initiated and terminated with a warm up and a cool down period to gradually increase and decrease training intensity and heart rate.

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4 This cardiovascular adjustment has been proven to reduce the risk of ischemia and arrhythmia in  
5 relation to exercise training<sup>45,46</sup>. Training is predominantly performed in the upright position to  
6 reduce left ventricle preload (diastolic volume) and the risk of ischemia and arrhythmias due to  
7 heart failure<sup>46</sup>.  
8  
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### 14 3) ~~Continuous-Sustained~~ moderate daily physical exercise

15  
16 Participants are instructed to perform moderate physical exercise at least 30 minutes a day during  
17 the intervention period, e.g., bicycling, walking, gardening, jogging or recreational sports. Daily  
18 moderate physical exercise is encouraged to be continued throughout life.  
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#### 23 Intervention deviations

24 Both components of the intervention will be supervised regularly by the primary investigator to  
25 ensure protocol compliance. Modification of the allocated intervention due to surgery  
26 complications, rehospitalisation or emerging co morbidities (e.g. pneumonia, pericardial exudation,  
27 musculoskeletal problems) will be individually assessed, and the time of the primary outcome  
28 assessment at four months (described in section below) will be corrected in accordance with  
29 changes in the intervention.  
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#### 40 *The usual care control group*

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42 Patients in the control group will follow standard follow-up for patients treated for IE, with 1 to 2  
43 visits within the first month post-discharge, including blood work and clinical assessment.  
44

45 Haemoglobin level, infection variables, kidney function, and, on indication, liver status is assessed,  
46 and blood cultures are drawn on suspicion of IE relapse. Blood pressure, pulse and temperature  
47 parameters are obtained. If results give cause for concern, the patient will see a specialist physician  
48 during the follow-up visit. A transthoracic echocardiogram will be performed within the first year  
49 post-discharge, typically between 1 and 6 months post-discharge and again at 12 months, depending  
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4 on whether the individual patient has had heart valve surgery and on the status of the native or  
5 replaced valve. These patients will be contacted at 1, 4, 6, 12, and 24 months for outcome  
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8 assessment including functional test, questionnaires and clinical data collection (see figure 2).  
9

### 10 11 ***Outcomes and data collection*** 12

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14 Numerous data will be collected to evaluate the effect and meaning of the intervention. The primary  
15 and the secondary outcome reflect the primary modifiable factors of the intervention. Since almost  
16 no evidence exists, a number of explorative outcomes will also be collected.  
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21 *Primary outcome:* Mental health will be measured by the Mental Component Subscale (MCS) of  
22 the Medical Outcome Study Short Form 36 (SF-36) questionnaire<sup>47</sup> after 1 month (T<sub>1</sub>), 4 months  
23 (T<sub>4</sub>), 6 months (T<sub>6</sub>), 12 months (T<sub>12</sub>) and 24 months (T<sub>24</sub>). The SF-36 questionnaire is a measure of  
24 self-rated health. It is a validated multipurpose health survey comprised of 36 items that address the  
25 following 8 dimensions: physical functioning (PF), role physical (RP), bodily pain (BP), general  
26 health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH).  
27 The first four scales (PF, RP, BP, GH) are then combined into a physical component scale and the  
28 latter four (VT, SF, RE, MH) into a mental component scale<sup>47</sup>. The instrument was chosen for its  
29 ability to detect changes in self-rated health within domains that could potentially be influenced by  
30 the CopenHeart<sub>IE</sub> intervention. Mental health was chosen as the primary outcome as other studies  
31 have shown that mental health is affected in patients with IE compared to healthy controls<sup>13, 14</sup> and  
32 the rehabilitation intervention focuses on this modifiable factor.  
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50 *Secondary outcome:* Physical capacity will be measured by peak VO<sub>2</sub> using cardiopulmonary  
51 exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland) by investigators blinded to the  
52 intervention group. The test will be performed according to current guidelines for ergospirometry  
53 testing<sup>48-50</sup>, using an ergometer-bicycle with spirometry, monitoring heart-rhythm, blood pressure,  
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4 electrocardiogram (ECG), and measuring gas-exchange during workload and in the following  
5  
6 recovery period. Average test duration ~~is will be~~ 10-15 minutes including pre- and post- test phase  
7  
8 without work load. Before each session calibration will be performed to address changes in room  
9  
10 temperature, humidity and air O<sub>2</sub> content. A standardised ramp-protocol will be used with an initial  
11  
12 work load of 25 or 50 watts, increasing gradually by ~~12.525~~ watts/~~every second~~ minute until peak  
13  
14 exhaustion ~~Peak exhaustion is evaluated by a, aiming to reach~~ respiratory exchange ratio (RER) ≥  
15  
16 1.10 ~~or subjective exhaustion of the patient. and obtain anaerobic threshold.~~ In order to encourage  
17  
18 patients equally, independent of the tester, a standardised guide has been developed. During the test,  
19  
20 clinical manifestations, ECG abnormalities (ST depression, ST elevation, q-and t-wave changes,  
21  
22 supraventricular or ventricular arrhythmias), blood pressure response and several physiological  
23  
24 parameters will be observed and documented. ~~The test will be performed by either a cardiac care~~  
25  
26 ~~nurse or a physician. For safety reasons preset criteria for initiation and/or termination of the test~~  
27  
28 ~~has been defined.~~ The test will be performed prior to the exercise training programme (T<sub>1</sub>), after 12  
29  
30 weeks of exercise training (T<sub>4</sub>) and at 12 months follow-up (T<sub>12</sub>). Physical capacity was chosen as  
31  
32 the secondary outcome measure, as studies indicate that patients treated for IE are physically  
33  
34 deconditioned after long-term illness and hospitalisation <sup>14</sup>.

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41 *Exploratory outcomes:* A more extensive evaluation of the physical and psychological status of the  
42  
43 patients over time will be performed, exploring demographic, clinical, paraclinical and imaging  
44  
45 variables, as well as additional physical capacity tests and additional questionnaires exploring for  
46  
47 example fatigue, sleep quality and anxiety and depression (see Table 2).  
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50  
51 **Table 2. CopenHeart<sub>IE</sub> – Exploratory quantities subjected to post-hoc analysis**

Quantity	Time of measure	Type of quantity
<b>Demographic</b>		
Sex	Baseline	Binary (M/F)

Age, height, weight,	Baseline	Continuous
Marital, occupational, educational status	Baseline	Categorical
<b>Clinical</b>		
NYHA- classification	Baseline, 1, 4, 12	Continuous
Previous heart disease, diabetes mellitus, kidney disease, pulmonary disease (COLD), co-morbidities, hypertension, dyslipidaemia, smoking	Baseline	Binary (Y/N)
Medication	Baseline, 1, 4, 12	Binary (Y/N)
BMI, Nutritional screening	Baseline, 1, 4, 12	Continuous
Endocarditis specific data:		
Valve-/device affected, type of surgery due to IE	Baseline	Categorical
Cerebral insult +, hemodialysis +	Baseline	Binary (Y/N)
Length of hospitalisation (days), weight loss related to IE (kilograms)	Baseline	Continuous
<b>Paraclinical and imaging</b>		
Blood work (Haemoglobin, infection-, kidney- liver and selected nutritional parameters, electrolytes, cholesterol- and thyroid status, ProBNP)	Baseline, 1, 4, 12	Continuous
Echocardiogram	Baseline, 4, 12	Continuous
<b>Physical function</b>		
6 minute walking test <sup>51</sup>	Baseline, 1, 4, 12	Continuous
Sit to stand test <sup>52</sup>	1, 4, 12	Continuous
<b>Questionnaires</b>		
Physical activity level <sup>53</sup>	BL, 1, 4, 6, 12, 24	Binary (Y/N)
SF-36 <sup>47</sup> HADS <sup>54</sup> , QoL-CV <sup>55</sup>	BL, 1, 4, 6, 12, 24	Continuous
Emotions and Health <sup>56</sup>	BL	Continuous
Rehabilitation <sup>57</sup>	12	Continuous
HeartQoL R <sup>58</sup> , EQ-5D <sup>59</sup>	BL, 6, 12, 24	Continuous
IPAQ <sup>60</sup>	1, 4, 12, 24	Continuous
MFI-20 <sup>61</sup>	BL, 1, 4, 12	Continuous
PSQI <sup>62</sup>	1, 6	Continuous
BIQOL <sup>63</sup>	BL, 6	Continuous

Data collected from official national registers regarding mortality, hospitalisation, emergency room visits, outpatient visits, medication, employment status, and payment of welfare benefits (sick leave payment and early retirement pension) will be collected at 24 months to assess the long term effects of the intervention. The Danish official national registers are well-functioning with a small

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4 percentage of lost data <sup>64</sup>. Consequently, the method is well suited as an outcome measure in small  
5  
6 patient populations. Data will be collected from the Danish National Patient Register <sup>65</sup>, the Danish  
7  
8 National Health Service Register <sup>66</sup>, the Danish National Prescription Registry <sup>67</sup>, the Danish  
9  
10 National Causes of Death Register <sup>68</sup>, and registers on transfer payments and labour market  
11  
12 affiliation <sup>69, 70</sup>.

### 13 14 15 ***Economic evaluation***

16  
17 An economic evaluation will be conducted alongside the trial to assess the cost-utility of  
18  
19 comprehensive cardiac rehabilitation compared with usual care in the study population. The  
20  
21 economic evaluation will compare the costs to QALYs (quality adjusted life years) and take a  
22  
23 societal perspective as recommended nationally. QALYs and costs will be assessed at the end of the  
24  
25 intervention, 6 months from randomisation and later after 24 months from randomisation using  
26  
27 register-based follow-up.  
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31  
32 QALYs will be estimated using the self-completed EQ-5D instrument, which is a standardised  
33  
34 instrument assessing 5 dimensions of self-reported health status (mobility, self-care, usual activities,  
35  
36 pain/discomfort and anxiety/ depression) <sup>71, 72</sup>. The estimated calculations will be evaluated using  
37  
38 Danish preference weights <sup>73</sup>. Information on costs will only include costs that are expected to differ  
39  
40 between the intervention and usual care group <sup>59</sup>. Included costs in the evaluation are health costs  
41  
42 associated with the rehabilitation programme, other health care costs (health care utilisation apart  
43  
44 from rehabilitation), patient costs and costs of productivity losses. Information on costs will be  
45  
46 collected by a mixture of activity-based costing, surveys, patient diaries and by the use of registers.  
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51 Results from the analysis will be reported as an incremental cost-effectiveness analysis (ICER).

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53 Sensitivity-analysis will be conducted to express uncertainty in the estimates <sup>74</sup>. The reporting of  
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4 ICER is presented using Bayesian methods, including bootstrapping and presented as cost-  
5 effectiveness acceptability curves <sup>75</sup>.  
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### 9 *Sample size, power calculations and interim analysis*

10 We will perform a randomised trial with a continuous response variable from independent control  
11 and intervention group participants with one control per intervention group participant. A previous  
12 study on an IE population found that the mental component scale was normally distributed with a  
13 standard deviation of 13 <sup>13</sup>. If the true difference between the intervention and control group means  
14 is 6 points, we will need to include 75 participants in each study group (a total of 150 participants)  
15 to be able to reject the null hypothesis, stating that the mean in the intervention and the control  
16 groups are the same with a power of 80%. The type I error probability associated with this test of  
17 this null hypothesis is 5%.  
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30 For the secondary outcome, VO<sub>2</sub>, we will be able to reject the null hypothesis that the population  
31 means of the experimental and control groups are equal with a probability (power) of 75.4%,  
32 assuming the VO<sub>2</sub> is normally distributed with a standard deviation of 6.9 <sup>27,28</sup>, and the true  
33 difference in the experimental and control means is 3 ml/kg per minute.  
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40 A data monitoring and safety committee will be informed, every nine months, of all serious adverse  
41 events occurring in the two study groups. An interim analysis meeting will be held by the data  
42 monitoring and safety committee to review data relating to intervention efficacy, participant safety,  
43 and quality of trial conduct. The committee will evaluate data on the primary and secondary  
44 outcome measures; mental health (SF-36) / peak VO<sub>2</sub> (efficacy) and all serious adverse events  
45 (safety/tolerability). After the interim analysis meeting, the committee will make a recommendation  
46 to the steering committee whether to continue, hold or terminate the trial. This recommendation will  
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4 be based primarily on safety and efficacy considerations and will be guided by statistical monitoring  
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6 guidelines defined by the trial safety charter.  
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### 9 10 *Statistical analysis*

11 Data will be pseudo- anonymised and analysed, blinded by a trial-independent statistician using  
12 intention-to-treat analyses and a mixed model with repeated measures (MMRM) for continuous  
13 outcome measures<sup>76</sup>. Using MMRM ensures that missing data values (in the case of the primary  
14 and secondary outcome) will not create bias as long as the missing values are random. Two sided  
15 tests will be performed. The level of significance is set at 5%. Dealing with multiplicity, gate  
16 keeping will be used to adjust the observed P values for primary and secondary outcomes<sup>77</sup>. Both  
17 original and adjusted P values will be reported.  
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28 For the primary and secondary outcomes, we will conduct sensitivity analysis to assess the potential  
29 impact of non-random missing values. For each intervention group (A and B) some quantities  
30 (imputing quantities) will be computed to be used to impute missing values in a group (A or B) as  
31 explained below. A comparison between group A and group B where missing values in group A are  
32 imputed using imputing quantities obtained from group A and missing values from group B are  
33 imputed using imputing quantities obtained from group B is referred to as a best case analysis. If  
34 missing values in group A are imputed using imputing quantities obtained from group B and vice  
35 versa the comparison is called a worst case analysis. The imputed quantities for the primary  
36 outcome would be the group mean at T1 ( $X1\text{-bar}$ ), the group mean at T4 ( $X4\text{-bar}$ ), the group mean  
37 at T6 ( $X6\text{-bar}$ ), the mean difference between the value measured at T4 and that measured at T1  
38 ( $\Delta 1$ ), and the mean difference between the value measured at T6 and that measured at T4 ( $\Delta$ -  
39 2). Table 3 explains how the quantities will be used to impute missing values in a group (either the  
40 same group or the other intervention group).  
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**Table 3. Statistical appendix**

The use of imputed quantities derived from observed values in a group (group A) to impute missing values in a group (group B).

Observed pattern in group B at the times (T1, T4, T6)	Imputed value in group B at T1	Imputed value in group B at T4	Imputed value in group B at T6
mis <sup>A</sup> , mis, mis	X1-bar <sup>B</sup>	X4-bar <sup>C</sup>	X6-bar <sup>D</sup>
mis, mis, Y3 <sup>E</sup>	$Y3 - (\text{delta1}^F + \text{delta2}^{G,H})$	Y3 – delta2	
mis, Y2, mis	Y2 – delta1		Y2 + delta2
Y1, mis, mis		Y1 + delta1	Y1 + delta1 + delta2
Y1, Y2, mis			Y2 + delta2
Y1, mis, Y3		$(Y1 + \text{delta1} + Y3 - \text{delta2})/2$	
mis, Y2, Y3	Y2 – delta1		

A) The value at T<sub>4</sub> is missing in group B

B) Mean of values observed in group A at time T<sub>1</sub>

C) Mean of values observed in group A at time T<sub>4</sub>

D) Mean of values observed in group A at time T<sub>6</sub>

E) Observed value in group B at time T<sub>6</sub>

F) The mean of difference between value observed at time T<sub>4</sub> and observed at time T<sub>1</sub> in group A

G) The mean of difference between value observed at time T<sub>6</sub> and observed at time T<sub>1</sub> in group A

H) If an imputed value is < 0 it is set equal to 0

If the standard error (SE) of a parameter estimate calculated using imputed data is smaller than that of the corresponding parameter calculated using complete case data it will be replaced by the latter SE when the p value is calculated.

Long term register-based outcomes will be analysed by two different models: non-negative count outcomes (e.g., number of contacts to hospital or number of visits to general practitioners) will be analysed by a Poisson model or a zero-inflated Poisson model if the number of zeros are large, and time-to-event data (e.g., cause-specific mortality and leaving the labour market) will be analysed with survival methods (Kaplan-Meier estimator and Cox regression model). Especially for socio-

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4 economic outcomes, competing risk due to mortality will be considered if a large proportion of  
5  
6 patients die during follow-up.  
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9 Explorative data will be analysed using appropriate statistical methods according to type of data  
10  
11 (see Table 2). SPSS version 19.0 and SAS version 9.3 will be used.  
12

### 13 14 15 **Complementary studies**

#### 16 17 *Qualitative study on post discharge experiences*

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19 The post-discharge experiences of patients treated for IE will be explored through semi-structured  
20  
21 qualitative interviews, which take a phenomenological-hermeneutic approach. The data derived  
22  
23 from this study will be used to address relevant issues designing the rehabilitation intervention.  
24  
25 Patients treated for IE, 3-6 months post-discharge will be identified through hospital admission lists.  
26  
27 A sample sufficient to achieve data saturation will be included. The study aims to answer the  
28  
29 following thematic research questions: What are the experiences of returning home after treatment  
30  
31 for IE? What are the new experiences, if any, in daily living? Which health problems, if any, have  
32  
33 patients experienced? What are the concerns, if any, for the future? The data-analysis is inspired by  
34  
35 Ricoeur's theory of interpretation and consists of three levels: naive reading, structured analysis and  
36  
37 critical interpretation and discussion. Qualified interviewees will be chosen, ensuring a  
38  
39 representative sample in relation to sex, age and surgery/non-surgery.  
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#### 44 45 *Survey-based study*

46  
47 The post-discharge status of the patients treated for IE will be explored through a national survey.  
48  
49 The standardised questionnaires Short Form-36 (SF-36)<sup>47, 78-82</sup>, Hospital Anxiety and Depression  
50  
51 Scale (HADS)<sup>54</sup>, Multidimensional Fatigue Inventory (MFI-20)<sup>61, 83</sup>, EuroQoL - EQ-5D<sup>59, 84</sup>,  
52  
53 Heart Related Quality of Life (HeartQoL R)<sup>58</sup>, International Physical Activity Questionnaire  
54  
55 (IPAQ)<sup>60, 85</sup> and a questionnaire developed by the Danish Heart Foundation on the extent and  
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4 quality of rehabilitation offered will be sent out to patients who have undergone treatment for IE, 6-  
5  
6 12 months post-discharge. The instruments are all validated and have good reliability and  
7  
8 responsiveness<sup>54, 58, 60, 61, 84, 86</sup>. The data will provide knowledge on patients' self-rated health,  
9  
10 quality of life, fatigue, anxiety and depression, body image and extent and quality of the  
11  
12 rehabilitation currently received. Patients will be identified through the National Patient Register<sup>65</sup>  
13  
14 and questionnaires will be sent out to 210 of them. We aim to achieve a response rate of 70%, using  
15  
16 repeat mailing strategies and/or telephone reminders to maximize response if necessary<sup>87</sup>. This  
17  
18 should result in an estimated 150 questionnaire respondents. Data will be anonymised and analysed  
19  
20 by relevant descriptive statistical methods.  
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### 23 24 25 *Qualitative study on rehabilitation participation experiences*

26  
27 After the intervention, an interview study, including 10% of the intervention population or until data  
28  
29 saturation has been reach, will be conducted, in order to explore the experiences and processes  
30  
31 behind the potential effect of the intervention. The study aims to answer the following thematic  
32  
33 research questions: What are the experiences of participating in the integrated rehabilitation  
34  
35 programme? Which components of the programme are meaningful? In what way? Participant  
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37 selection and applied methods in this study are consistent with that of the qualitative study on post-  
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39 discharge experiences.  
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### 43 **Ethics**

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45 The trial has been approved by the Regional Research Ethics Committee (no H-1-2011-129) and the  
46  
47 Danish Data Protection Agency (no 2007-58-0015). All eligible patients will be informed about the  
48  
49 trial verbally and in writing, and the patients are included after written informed consent is  
50  
51 obtained. All data will be handled confidentially and patients are ensured anonymity. The study  
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53 complies with the latest Declaration of Helsinki and is registered at ClinicalTrials.gov  
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(NCT01512615). An independent safety committee comprised by an international group of experts is monitoring the trial; ensuring good clinical practice standards are being upheld. No serious risks are anticipated to receiving rehabilitation. No risks have previously been reported in relation to psycho-educational consultations. The physical exercise training and the cardiopulmonary exercise testing will be supervised by competent health care professionals and will be in accordance with current guidelines on safety when testing and training cardiac patients<sup>88,89</sup>. Efforts will be made to avoid arrhythmias during workload testing and exercise training by protocol with a cool-down period, which positively affects serious complications. Staff members will be trained according to guidelines to handle cardiac arrest or other disease- or device-specific emergencies. All serious and moderate adverse events will be registered and reported according to protocol.

Not providing rehabilitation to the control group can be ethically justified, as current national and international guidelines give no specific recommendations on cardiac rehabilitation for patients treated for infective endocarditis. The scope and quality of rehabilitation offered to this population is unknown, but suspicions are, that often no or suboptimal rehabilitation is provided. The survey based complementary study, described previously in this paper, will hopefully provide more insight. In screening patients for participation, the enrolling nurse or physician will exclude patients with a compelling rehabilitation need, for instance after a cerebral embolic event. Furthermore patients are informed of the study design before giving their consent, and are free to decline participation.

## Discussion

This randomised clinical trial is the first to examine physical functioning by cardiopulmonary exercise testing and to test a comprehensive rehabilitation programme on a large heterogeneous population of patients treated for IE. CopenHeart<sub>IE</sub> will provide much needed evidence and insight on the post-discharge status and rehabilitation needs of patients treated for IE for health care

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4 professionals and policymakers to make qualified, evidence-based decisions in everyday clinical  
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6 practice and as a foundation for national and international guidelines. With increased physical and  
7  
8 psychological well-being of patients, lower morbidity and health care utilisation expected in case of  
9  
10 a positive outcome, patients and society are anticipated to benefit greatly. Whether it produces  
11  
12 neutral, negative or positive results, the CopenHeart<sub>IE</sub> trial will have implications for clinical  
13  
14 practice in follow-up care of patients treated for IE in the western world.

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18 Patients may decline participation due to an unwillingness to return to hospital after a lengthy  
19  
20 illness and hospitalisation. We will attempt to avoid this problem by informing patients of the  
21  
22 potential benefits of participation, e.g., the security we provide by following them closely after post-  
23  
24 discharge and the value to science of their participation for future patients. Furthermore, it is  
25  
26 documented that a substantial number of patients in rehabilitation studies control group perform  
27  
28 self-initiated physical exercise training, possibly motivated by the study information during the  
29  
30 recruitment process<sup>39</sup>. Hence we will abstain from giving extensive information about the training  
31  
32 programme, or elaborate on the health benefits of physical training before knowing to which group  
33  
34 the patient is randomised.  
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39 The study has been designed to meet the criteria for high quality in non-pharmacological  
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41 randomised clinical trials<sup>90</sup> with central randomisation, multi-centre participation, blinded  
42  
43 assessment of the exercise outcome, blinded analysis by study independent statisticians and  
44  
45 furthermore, detailed information on the intervention received and usual care will be collected,  
46  
47 including information on self-initiated exercise training during the trial period. For the primary  
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49 outcome, the mental-health component subscale, we are aware of the subjective nature of the data  
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51 collected. Accordingly, we will interpret the findings conservatively.  
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56 [Safety aspects and Data Monitoring Safety Committee \(DMSC\)](#)  
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In supervised exercise training and testing of other cardiac patient groups than patients after infective endocarditis, the risk of adverse effects is low (e.g. ischaemic heart disease, chronic heart failure), however, no current national safety instructions exist. Patient safety is given highest priority, and exercise training after heart valve surgery is considered safe based on results from exercise testing and training with heart failure patients<sup>88, 89</sup>. Any serious adverse events will be registered as part of the data collection.

The DMSC works independently from the funder and has no competing interests, and consists of two clinicians and a statistician. The committee is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The steering committee and the DMSC communicate regularly and at least every nine month the overall number of all serious adverse events are reported.

### **Dissemination plan**

The results of the trial and complementary studies will be published in relevant international peer-reviewed journals. Authorship will be determined according to the guidelines of the International Committee of Medical Journal Editors. Due to the comprehensiveness of the outcome measures the results will be presented in more than one scientific paper as relevant. Economic and long term follow up will be reported as data becomes accessible.

### **Trajectory**

Inclusion was initiated in December 2011 and is expected to be completed at the end of 2013.

Results from two of the complementary studies are expected during 2012, and from the clinical trial in 2014. To achieve adequate participant enrolment, patients are recruited from two independent heart centres, and another heart centre, already in partnership of the trial, will be invited for

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4 inclusion if enrolment rate declines. The inclusion rate is carefully monitored weekly. Patients in  
5  
6 doubt are contacted several times during hospitalisation, and if necessary after hospital discharge by  
7  
8 phone.  
9

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26  
27 interpretation of data.  
28  
29

### 30 31 **Competing interests**

32  
33 The authors declare that they have no competing interests.  
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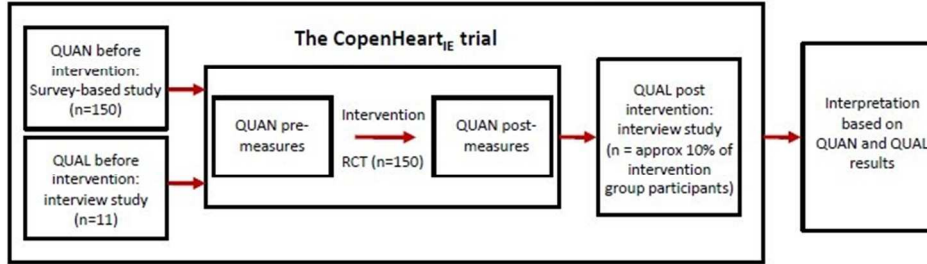
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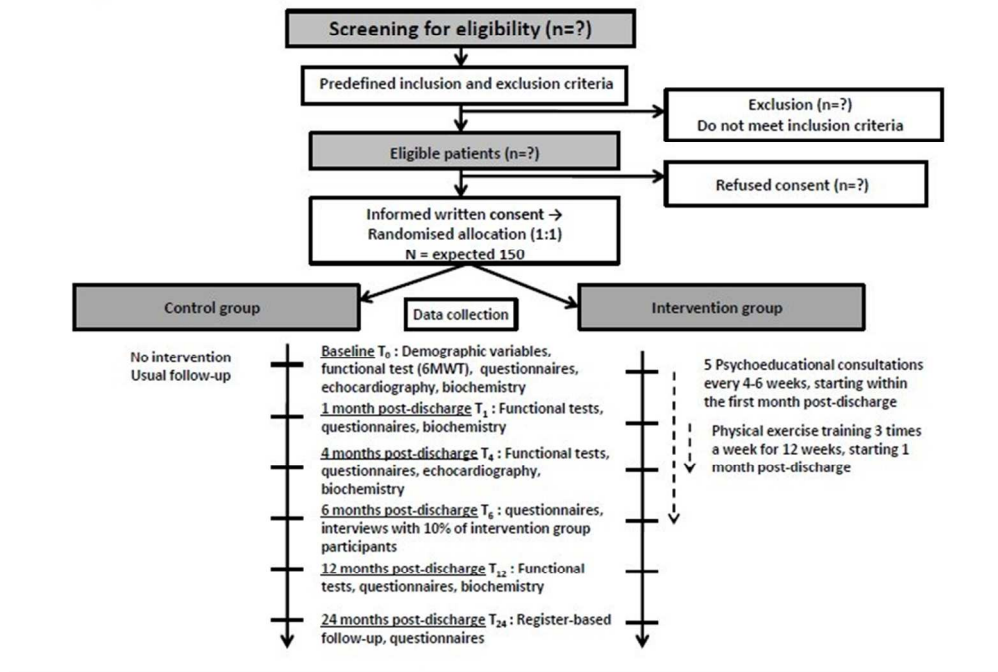
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Figure 1. The CopenHeart<sub>IE</sub> study. Mixed method - Embedded Experimental Model.



Review only

Figure 2. Patient flow.





## CONSORT 2010 checklist of information to include when reporting a randomised trial\*



Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction Background and objectives	2a	Scientific background and explanation of rationale	5-7
	2b	Specific objectives or hypotheses	7
Methods Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	9
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-16
	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	16-20
Sample size	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
	7a	How sample size was determined	20
Randomisation: Sequence generation	7b	When applicable, explanation of any interim analyses and stopping guidelines	20
	8a	Method used to generate the random allocation sequence	10
Allocation concealment mechanism Implementation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Blinding	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	16

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	assessing outcomes) and how	
	If relevant, description of the similarity of interventions	N/A
Statistical methods	11b	
	12a	21-23
	12b	23-24
<b>Results</b>		
Participant flow (a diagram is strongly recommended)	13a	N/A
Recruitment	13b	N/A
	14a	N/A
	14b	N/A
Baseline data	15	N/A
Numbers analysed	16	N/A
Outcomes and estimation	17a	N/A
	17b	N/A
Ancillary analyses	18	N/A
Harms	19	N/A
<b>Discussion</b>		
Limitations	20	25-26
Generalisability	21	25-26
Interpretation	22	N/A
<b>Other information</b>		
Registration	23	24-25
Protocol	24	N/A
Funding	25	

\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).