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# BMJ Open

## HEART Rehabilitation in patients awaiting Open-heart surgery to prevent Complications and to improve Quality of life (Heart-ROCQ): a Prospective Randomised Open Blinded End-point (PROBE) trial

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5 2 **Title**  
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7 3 **HEART** Rehabilitation in patients awaiting **Open**-heart surgery to prevent **Complications** and to  
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9 4 improve **Quality of life (Heart-ROCQ)**: a **Prospective Randomised Open Blinded End-point (PROBE)**  
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## 28 ABSTRACT

### 29 Introduction

30 The rising prevalence of modifiable risk factors (e.g. obesity, hypertension, and physical inactivity) is  
31 causing an increase in possible avoidable complication rates in patients undergoing cardiac surgery  
32 (CS). This study therefore aims to assess whether a combined pre- and postoperative  
33 multidisciplinary cardiac rehabilitation (CR) program (Heart-ROCQ program) can improve functional  
34 status and reduce surgical complications, readmissions and major adverse cardiac events (MACE)  
35 as compared to standard care.

### 36 Methods and analysis

37 Patients (n=350) are randomised to the Heart-ROCQ program or standard care. The Heart-ROCQ  
38 program consists of a preoperative optimization phase during the waiting time (3 times p/week,  
39 minimal 3 weeks), a post-operative inpatient phase (3 weeks) and an outpatient CR phase (2 times  
40 p/week, 4 weeks). Patients receive multidisciplinary (e.g. physical, dietary, psychological, and  
41 smoking cessation) treatment. Standard care consists of 6 weeks post-surgery outpatient CR with  
42 education and physical therapy (2 times p/week). The primary outcome is a composite weighted  
43 score of functional status, surgical complications, readmissions, and MACE and is evaluated by a  
44 blinded end-point committee. Secondary outcomes are length of stay, physical, and psychological  
45 functioning, life style risk factors, and work participation. Finally, an economic evaluation is  
46 performed. Data is collected at six time points: at baseline (start of the waiting period), the day before  
47 surgery, at time of discharge from the hospital, and at 3, 7, and 12 months after surgery.

### 48 Ethics and dissemination

49 This study will be conducted according to the principles of the Declaration of Helsinki (version 8,  
50 October 2013). The protocol has been approved by the Medical Ethical Review Board (METc) of the  
51 UMCG (No. 2016/464). Results of this study are submitted to a peer-reviewed scientific journal and  
52 can be presented at national and international conferences.

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2  
3 53 **Registration:** The Heart-ROCQ study has been registered at ClinicalTrials.gov (No. NCT02984449).  
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5

6 54 **Strength and limitations of this study**  
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- 9 55 • A prospective randomised open, blinded end-point (PROBE) trial  
10  
11 56 • Comparison of a unique multidisciplinary pre- and post-operative CR program with a standard  
12  
13 57 care post-operative outpatient CR program  
14  
15 58 • Patient-oriented: primary and secondary outcomes provide a comprehensive and clinically  
16  
17 59 relevant evaluation of patients' recovery from surgery (e.g. on physical, psychological, social  
18  
19 60 domains)  
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21  
22 61 • Both short- and long term effects of the CR programs are included  
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24 62 • Single centre study, albeit that patients are referred from four hospitals  
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## 63 INTRODUCTION

64 The leading cause of death in Western countries is ischemic heart disease.(1) One of the treatments  
65 for severe ischemic heart disease is cardiac surgery (CS). The risk of complications related to CS is  
66 substantial; post-operatively, pulmonary complications (up to 33%), delirium (~26%), and  
67 arrhythmias (~30%) have been reported to occur.(2–4) In turn, these complications are associated  
68 with prolonged hospitalisation, increased adverse events (i.e. readmission, stroke, myocardial  
69 infarction, and mortality), reduced health related quality of life (HRQoL), and higher health care  
70 costs.(5–10) Patients with poor dietary habits (present in ~80% of the candidates for CS), who are  
71 physical inactive (~45%), who smoke (22%), or who experience depression and/or anxiety disorders  
72 (~30%) are at higher risk for post-operative complications and are at risk for lack of functional  
73 benefits after CS.(8,11–19)

74 Over the last decades risk factors such as age, obesity, diabetes, hypertension and  
75 dyslipidemia have steadily increased in patients undergoing CS.(20,21) Yet, despite their adverse  
76 effects on treatment outcomes, reducing the burden of modifiable risk factors are currently not part of  
77 standard clinical care before and after CS. Before CS, patients often have a preoperative period of  
78 several weeks on the waiting list in which they receive little or no guidance. This waiting period has  
79 been associated with increased psychological stress, feelings of anxiety and reduced functional  
80 status.(22,23) With respect to inactivity during hospitalisation after CS, research has shown that  
81 during the 8 to 11 days of hospitalisation, patients spent the majority of time in sitting or supine  
82 position.(24,25) In-hospital physical inactivity is a predictor of a longer hospital stay and re-  
83 hospitalisation.(24,26,27) It causes a decrease in muscle strength and aerobic capacity, both  
84 fundamental in the performance of activities of daily living.(28,29) This reduced physical capacity  
85 may seriously impact CS patients' independence, especially since these patients are often elderly  
86 and thus the functioning of their entire physiological system is already reduced.(30)

87 Cardiac rehabilitation (CR) targets to improve the pre- and post-operative status of patients  
88 undergoing CS. CR has the aim "to favourably influence the underlying cause of cardiovascular  
89 disease, as well as to provide the best possible physical, mental, and social conditions".(31) Post-

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3 90 operative CR is already an essential part of standard care in the Netherlands, although many  
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5 91 hospitals in the Netherlands provide a phase II outpatient CR program, starting 3 to 6 weeks after  
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7 92 CS.(32,33) Benefits of post-operative CR are reported for a variety of cardiac patients,(34) however  
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9 93 the evidence in patients undergoing CS is still lacking with regard to patient-relevant outcomes and  
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11 94 mortality.(35) In addition to post-operative CR, small trials suggested that preoperative CR is  
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13 95 effective in reducing post-operative pulmonary complications, duration of hospital stay, improving  
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15 96 HRQoL, and increasing the compliance to post-operative CR.(23,36) However, long-term effects and  
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17 97 the effects on other complications remain unclear. Furthermore, most studies investigated the effect  
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19 98 of preoperative CR *or* post-operative CR, but not the effect of both CR methods combined. The  
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21 99 hypothesis is that a combined pre- and post-operative CR program is more beneficial when  
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23 100 compared to a separate preoperative CR program *or* a single post-operative CR program.  
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26 101 The aim of the Heart-ROCQ study is to determine the effect of a comprehensive pre- and  
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28 102 post-operative CR program (the Heart-ROCQ program) on functional status, post-operative surgical  
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30 103 complications, readmissions to the hospital, and major adverse cardiac events (MACE) compared to  
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32 104 a regular Dutch post-operative outpatient CR program (the Standard Care CR program).(32) In  
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34 105 addition, the effect of the Heart-ROCQ program on physical and psychological functioning, including  
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36 106 HRQoL, life style risk factors, work participation, and cost-effectiveness are evaluated in comparison  
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38 107 to the Standard Care CR program. To assess for whom and why the CR programs are effective,  
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40 108 moderator and mediator analyses are performed.  
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## METHODS AND ANALYSIS

### Study design and organization

This investigator-initiated prospective randomised open, blinded end-point (PROBE) trial is executed in a single Centre (University Medical Centre Groningen [UMCG]). Patients from three referral hospitals (Ommelander Hospital Groningen [OZG], Martini Hospital Groningen [MZH], and Wilhelmina Hospital Assen [WZA]) who are accepted for CS at the UMCG are also approached to participate. Patients are randomly assigned to a combined pre- and post-operative multidisciplinary CR program (the Heart-ROCQ group) or a regular phase II outpatient CR program after surgery (the Standard Care group).<sup>(32)</sup> Figure 1 provides an overview of the study design.

### Ethical considerations and dissemination

This study is conducted according to the principles of the Declaration of Helsinki (version 8, October 2013) and according to the research code of the UMCG. It has been registered at ClinicalTrials.gov (No. NCT02984449) and the protocol (version 2, 2016-Dec-19) has been approved by the Medical Ethical Review Board (METc) of the UMCG (No. 2016/464). If applicable, substantial amendments will be notified to the METc for approval and changes will be written in the articles describing the results of the study. Results of this study will be submitted to a peer-reviewed scientific journal and can be presented at national and international conferences. In addition, the results will be distributed by various information channels (e.g. websites of cardiac patient organisations, social media). Two to three times a year a newsletter about the progress and (in the end) the results of the study is sent to participants, who are interested.

### Patient and public involvement

In a pilot study (to be submitted) the patient satisfaction and the feasibility (in terms of accessibility, compliance, training load and safety) of the Heart-ROCQ program have been evaluated. These results were taken into account when further developing the Heart-ROCQ program and the protocol of this study.



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### 136 Funding

137 The Heart-ROCQ study is financially supported by Edwards Lifesciences SA, Abbott (former St. Jude  
138 Medical Nederland B.V.) and 'Stichting Beatrixoord Noord-Nederland'. The sponsors are not involved  
139 in the design or execution of the study.

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### 141 Participants

142 Patients ( $\geq 18$  years) admitted to elective coronary artery bypass grafting (CABG), valve surgery,  
143 aortic surgery, or combined procedures are eligible. Patients accepted for congenital procedures,  
144 transcatheter aortic valve implantations (TAVI), aortic dissections, or aortic descending repair are  
145 excluded. Other exclusion criteria are: being unable to participate in all program elements of the  
146 Heart-ROCQ program due to disorders of the nervous or musculoskeletal system that limits exercise  
147 capacity, chronic obstructive pulmonary disease (COPD) with Global Initiative for Chronic  
148 Obstructive Lung Disease (GOLD) criteria classification 3 or 4,(37) addiction to alcohol or drugs, a  
149 serious psychiatric illness (i.e. recently experienced psychosis, bipolar disorder, diagnosis of  
150 schizophrenia, serious cognitive, or neurological problems, and acute suicidal ideations or  
151 behaviour), or when it is undesirable to exercise (i.e. hypertrophic cardiomyopathy, unstable angina,  
152 advice from cardiologist); any treatment which is planned during one of the CR programs and which  
153 is expected to interrupt attendance to the CR program (e.g. planned organ transplantation,  
154 preoperative endocarditis, or planned chemotherapy etc.); playing a sport at (inter)national level;  
155 being unable to read, write, or understand Dutch.

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### 157 Study enrolment, randomization and registry

158 Figure 2 shows the flow chart of the Heart-ROCQ study. Patients on the waiting list of the thoracic  
159 surgery department and meeting the study criteria for type of surgery are asked to participate by their  
160 cardiologist. The cardiologist provides the patients with study information and an invitation to meet  
161 the researcher at the preoperative consultation. At the preoperative consultation, the researcher will  
162 obtain informed consent and conduct the baseline measurements. Eligible patients who have signed  
163 informed consent and performed the baseline measurements, are randomised to the Heart-ROCQ

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3 164 group or Standard Care group. Randomization (concealed group allocation in REDCap, random  
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5 165 blocks of 2-4, 1:1 ratio) is stratified for weight of the surgery (isolated CABG, single non-CABG [i.e.  
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7 166 replacement or repair of part of aortic or valve], 2 procedures or 3 procedures), gender, and age ( $\geq 65$   
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10 167 and  $< 65$  years). Prior to the start of the study, the randomization lists were created (using the 'ralloc'  
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12 168 function of Stata/SE, version 13.0) and imported into the secure data collection tool REDCap  
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14 169 (version 7.3.2), by an independent researcher. Medical staff and researchers are not blinded to  
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16 170 group allocation, because of logistic reasons. The primary end point is evaluated by an independent  
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18 171 end-point committee, blinded for group allocation.  
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20 172 Patients who are not willing to participate are asked to give written consent for using data that  
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22 173 are collected during routine care. These data are collected in the Heart-ROCQ study registry to get  
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24 174 more insight in potential differences between patients who participated in the study and patients who  
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26 175 did not. The Heart-ROCQ registry will thus provide more insight in the generalizability of the results.  
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28 176 Data of this registry are not used for the primary statistical analyses.  
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## Intervention

### *Heart-ROCQ group*

The Heart-ROCQ group receives a CR program at the Centre of Rehabilitation of the UMCG (location Beatrixoord, which is located 6 km from the hospital of the UMCG) consisting of 3 phases. The first phase is an outpatient preoperative optimization phase during the waiting period (3 times per week, minimum of 3 weeks). The second phase is a post-operative inpatient CR phase (3 weeks, only during weekdays) followed by the third phase, an outpatient CR phase (2 times per week, for 4 weeks). During each phase, all participants receive physical therapy including group sessions of inspiratory muscle training (IMT),(38) strength training, aerobic cycling, breathing, coughing and relaxation. In addition, patients have an intake with a dietician and a psychologist and take part, on indication, in individual sessions to optimize their health. Moreover, different group education sessions are organized regarding coping with stress, awareness of risk factors, and maintaining a healthy life style. Two additional modules, namely coaching to stop smoking and to return to work, are available for patients who respectively smoke or are employed. A detailed description of the CR program is given in the supplementary information.

### *Standard Care group*

In the Netherlands, the current standard of care consists of a phase II outpatient CR program, which is conducted at the referred hospital.(32,33) In general, this CR program starts 3 to 6 weeks after discharge from the hospital and lasts for 6 weeks. The program consists of four educational sessions (regarding risk factors and retaining a healthy life style) and physical therapy (2 times per week: 30 min. cycling together with 30 min. sports and games, relaxation therapy, or strength training). Furthermore, patients can be referred to a psychologist or a dietician when needed. The content of this CR program is based on the Dutch CR guidelines.(39)

### Composite primary end point: functional status, complications and events

The primary outcome is a composite weighted score of functional status, post-operative surgical complications, readmissions to the hospital, and MACE. Each event is scored (ranging from 1 to 3 points), separately. Table 1 shows an overview of the primary outcome and the scoring system.

The scores of all events are summed up to calculate a total score. Only the most serious complication is counted per event (e.g. when a percutaneous coronary intervention [score 1] is complicated by a stroke [score 2], the score will be 2 and not 3 [1 + 2]).

The concept of the composite weighted score is adapted from the African-American Heart Failure Trial (A-HeFT).(40) Functional status is assessed through two health domains of the Medical Outcome Study 36-item General Health Survey (RAND-36 version 2)(41): physical functioning and physical health problems. The primary end point is evaluated at 3 months (T4) and 1 year (T6) after surgery (Figure 1). Deep wound infections and surgical re-explorations are screened up to 120 days, after surgery. Other post-operative surgical complications are measured in the period between the surgery and when a patient meets the UMCG discharge criteria (Table 2). Hospital admissions are checked between baseline and one year after surgery. To prevent bias (since the Heart-ROCC group follows the in-patient CR phase after surgery) hospital admissions between the day of admission before surgery and 30 days after surgery are not included when determining the (calculated) primary end point.

### Secondary outcomes

#### *Complications and events*

All individual components of the composite end point regarding the complications and events will be analysed separately as secondary outcomes. Table 3 summarizes the definitions of the secondary complications and events, including the moments of screening.

All documents concerning the composite primary end point and the secondary complications are encrypted and subsequently adjudicated by the independent end-point committee. The end-point committee consists of four members (cardiologists and cardiothoracic surgeons), who are not employed in the UMCG and are blinded for group allocation.

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Table 1: definitions and score of the components of the composite primary end point

Functional status	Score
Worsening in physical functioning ( <i>domain score of health related quality of life, rand36_v2</i> ) <sup>†</sup>	1
No change or improvement in physical functioning <sup>†</sup>	0
Worsening in physical problem ( <i>domain score of health related quality of life, rand36_v2</i> ) <sup>†</sup>	1
No change or improvement in physical problem <sup>†</sup>	0
A clinical relevant worsening is classified as minimal change according to <i>Wyrwich et al., 2004</i> (42)	
<b>(Serious) Adverse Events</b>	
No serious adverse event	0
Prolonged mechanical ventilation <i>Mechanical ventilation longer than 24 hours</i>	1
Lung infection 1) A new lung radiographic infiltrate AND 2) two signs that the infiltrate is infectious origin (i.e. a) fever - body temperature >38°C or <36°C -, b) leukocytosis - white blood cells >10,000 or <4000, c) positive sputum culture AND/OR d) decline in oxygenation	1
Delirium 1) A DOS score ≥ 3 at hospital ward AND/OR 2) Diagnosis confirmed by a psychiatrist, geriatrist, or supervising specialist according to the DSM-IV criteria resulting in treatment with medication	1
Readmissions to intensive care unit <i>Unrelated to a secondary end point</i>	1
Deep wound infection <i>Deeper tissues are affected (muscle, sternum, and mediastinum) and must include: 1) surgical drainage / re-fixation OR 2) an organism is isolated from culture of mediastina tissue or fluid, OR 3) antibiotic treatment, because of sternum wound</i>	2
Readmissions to hospital <i>An unplanned hospital stay with different dates of admission and discharge with a medical indication (i.e. clinical signs and symptoms or change of treatment)</i>	1
Any cardiothoracic surgical interventions <i>Graft- or valve failure, CABG, valve, aortic, or other cardiac surgery<sup>‡</sup></i>	2
Any percutaneous interventions <i>PCI, TAVI, etc.</i>	1
Myocardial infarction <i>According to the third universal definition of myocardial infarction<sup>§</sup></i>	2
Cerebral vascular accident / stroke <i>Acute neurological event of at least 24 hours of duration, with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnosis of stroke requires confirmation by CT, MRI, or pathological confirmation.</i>	2
Sudden death survivor <i>The sudden onset of symptoms, such as chest pain and cardiac arrhythmias, ventricular tachycardia, which lead to the loss of consciousness and cardiac arrest followed by reanimation and does not lead to biological death.</i>	2
Death <i>All-cause mortality</i>	3
Total score = sum of physical status and SAE's at 3 months and 1 year (worst score of each event)	

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<sup>†</sup>Compared with baseline; <sup>‡</sup>According to the definitions of the 'Begeleidingscommissie Hartinterventies Nederland'; <sup>§</sup>Thygesen et al., 2012(43); DOS: Delirium Observation Screening scale(44); CABG: Coronary arterial bypass graft; PCI: Percutaneous coronary intervention; TAVI: Transcathetic aortic valve implantation; In gray: post-operative complications can be scored ones; SAE: Serious adverse event.

Table 2: Discharge criteria of the University Medical Centre Groningen (UMCG)

- 1) no drain, no external pacemaker lead, no infusion, or oxygen present,
- 2) stable clinical conditions (stable lab results, X-ray, and haemodynamic parameters),
- 3) able to perform basic activity of daily living (ADL)-activities (i.e. going independently to the toilet).

Table 3: definitions of the secondary complications and events

Definitions	Time of measure
Atrial fibrillation <i>New onset of atrial fibrillation or atrial flutter requiring medical treatment or cardioversion</i>	Surgery to T3
Prolonged ICU stay <i>When the number of calendar days is two or more from ICU admission to discharge</i>	Initial stay
Readmissions to hospital <i>The number of unplanned hospital stays with different dates of admission and discharge with a medical indication (i.e. clinical signs and symptoms or change of treatment)</i> a) directly related to a cardiac cause b) not directly related to a cardiac cause	Baseline to T6 <sup>§</sup>
Hospitalisation days <i>Total number of days of hospitalisation</i> a) directly related to a cardiac cause b) not directly related to a cardiac cause	Baseline to T6 <sup>§</sup>
Cardiovascular death <i>Any death due to proximate cardiac or cardiovascular cause (e.g. Myocardial infarct, low-output failure, fatal arrhythmia, death secondary to a cerebral vascular accident, pulmonary embolism, ruptured or dissecting aortic aneurysm, or other vascular diseases), un-witnessed death, and death of unknown cause, and all procedure related deaths (e.g. PCI, CABG), including those related to concomitant treatment<sup>†</sup>.</i>	Baseline to 5 years after surgery
Non-cardiovascular death <i>Any death not covered by above definition, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma</i>	Baseline to 5 years after surgery
<b>Concerning safety</b>	
Surgical re-exploration for bleeding/ tamponade <i>Surgical incision into the sternum as a result of a bleeding or tamponade</i> a) acute: presented within 24 hours after surgery b) late: presented after 24 hours after surgery	Surgery to T4
Surgical re-exploration dehiscence <i>Aseptic wound dehiscence</i>	Surgery to T4

<sup>†</sup>Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) will be classified as cardiac death; <sup>§</sup>Not measured between the day of admission before surgery and 30 days after surgery, because of POST-in phase of Heart-ROCC program; ICU: Intensive care unit; T4: Follow-up at 3 months after surgery; T6: Follow-up at 12 months after surgery.

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### 244 *Questionnaires and physical tests*

245 Table 4 shows the physical tests and questionnaires of the secondary outcomes regarding physical  
246 and psychological health, life style risk factors, and the economic evaluation. Physical tests and  
247 questionnaires are completed at six assessment points (Figure 1). The preoperative measurements  
248 (T1 and T2) are conducted at the start (preoperative consultation) and the end (1 to 8 days before  
249 surgery) of the waiting period. The third measurement (T3) is performed when patients meet the  
250 UMCG discharge criteria (Table 2). The follow-up measurements (T4, T5, and T6) are at 3, 7, and 12  
251 months after surgery. Patients are asked to fill in questionnaires online or when requested on paper,  
252 prior to the visits, to execute physical tests. All adverse events reported spontaneously by the patient  
253 or observed by the investigator are recorded. In addition, serious adverse events are reported to the  
254 METc. Data are stored in REDCap and on a secure drive at the department CardioResearch in the  
255 UMCG. Two times per year, the study is monitored by a trained research monitor from another  
256 department of the UMCG. Details of procedures, data collection, management and monitoring can be  
257 found in the Trial Master File of the Heart-ROCQ study (can be obtained by the investigators). On the  
258 12<sup>th</sup> of June 2018, the study was audited and certified for the ISO 9001: 2015 independently by DNV  
259 GL.

### 261 Potential moderators

262 Preoperative risk profile (i.e. Euroscore II, medical history, life style risk factors, physical, and mental  
263 status), surgery parameters, and demographics are collected from the medical record and baseline  
264 measurements. The content of the CR program is described in terms of compliance, duration of CR  
265 program, type of treatment, frequency, and training load (i.e. for bicycle training: external workload,  
266 heart rate response, rate of perceived exertion using the Borg scale, and for strength training: sets,  
267 repetitions, and intensity) for both the Heart-ROCQ group as the Standard Care group.

268 **Table 4: Time of measure, physical tests, and questionnaires of the secondary outcomes**

Secondary outcomes	Measure	Time of measure
<i>Physical health</i>		
Cardiorespiratory fitness	6MWT(45)	T1-T4, T6
Muscle strength	STS_10, grip & leg strength(46,47)	T1-T4, T6
Independence in ADL	KATZ(48,49)	T1, T4, T6
<i>Psychological health</i>		
General anxiety	GAD-7(50)	T1,T2, T4, T6
Feelings of depression	PHQ-9(51,52)	T1,T2, T4, T6
Health related Quality of Life	Rand-36_v2(41)	T1, T4, T6
<i>Life style risk factors</i>		
Physical activity	iPAQ(53) & Actigraph <sup>†</sup> (54)	T1, T4, T6
Obesity indices	BMI, waist-to-hip ratio	T1, T4, T6
Smoking behaviour	Number of cigarettes per day	T1, T4, T6
<i>Economic evaluation</i>		
Health care use & related medical costs	iMCQ(55)	T1, T4-T6
Work participation <sup>‡</sup>	iPCQ(56)	T1, T4-T6
QALYs	EQ-5D-5L(57)	T1, T4-T6
<i>Potential mediators</i>		
Cardiac self-efficacy	CSE(58)	T1, T2, T4, T6
Illness representations	IPQ-R(59)	T1, T2, T4, T6

†Patients are asked to wear the Actigraph during waking hours for 1 consecutive week; ‡Health-related productivity losses of paid work and unpaid work; T1: Begin of waiting time; T2: 1 to 8 days before surgery; T3: Moment that patients meet the UMCG discharge criteria; T4-T6: Follow-up at 3, 7, and 12 months after surgery; 6MWT: Six minutes walking test; STS\_10: Ten times sit to stand test; ADL: Activities of Daily Living; KATZ: Katz Index of Independence in Activities of Daily Living; GAD-7: Generalized Anxiety Disorder 7-item scale; PHQ-9: Patient Health Questionnaire 9-item scale; iPAQ: International Physical Activity Questionnaire; BMI: Body Mass Index; iMCQ: iMTA Medical Cost Questionnaire; iPCQ: iMTA Productivity Cost Questionnaire; QALY: Quality-adjusted life years; EQ-5D-5L: EuroQol five-dimensional questionnaire; CSE: Cardiac Self-efficacy; IPQ-R: Illness Perception Questionnaire, Revised.

#### Potential mediators

Illness perceptions (i.e. patients mental representations of their illness based on different sources of information) are measured with three subscales (personal control, treatment control, and consequences) of the revised illness perception questionnaire (IPQ-R).(59) These subscales are chosen because of their sensitivity to change and because of their relation to psychological distress(60). The cardiac self-efficacy (CSE) scale(58) is used to measure CSE (i.e. patients confidence to perform a specific task related to cardiac disease).



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3 286 Statistical analyses

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5 287 *Sample size*

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7 288 Assuming a normal distribution, the mean weighted score of the primary end point is estimated on  
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9 289 1.0 with a standard deviation of 0.9 at 1 year after surgery. This estimation is based on historical data  
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11 290 of the UMCG, an unpublished on-going pilot study in the UMCG, the Dutch registration database,(61)  
12  
13 291 and data reported in literature.(6,62–64) A decrease of 0.3 is expected in the Heart-ROCQ group,  
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15 292 based on previous studies comparing CR with standard care(36,63,65) (i.e. no CR) and is  
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17 293 considered to be clinically relevant (i.e. on average a 30% decrease in complications/events or  
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19 294 worsening in functional status or 10-20% decrease in MACE or death). To detect this decrease and  
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21 295 achieve 80% power (significance level of 5%) a group of 286 patients (143 in the Heart-ROCQ group  
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23 296 and 143 in the Standard Care group) is needed. To incorporate a withdrawal of  $\pm 20\%$  a total sample  
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25 297 size of 350 is needed at baseline.  
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31 299 *Interim analysis*

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33 300 An interim analysis will be conducted when 40% of the included patients have had the  
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35 301 measurements one year after surgery. The study will be terminated prematurely when the primary  
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37 302 outcome of one of the CR programs is obviously ( $P < 0.001$ ) different from the other CR program.  
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41 304 *Primary and sensitivity analyses*

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43 305 All end points are primary analysed according to the 'intention-to-treat' principles and missing values  
44  
45 306 are counted as worst-case score (nominal variables) or estimated using Maximum Likelihood  
46  
47 307 estimation (interval variables). As supplementary analyses, the end points are analysed on a per-  
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49 308 protocol principle with and without using imputation methods for missing values. In all analyses, a  
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51 309 two-sided  $p < 0.05$  is considered statistically significant.

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54 310 Statistical methods and clinical relevance for analysing secondary outcomes are written in the  
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56 311 research protocol (ClinicalTrials.gov : NCT02984449).

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3 313 *Economic evaluation*  
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5 314 For the evaluation of health-care utilization, standard prices published in the Dutch costs guidelines  
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7 315 are used.(66) To compare the costs to quality adjusted life years (QALYs), QALYs are estimated with  
8  
9 316 use of the EQ-5D-5L.(57) Utility values for the EQ-5D-5L are calculated based on the new Dutch  
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11 317 tariff.(67) Results from the analysis are reported as an Incremental Cost Effectiveness Ratio (ICER),  
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13 318 dividing the difference in effect, by the difference in costs. Bootstrap re-sampling will be performed,  
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16 319 and cost-effectiveness acceptability curves will be plotted, to estimate the probability that the Heart-  
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18 320 ROCQ program is cost effective when compared to standard care. A societal perspective is applied.  
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22 322 Study status  
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24 323 From May 2017 to December 2018, 75 patients were enrolled. For next year's we expect that the  
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26 324 enrolment will increase to 85 patients per year. The last patient is expected to be included in July  
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28 325 2021.  
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## DISCUSSION

The Heart-ROCQ study is the first randomised clinical trial evaluating the effect of a combination of pre- and post-operative CR program compared to a post-operative CR program. Furthermore, unlike the vast majority of CR programs in previous studies, the current program is multidisciplinary targeting different aspects of surgical outcomes in patients undergoing CS. Because different aspects are targeted, a composite weighted score will better reflect the treatment benefits than a single outcome. Therefore, the primary end point is a composite end point of functional status, post-operative surgical complications, readmissions to the hospital and MACE. The components of the end point are of clinical importance to patients undergoing CS and reflect a comprehensive representation of the recovery of the patient.

Both the ideas of the combined primary end point and the weighting of the individual components were derived from other studies.(40,68,69) Assigning different weights to the components was needed for more accurate comparison. Since the components are not equal in clinical importance, equal weights would lead to inaccurate statistical analysis(69). In the current study, the weighted score of HRQoL is lower (1 point instead of 2 points) to minimize bias due to patients' knowledge of group allocation. Therefore, improvements in quality of life are not counted in the primary end point to prevent bias in positive direction. This also prevents that a score in quality of life and event cancel each other out (e.g. when a patient experiences an improvement in Quality in Life [+2 points] and has a stroke [-2 points] then the total score is 0). The scores of all-cause mortality, stroke, myocardial infarction and revascularization are in line with the results showed by Tong and colleagues (2013)(69). A disadvantage of composite end points is that the effect may be driven by complications that occur with the greatest frequency.(70) Therefore, post-operative complications which occur frequently, such as atrial fibrillation, is evaluated separately as secondary end point. The primary end point is evaluated by an end-point committee, which is blinded to group allocation and consists of four independent cardiologists and cardio-thoracic surgeons.

Previous preoperative CR studies were primarily focused on short-term effects; only a few post-operative CR studies have determined long-term effects.(23,35,36) In contrast to previous

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3 353 preoperative CR studies, the Heart-ROCQ study sets out to investigate both short- and long term  
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5 354 effects of the CR programs.(23,35,36) Due to the trends in, among others, increasing age, obesity,  
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7 355 and physical inactivity, patients undergoing CS are nowadays more complex. The Heart-ROCQ  
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10 356 program aims to address these issues, which make the program clinically relevant for all CS patients.  
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12 357 Therefore, we chose to include different types of CS. Since different moderators and mediators are  
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14 358 assessed before, during and after CR, we can explore which factors are associated with better  
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16 359 outcomes and which working mechanisms contribute to its effectiveness. These findings may provide  
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18 360 a more in-depth understanding of who benefits the most from CR and the underlying mechanisms of  
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20 361 CR, which are still not fully understood in patients undergoing CS on short and long-term.(35) In  
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22 362 addition, the present study is thought to considerably contribute to the evidence to develop guidelines  
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24 363 for clinical practice, especially regarding the preoperative CR program.

26 364 The Heart-ROCQ program is expected to be cost-effective in the long-term, which is also of  
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28 365 interest for policymakers and health care takers. Therefore, an economic evaluation is performed to  
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30 366 assess the cost-effectiveness of CR, since little is known about the cost-effectiveness of CR.(63) A  
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32 367 societal perspective of this economic evaluation is chosen, meaning that not only health-care costs,  
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34 368 but also patient- and productivity related costs and benefits are taken into account. If the Heart-  
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36 369 ROCQ program is proven to be effective, it might be advisable to include a supportive prevention-  
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38 370 oriented waiting period prior to surgery as an integral part of the treatment for patients undergoing  
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40 371 elective CS. This implies a paradigm shift from curative care following CS to an additional preventive  
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42 372 care attitude before surgery. Extensions of rehabilitation options in, or in the vicinity of cardiac  
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44 373 centres, will then be required.

## 47 48 374 CONCLUSION

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50 375 The Heart-ROCQ study is the first randomised clinical trial comparing the effect of a combined pre-  
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52 376 and post-operative CR program to a regular Dutch phase II post-surgery outpatient rehabilitation CR  
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54 377 program in a population undergoing elective CS. This study is expected to provide new  
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56 378 understanding of the effectiveness and underlying working mechanisms of CR, and subsequently to  
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58 379 improve value-based health care.  
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16 386  
17 help with executing the Heart-ROCQ study.  
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22 389 Declaration of interest  
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31 393  
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33 394  
34 disclose.  
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39 397 Authors' contributions  
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41 398 Conception and design of the study: JH, FZ, MJLdJ, MFR, WD, JF, LHVvdW, PvdH, and MAM;  
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43 399 Methodology: JH, FB, SD, MJLdJ, MFR, and PvdH; Acquisition of data: JH, FB and SD; Writing –  
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45 400 Original draft, tables, and figures: JH; Writing- Reviewing and Editing: FB, SD, MJLdJ, MFR, WD,  
46  
47 401 ICCvdH, JF, LHVvdW, PvdH, and MAM; Supervision: MJLdJ, MFR, WD, JF, ICCvdH, LHVvdW,  
48  
49 402 PvdH, and MAM; Funding Acquisition: JH, SD, JF, LHVvdW, PvdH, and MAM. All authors approved  
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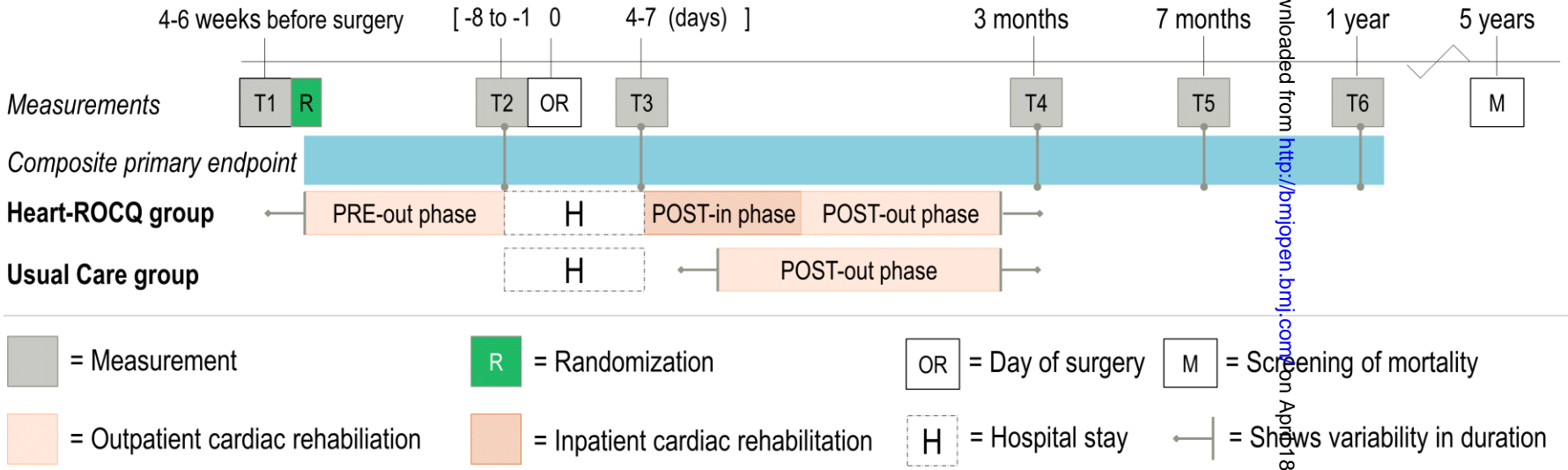
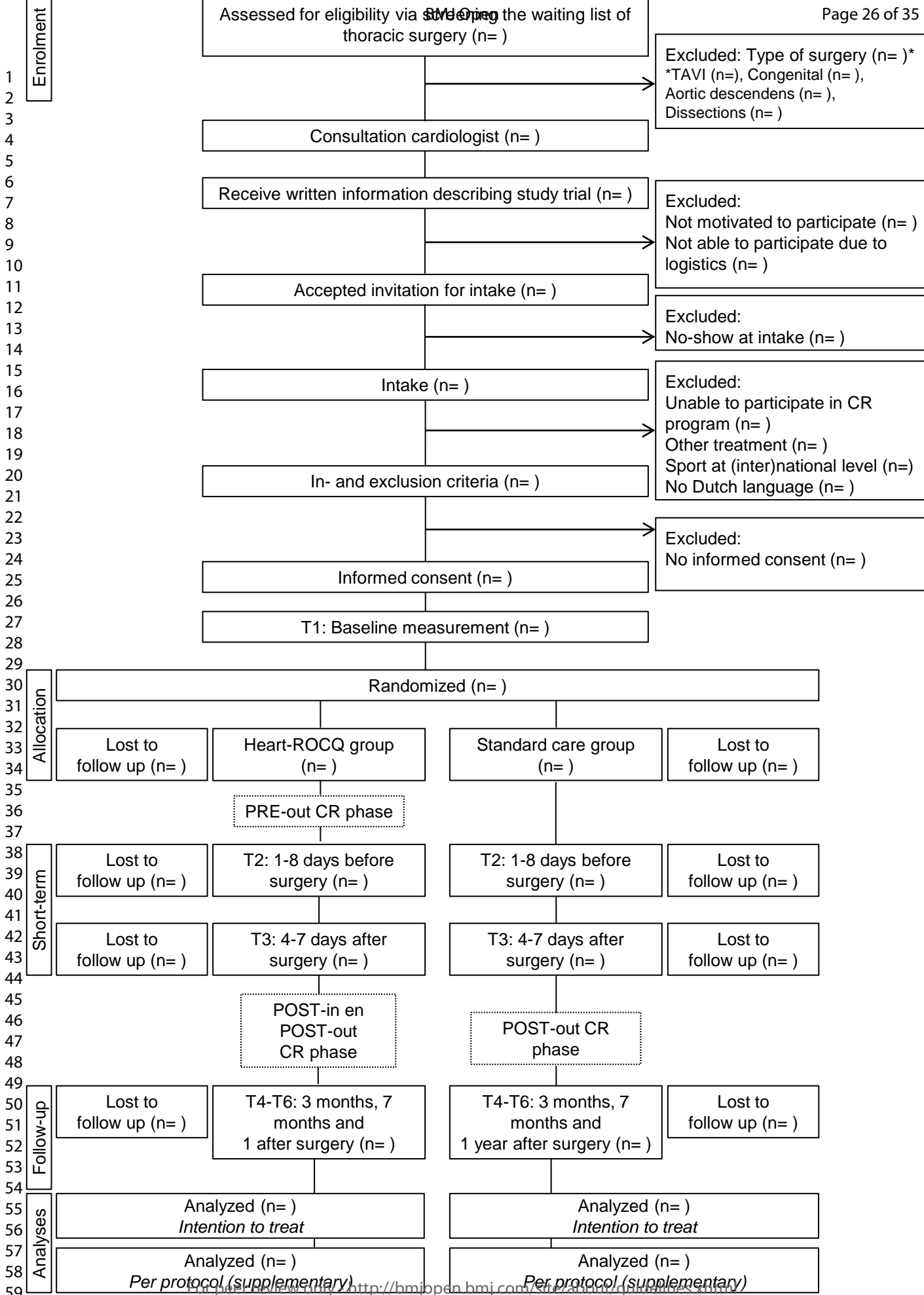


Figure 1: Research design of the Heart-ROCQ PROBE trial. The phases of both cardiac rehabilitation programs and the measurements are shown relative to the moment of surgery.



## SUPPLEMENTARY INFORMATION - DESCRIPTION OF THE HEART-ROCQ PROGRAM

<b>PRE-out phase – An outpatient cardiac rehabilitation phase during the waiting period</b>			
<i>Three times per week, a minimum of three weeks</i>			
<b>Physical therapy</b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients physical capacity before surgery</li> <li>- Patient learns to apply the stress-strain training principles</li> <li>- To optimize pulmonary muscle strength</li> <li>- Patient knows which breathing and coughing techniques should be used after surgery to prevent pulmonary complications</li> </ul>			
When needed:			
<ul style="list-style-type: none"> <li>- Patient learns to recognize body signals and boundaries.</li> <li>- Patient is able to exercise despite of possible kinesiphobia</li> </ul>			
<b>Type of exercise</b>	<b>Frequency</b>	<b>Intensity</b>	<b>Monitoring</b>
IMT	3 x p / wk	- 6 cycles of 6 repetitions, - rest periods of resp. 60, 45, 30, 15 and 5 s. - 60-80% of maximal inspiratory pressure <sup>65</sup>	- Week 1: each training ↑ intensity with 10% - Intensity ↑ with 5% if RPE <5 <sup>1</sup>
Aerobic cycle	3 x p / wk	- 25 min. at RPE 3 <sup>1</sup> - Interval training will be given, if the patient is not able to perform endurance training.	- First training: 50% of POpeak - Load ↑ if RPE < 3 <sup>1</sup> - Interval training: guided by complaints and RPE of 3
Resistance training	3 x p / wk	- 1-3 cycles of 10-15 repetitions - Rest: 30-60 s. - 50-80% of estimated 1RM - On six fitness apparatus	- First training: 6-10 RM per fitness apparatus
Body awareness	1 x p / 2 wks	- 30 min. breathing and relaxation techniques	Not Applicable
Group education	Two sessions	- Basic training principles - Forced expiration, huff- and cough techniques	Not Applicable
<b>Dietary advice<sup>2</sup></b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients nutritional status</li> <li>- Patient knows which nutrients are important focusing on the surgery</li> <li>- Patients knows the importance of food in relation to cardiovascular disease and cardiovascular risk management</li> </ul>			
<b>Type</b>	<b>Frequency</b>	<b>Content</b>	
Intake interview	One session	- Anamnesis about nutritional status	
Counselling	On indication	- Individual sessions according to existing guidelines	
Group education	One session	- 60 min., cardiovascular risk factors and dietary intake	
<b>Psychological guidance<sup>2</sup></b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To optimize mental status of the patients before surgery</li> <li>- Patient has made a start with the awareness of cardiovascular risk factors</li> </ul>			
Intake interview	One session	- Anamnesis about mental status	
Counselling	On indication	- Individual sessions according to evidence-based treatment protocols dependent on mental problems of patient <sup>3</sup>	
Group education	One session	- Coping with psychological tension/stress, to process the mental trauma of cardiac surgery, and risk factors	
<b>No-smoking consultation (For patients who smoke)</b>			
<u>Aim</u>			
- Patient gives up smoking during the waiting time before surgery			
Intake interview & counselling	One session per wk	- 30 min., individual session based on existing guidelines	

IMT: Inspiratory muscle training; RPE: Rate perceives exertion; POpeak: Maximum power output achieved during submaximal Ergometry test. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Involvement of partner/relatives during group and individual sessions; <sup>3</sup>like cognitive behavioural therapy, eye movement desensitization and reprocessing (EMDR), acceptance and commitment therapy etc.

<b>POST-in phase – An inpatient cardiac rehabilitation phase</b>			
<i>Starting 4-7 days after surgery, duration of three weeks, weekends at home</i>			
<b>Physical therapy</b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- To recover patients physical capacity</li> <li>- Patient performs breathing and coughing techniques to prevent pulmonary complications</li> <li>- Patient mobilize and can perform activities of daily living independently</li> <li>- Patient knows about risk factors according to physical activity, knows the ACSM recommendations (moderate-intensity cardiorespiratory exercise training for ≥30min/day ≥5 days/week or vigorous-intensity cardiorespiratory exercise training for ≥20 min/day on ≥3 days/week or a combination<sup>66</sup>) and makes a plan to apply the ACSM recommendations in his own life</li> <li>- Patient works on personal goals</li> </ul>			
Type of exercise	Frequency	Intensity	Monitoring
Individual therapy	2 x p / day	<ul style="list-style-type: none"> <li>- Practice at transfers, walking, and climbing stairs</li> <li>- Very light mobilizing exercises for upper extremity</li> </ul>	<ul style="list-style-type: none"> <li>- During the first 2 days of this phase.</li> <li>- Extended, if patient is not able to participate in the group sessions.</li> </ul>
Individual therapy	2 x p / wk	<ul style="list-style-type: none"> <li>- Attention to personal goals</li> </ul>	<ul style="list-style-type: none"> <li>- Week 2 and 3</li> </ul>
IMT <sup>2</sup>	3 x p / wk: 2 x under supervision, 1 x without supervision	<ul style="list-style-type: none"> <li>- 6 cycles of 6 repetitions, - rest periods of resp. 60, 45, 30, 15 and 5 s.</li> <li>- intensity of 60-80% of maximum inspiratory pressure<sup>65</sup></li> </ul>	<ul style="list-style-type: none"> <li>- First training: 50% of resistance of last preoperative training</li> <li>- Intensity ↑ with 5% if RPE &lt;5<sup>1</sup></li> <li>- IMT stops when resistance of preoperative training is reached</li> </ul>
Aerobic cycle <sup>2</sup>	1 x p / day	<ul style="list-style-type: none"> <li>- Week 1: duration of 5-20 min. at light intensity (RPE 2<sup>1</sup>)</li> <li>- Week 2 and 3: Work up to 25 min. at moderate intensity (RPE 3<sup>1</sup>)</li> <li>- Interval training will be given, if the patient is not able to perform endurance training.</li> </ul>	<ul style="list-style-type: none"> <li>- First training: at 50% of power output of last preoperative training</li> <li>- Load ↑ if RPE &lt; 2 à 3<sup>1</sup></li> <li>- Interval training: guided by complaints and RPE of 3.</li> </ul>
Resistance training <sup>2</sup>	3-4 x p / wk	<ul style="list-style-type: none"> <li>- 3 cycles of 15-20 repetitions</li> <li>- Rest periods of 30-60 seconds</li> <li>- On 6 fitness apparatus</li> </ul>	<ul style="list-style-type: none"> <li>- First training: 50% of resistance of last preoperative training for LE and 25% for UE.</li> <li>- Gradual build up to 50-80% van 1RM based on RPE 3<sup>1</sup></li> </ul>
Body awareness <sup>2</sup>	1 x p / wk	<ul style="list-style-type: none"> <li>- 30 min. breathing and relaxation techniques</li> </ul>	Not Applicable
<b>Dietary advice<sup>3</sup></b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients nutritional status</li> <li>- Patient knows which nutrients are important focusing on the recovery of surgery</li> <li>- Patients knows the importance of food in relation to cardiovascular disease and cardiovascular risk management</li> </ul>			
Type	Frequency	Content	
Intake interview	One session	- Anamnesis about nutritional status post-surgery	
Counselling	Sessions on indication	- Treatment according to existing guidelines	
Group education	One session	- 90 min., skills needed to maintain a healthy life style	
<b>Psychological guidance<sup>3</sup></b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- Patient start to process the mental trauma of cardiac surgery and the consequences of it</li> <li>- Patient has self-management competence to maintain a healthy life style</li> <li>- Patient and partner/relatives are able to support each other in the processing process</li> </ul>			
Intake interview	One session	- Anamnesis about mental status post-surgery	
Intake interview & counselling	Sessions on indication	- Individual sessions according to evidence-based treatment protocols dependent on mental problems of patient <sup>4</sup>	
Group education	One session	- 90 min., processing the cardiac surgery: possible reactions en consequences, coping with stress and healthy life style	

IMT: Inspiratory muscle training; RPE: Rate perceives exertion; LE: Lower extremities; UE: Upper extremities. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Group sessions start from day three of the inpatient phase or when patient is able to perform in the group activities; <sup>3</sup>Involvement of partner/relatives during group and individual sessions; <sup>4</sup>like cognitive behavioural therapy, eye movement desensitization and reprocessing (EMDR), acceptance and commitment therapy etc.

<b>POST-in phase – An inpatient cardiac rehabilitation phase (continuation)</b>		
<i>Starting 4-7 days after surgery, duration of three weeks, weekends at home</i>		
<b>No-smoking consultation<sup>1</sup> (For patients who smoke)</b>		
<u>Aim</u>		
- Patient is still motivated to stop smoking or patient is motivated to give up smoking (when patient did not give up smoking before cardiac surgery).		
Intake interview & counseling	1 x p / wk	- 30 min., individual sessions based on
Group education	One session	- 60 min., general information about smoking addiction and support from fellow smokers
<b>Return to work consultation<sup>1</sup> (for patients who are employed)</b>		
<u>Aim</u>		
- Patient is informed about laws and regulation for illness, social security contributions, and medical examinations		
- Patient knows their rights and obligations, the rights and obligations of the employer, the working conditions agency, the employee insurance agency, and re-integration companies		
- Patient received tools to return adequately back to work (knows positive and negative factors that can impact the re-integration)		
Group education	One session	- 60 min., laws and regulation for illness, procedures, roles, rights and obligations of different involved persons, communication to involved persons (e.g. colleagues, employer), working during rehabilitation, positive and negative factors regarding to return to work
Counseling	Sessions on indication	- Individual sessions with labour consultant dependent on problems of patient

<sup>1</sup>Involvement of partner/relatives during group and individual sessions.

<b>POST-out phase – An outpatient cardiac rehabilitation phase</b>			
<i>Starting on Tuesday after discharge of the POST-in phase, two times per week, four weeks</i>			
<b>Physical therapy</b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- Patient has optimized his/her physical capacity</li> <li>- Patient knows his/her boundaries and limitations</li> <li>- Patient knows about cardiovascular risk factors according to physical activity, knows the ACSM recommendations (moderate-intensity cardiorespiratory exercise training for <math>\geq 30</math> min/day <math>\geq 5</math> days/week or vigorous-intensity cardiorespiratory exercise training for <math>\geq 20</math> min/day on <math>\geq 3</math> days/week or a combination<sup>65</sup>) and makes a plan to apply the ACSM recommendations in his own life</li> <li>- Patient resumes his/her work or hobbies</li> <li>- Patient experiences pleasure during exercise</li> <li>- Patients achieves their personal goals</li> </ul>			
<b>Type of exercise</b>	<b>Frequency</b>	<b>Intensity</b>	<b>Monitoring</b>
Aerobic cycle	2 x p / wk	Depending on trainability of patient - 25 min. at 50-80% HRR or RPE 5 <sup>1</sup>	- Work up to 25 minutes at moderate intensity (RPE 3 <sup>1</sup> ), when patient was not able to do it in POST-in phase - Load $\uparrow$ if RPE < 5 <sup>1</sup> or HRR < 50-80%
Resistance training	2 x p / wk	UE: - 3-4 cycles of 10-15 repetitions - Rest: 30-60 s. - 50-80% of estimated 1RM - On six fitness apparatus LE: - Focus on mobilization in week 1 & 2 - Focus on strength and endurance in week 3 & 4	- UE: Load $\uparrow$ if RPE < 5 <sup>1</sup> - LE: Under guidance of complaints
Sport and games	1 x p / wk	Focus on: - Experiencing pleasure during exercise, regaining trust and handling boundaries. - Exploring different types of sports and knowing the possibilities after CR	
Swimming	1 x p / wk		
Education	1 x p / wk	- Training principles of POST-out phase and a repetition of ACSM recommendations - Awareness of exercise after CR; making a plan to exercise after CR - Explanation of the results of the exercise test - Discussing the plan to exercise, share experiences to expand exercise in home situation	
<b>Dietary advice, psychological guidance, no-smoking consultation, and return to work consultation</b>			
Individual sessions are continued when aims are not achieved			

RPE: Rate perceives exertion; HRR: Heart rate reserve; LE: Lower extremities; UE: Upper extremities; ACSM: American College of Sports Medicine; CR: Cardiac Rehabilitation. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Involvement of partner/relatives during group and individual sessions.





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

## SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 3, 6 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ 3, 6 ___
Protocol version	3	Date and version identifier	___ 6 ___
Funding	4	Sources and types of financial, material, and other support	___ 7 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1, 19 ___
	5b	Name and contact information for the trial sponsor	___ 1 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 7 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ 7, 8, 10, 13 ___

## 1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	___ 4, 5 ___
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	___ 4, 5 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 5 ___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___ 6, 7, ___
12				
13				

## 14 Methods: Participants, interventions, and outcomes

15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	___ 6 ___
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	___ 7 ___
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	___ 9 ___
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___ NA ___
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	___ 13 ___
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 7 ___
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	___ 10-14 ___
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	___ 6-14 ___
35			participants. A schematic diagram is highly recommended (see Figure)	
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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 15

2  
3  
4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 7, 8, 16

5  
6 **Methods: Assignment of interventions (for controlled trials)**

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8 Allocation:

9  
10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions 7, 8

11  
12 generation  
13  
14 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned 7, 8

15  
16 concealment 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions 7, 8

17  
18 mechanism  
19  
20 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how 7, 8

21  
22 Implementation 16c  
23  
24 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial NA

25  
26  
27 **Methods: Data collection, management, and analysis**

28  
29 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol 11-14

30  
31 methods 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols NA

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13__
2				
3				
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__15, 16__
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__15__
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__15__
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__13__
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__15__
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__13__
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__13__
29				
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__6__
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__6__
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___7, 8___
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___7, 8___
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___13___
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___19___
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___13___
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15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___13___
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___6___
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	___6___
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___NA___
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___13___
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	___NA___
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license.

# BMJ Open

## HEART Rehabilitation in patients awaiting Open-heart surgery targeting to prevent Complications and to improve Quality of life (Heart-ROCQ): Study protocol for a Prospective Randomised Open Blinded End-point (PROBE) trial

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9 4 **HEART** Rehabilitation in patients awaiting **Open**-heart surgery targeting to prevent **Complications**  
10 and to improve **Quality of life** (Heart-ROCQ) - Study protocol for a **Prospective Randomised Open**  
11 **Blinded End-point** (PROBE) trial  
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## 29 ABSTRACT

### 30 Introduction

31 The rising prevalence of modifiable risk factors (e.g. obesity, hypertension, and physical inactivity) is  
32 causing an increase in possible avoidable complications in patients undergoing cardiac surgery. This  
33 study aims to assess whether a combined pre- and postoperative multidisciplinary cardiac  
34 rehabilitation (CR) program (Heart-ROCQ program) can improve functional status and reduce  
35 surgical complications, readmissions and major adverse cardiac events (MACE) as compared to  
36 standard care.

### 37 Methods and analysis

38 Patients (n=350) are randomised to the Heart-ROCQ program or standard care. The Heart-ROCQ  
39 program consists of a preoperative optimization phase whilst waiting for surgery (3 times p/week,  
40 minimum 3 weeks), a post-operative inpatient phase (3 weeks) and an outpatient CR phase (2 times  
41 p/week, 4 weeks). Patients receive multidisciplinary treatment (e.g. physical therapy, dietary advice,  
42 psychological sessions, and smoking cessation). Standard care consists of 6 weeks post-surgery  
43 outpatient CR with education and physical therapy (2 times p/week). The primary outcome is a  
44 composite weighted score of functional status, surgical complications, readmissions, and MACE and  
45 is evaluated by a blinded end-point committee. Secondary outcomes are length of stay, physical, and  
46 psychological functioning, life style risk factors, and work participation. Finally, an economic  
47 evaluation is performed. Data is collected at six time points: at baseline (start of the waiting period),  
48 the day before surgery, at discharge from the hospital, and at 3, 7, and 12 months post-surgery.

### 49 Ethics and dissemination

50 This study will be conducted according to the principles of the Declaration of Helsinki (version 8,  
51 October 2013). The protocol has been approved by the Medical Ethical Review Board (METc) of the  
52 UMCG (No. 2016/464). Results of this study will be submitted to a peer-reviewed scientific journal  
53 and can be presented at national and international conferences.



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**Registration:** The Heart-ROCQ study has been registered at ClinicalTrials.gov (No. NCT02984449).

**Data sharing statement:** Data are available upon reasonable request after the results have been published.

### **Strength and limitations of this study**

- A prospective randomised open, blinded end-point (PROBE) trial
- Comparison of a unique multidisciplinary pre- and post-operative CR program with a standard care post-operative outpatient CR program
- Patient-oriented: primary and secondary outcomes provide a comprehensive and clinically relevant evaluation of patients' recovery from surgery (e.g. on physical, psychological, social domains)
- Both short- and long term effects of the CR programs are included
- Single centre study, albeit that patients are referred from four hospitals

## INTRODUCTION

The leading cause of death in Western countries is ischemic heart disease.(1) One of the treatments for severe ischemic heart disease is cardiac surgery. The risk of post-operative complications related to cardiac surgery is substantial; pulmonary complications (up to 33%), delirium (~26%), and arrhythmias (~30%) have been reported to occur.(2–4) These complications are associated with prolonged hospitalisation, increased adverse events (i.e. readmission, stroke, myocardial infarction, and mortality), reduced health related quality of life (HRQoL), and higher health care costs.(5–10) Patients with poor dietary habits (present in ~80% of the candidates for cardiac surgery), who are physically inactive (~45%), who smoke (22%), or who experience depression and/or anxiety disorders (~30%) are at higher risk for post-operative complications and are at risk for lack of functional benefits after cardiac surgery.(8,11–19)

Over the last decades risk factors such as age, obesity, diabetes, hypertension and dyslipidemia have steadily increased in patients undergoing cardiac surgery.(20,21) Despite their adverse effects on treatment outcomes, reducing the burden of modifiable risk factors are currently not part of standard clinical care before and after cardiac surgery. Before cardiac surgery, patients often have a preoperative period of several weeks on the waiting list in which they receive little or no guidance. This waiting period has been associated with increased psychological stress, feelings of anxiety and reduced functional status.(22,23) With respect to inactivity during hospitalisation after cardiac surgery, research has shown that during the 8 to 11 days of hospitalisation, patients spent the majority of their time sitting or in a supine position.(24,25) In-hospital physical inactivity is a predictor of a longer hospital stay and re-hospitalisation.(24,26,27) It causes a decrease in muscle strength and aerobic capacity, both fundamental in the performance of activities of daily living.(28,29) This reduced physical capacity may seriously impact independence, especially since these patients are often elderly and the functioning of their entire physiological system is already reduced.(30)

The goal of Cardiac rehabilitation (CR) is to improve the pre- and post-operative status of patients undergoing cardiac surgery. CR aims “to favourably influence the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental, and social

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3 93 conditions".(31) Post-operative CR is already an essential part of standard care in the Netherlands,  
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5 94 although many hospitals in the Netherlands provide a phase II outpatient CR program, starting 3 to 6  
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7 95 weeks after cardiac surgery.(32,33) Benefits of post-operative CR are reported for a variety of  
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9 96 cardiac patients,(34) however the evidence in patients undergoing cardiac surgery is still lacking with  
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11 97 regard to patient-relevant outcomes and mortality.(35) In addition to post-operative CR, small trials  
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13 98 suggested that preoperative CR is effective in reducing post-operative pulmonary complications,  
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15 99 duration of hospital stay, improving HRQoL, physical fitness and increasing the compliance to post-  
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17 100 operative CR.(23,36,37) However, long-term effects and the effects on other complications remain  
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19 101 unclear. Furthermore, most studies investigated the effect of preoperative CR or post-operative CR,  
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21 102 but not the effect of both CR methods combined. The hypothesis is that a combined pre- and post-  
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23 103 operative CR program is more beneficial when compared to a separate preoperative CR program or  
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25 104 a single post-operative CR program.

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28 105 The aim of the Heart-ROCQ study is to determine the effect of a comprehensive pre- and  
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30 106 post-operative CR program (the Heart-ROCQ program) on functional status, post-operative surgical  
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32 107 complications, readmissions to hospital, and major adverse cardiac events (MACE) compared to a  
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34 108 regular Dutch post-operative outpatient CR program (the Standard Care CR program).(32) In  
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36 109 addition, the effect of the Heart-ROCQ program on physical and psychological functioning, including  
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38 110 HRQoL, life style risk factors, work participation, and cost-effectiveness are evaluated in comparison  
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40 111 to the Standard Care CR program. To assess who will benefit from CR and why the CR programs  
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42 112 are effective, moderator and mediator analyses are performed.

## METHODS AND ANALYSIS

### Study design and organization

This investigator-initiated prospective randomised open, blinded end-point (PROBE) trial is executed in a single Centre (University Medical Centre Groningen [UMCG]). Patients from three referral hospitals (Ommelander Hospital Groningen [OZG], Martini Hospital Groningen [MZH], and Wilhelmina Hospital Assen [WZA]) who are accepted for cardiac surgery at the UMCG are also approached to participate. Patients are randomly assigned to a combined pre- and post-operative multidisciplinary CR program (the Heart-ROCQ group) or a regular phase II outpatient CR program after surgery (the Standard Care group).<sup>(32)</sup> Figure 1 provides an overview of the study design.

### Ethical considerations and dissemination

This study is conducted according to the principles of the Declaration of Helsinki (version 8, October 2013) and according to the research code of the UMCG. It has been registered at ClinicalTrials.gov (No. NCT02984449) and the protocol (version 2, 2016-Dec-19) has been approved by the Medical Ethical Review Board (METc) of the UMCG (No. 2016/464). If applicable, substantial amendments will be notified to the METc for approval and changes will be written into articles describing the results of the study. Results of this study will be submitted to a peer-reviewed scientific journal and can be presented at national and international conferences.

### Funding

The Heart-ROCQ study is financially supported by Edwards Lifesciences SA, Abbott (former St. Jude Medical Nederland B.V.) and 'Stichting Beatrixoord Noord-Nederland'. The sponsors are not involved in the design or execution of the study.

### Participants

Patients ( $\geq 18$  years) admitted to elective coronary artery bypass grafting (CABG), valve surgery, aortic surgery, or combined procedures are eligible. Patients accepted for congenital procedures,

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3 140 transcatheter aortic valve implantations (TAVI), aortic dissections, or aortic descending repair are  
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5 141 excluded. Other exclusion criteria are: inability to participate in all program elements of the Heart-  
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7 142 ROCQ program due to disorders of the nervous or musculoskeletal system that limits exercise  
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10 143 capacity, chronic obstructive pulmonary disease (COPD) with Global Initiative for Chronic  
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12 144 Obstructive Lung Disease (GOLD) criteria classification 3 or 4,(38) addiction to alcohol or drugs, a  
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14 145 serious psychiatric illness (i.e. recently experienced psychosis, bipolar disorder, diagnosis of  
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16 146 schizophrenia, serious cognitive, or neurological problems, and acute suicidal ideations or  
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18 147 behaviour), or when it is undesirable to exercise (i.e. hypertrophic cardiomyopathy, unstable angina,  
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20 148 advice from cardiologist); any treatment which is planned during one of the CR programs and which  
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22 149 is expected to interrupt attendance to the CR program (e.g. planned organ transplantation,  
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24 150 preoperative endocarditis, or planned chemotherapy etc.); playing a sport at (inter)national level;  
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26 151 being unable to read, write, or understand Dutch.

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### 30 31 153 Study enrolment, randomization and registry

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33 154 Figure 2 shows the flow chart of the Heart-ROCQ study. Patients on the waiting list of the thoracic  
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35 155 surgery department and meeting the study criteria for type of surgery are asked to participate by their  
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37 156 cardiologist. The cardiologist provides the patients with study information and an invitation to meet  
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39 157 the researcher at the preoperative consultation. At the preoperative consultation, the researcher will  
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41 158 obtain informed consent and conduct the baseline measurements. Eligible patients who have signed  
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43 159 informed consent and performed the baseline measurements, are randomised to the Heart-ROCQ  
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45 160 group or Standard Care group. Randomization (concealed group allocation in REDCap, random  
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47 161 blocks of 2-4, 1:1 ratio) is stratified for weight of the surgery (isolated CABG, single non-CABG [i.e.  
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49 162 replacement or repair of part of aortic or valve], 2 procedures or 3 procedures), gender, and age ( $\geq 65$   
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52 163 and  $< 65$  years). Prior to the start of the study, the randomization lists were created (using the 'ralloc'  
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54 164 function of Stata/SE, version 13.0) and imported into the secure data collection tool REDCap  
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56 165 (version 7.3.2), by an independent researcher. Medical staff and researchers are not blinded to  
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58 166 group allocation, because of logistic reasons. The primary end point is evaluated by an independent  
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60 167 end-point committee, blinded for group allocation.

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3 168 Patients who are not willing to participate are asked to give written consent for using data that  
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5 169 are collected during routine care. The data are collected in the Heart-ROCQ study registry to  
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7 170 increase insight into-potential differences between patients who participated in the study and patients  
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10 171 who did not. The Heart-ROCQ registry will thus provide more insight into the generalizability of the  
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12 172 results. Data from this registry are not used for the primary statistical analyses.  
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### 14 173 15 16 174 Intervention

#### 17 18 175 *Heart-ROCQ group*

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20 176 The Heart-ROCQ group receives a CR program at the Centre of Rehabilitation of the UMCG  
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22 177 (location Beatrixoord, which is located 6 km from the hospital of the UMCG) consisting of 3 phases.  
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24 178 The first phase is an outpatient preoperative optimization phase during the waiting period (3 times  
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26 179 per week, minimum of 3 weeks). The second phase is a post-operative inpatient CR phase (3 weeks,  
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28 180 weekdays only) followed by the third phase, an outpatient CR phase (2 times per week, for 4 weeks).  
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31 181 During each phase, all participants receive physical therapy including group sessions of inspiratory  
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33 182 muscle training (IMT),(39) strength training, aerobic cycling, breathing, coughing and relaxation. In  
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35 183 addition, patients have an assessment with a dietician and a psychologist and take part, when  
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37 184 indicated, in individual sessions to optimize their health. In addition, different group education  
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39 185 sessions are organized regarding coping with stress, awareness of risk factors, and maintaining a  
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41 186 healthy life style. Two additional modules, namely coaching to stop smoking and to return to work,  
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43 187 are available for patients who respectively smoke or are employed. A detailed description of the CR  
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45 188 program is given in the supplementary information.  
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#### 47 189 48 49 190 *Standard Care group*

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51 191 In the Netherlands, the current standard of care consists of a phase II outpatient CR program, which  
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53 192 is conducted at the referred hospital.(32,33) In general, this CR program starts 3 to 6 weeks after  
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55 193 discharge from the hospital and lasts for 6 weeks. The program consists of four educational sessions  
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57 194 (regarding risk factors and retaining a healthy life style) and physical therapy (2 times per week: 30  
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59 195 min. cycling together with 30 min. sports and games, relaxation therapy, or strength training).

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3 196 Furthermore, patients can be referred to a psychologist or a dietician when needed. The content of

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5 197 this CR program is based on the Dutch CR guidelines.(40)

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9 Composite primary end point: functional status, complications and events

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11 200 The primary outcome is a composite weighted score of functional status, post-operative surgical

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13 201 complications, readmissions to the hospital, and MACE. Each event is scored (ranging from 1 to 3

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15 202 points), separately. Table 1 shows an overview of the primary outcome and the scoring system.

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17 203 The scores of all events are combined to calculate a total score. Only the most serious complication

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19 204 is counted per event (e.g. when a percutaneous coronary intervention [score 1] is complicated by a

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21 205 stroke [score 2], the score will be 2 and not 3 [1 + 2]).

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23 206 The concept of the composite weighted score is adapted from the African-American Heart

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25 207 Failure Trial (A-HeFT).(41) Functional status is assessed through two health domains of the Medical

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27 208 Outcome Study 36-item General Health Survey (RAND-36 version 2)(42): physical functioning and

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29 209 physical health problems. The primary end point is evaluated at 3 months (T4) and 1 year (T6) after

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31 210 surgery (Figure 1). Deep wound infections and surgical re-explorations are screened up to 120 days,

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33 211 after surgery. Other post-operative surgical complications are measured in the period between the

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35 212 surgery and when a patient meets the UMCG discharge criteria (Table 2). Hospital admissions are

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37 213 checked between baseline and one year after surgery. To prevent bias (since the Heart-ROCC

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39 214 group follows the in-patient CR phase after surgery) hospital admissions between the day of

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41 215 admission before surgery and 30 days after surgery are not included when determining the

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43 216 (calculated) primary end point.

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47 218 Secondary outcomes

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49 219 *Complications and events*

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51 220 All individual components of the composite end point regarding the complications and events will be

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53 221 analysed separately as secondary outcomes. Table 3 summarizes the definitions of the secondary

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55 222 complications and events, including at the time of screening.

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3 223 All documents concerning the composite primary end point and the secondary complications  
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5 224 are encrypted and subsequently adjudicated by the independent end-point committee. The end-point  
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7 225 committee consists of four members (cardiologists and cardiothoracic surgeons), who are not  
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10 226 employed in the UMCG and are blinded for group allocation.  
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Table 1: definitions and score of the components of the composite primary end point

Functional status	Score
Worsening in physical functioning ( <i>domain score of health related quality of life, rand36_v2</i> ) <sup>†</sup>	1
No change or improvement in physical functioning <sup>†</sup>	0
Worsening in physical problem ( <i>domain score of health related quality of life, rand36_v2</i> ) <sup>†</sup>	1
No change or improvement in physical problem <sup>†</sup>	0
A clinical relevant worsening is classified as minimal change according to <i>Wyrwich et al., 2004</i> (43)	
<b>(Serious) Adverse Events</b>	
No serious adverse event	0
Prolonged mechanical ventilation <i>Mechanical ventilation longer than 24 hours</i>	1
Lung infection 1) A new lung radiographic infiltrate AND 2) two signs that the infiltrate is infectious origin (i.e. a) fever - body temperature >38°C or <36°C -, b) leukocytosis - white blood cells >10,000 or <4000, c) positive sputum culture AND/OR d) decline in oxygenation	1
Delirium 1) A DOS score ≥ 3 at hospital ward AND/OR 2) Diagnosis confirmed by a psychiatrist, geriatrist, or supervising specialist according to the DSM-IV criteria resulting in treatment with medication	1
Readmissions to intensive care unit <i>Unrelated to a secondary end point</i>	1
Deep wound infection <i>Deeper tissues are affected (muscle, sternum, and mediastinum) and must include: 1) surgical drainage / re-fixation OR 2) an organism is isolated from culture of mediastina tissue or fluid, OR 3) antibiotic treatment, because of sternum wound</i>	2
Readmissions to hospital <i>An unplanned hospital stay with different dates of admission and discharge with a medical indication (i.e. clinical signs and symptoms or change of treatment)</i>	1
Any cardiothoracic surgical interventions <i>Graft- or valve failure, CABG, valve, aortic, or other cardiac surgery<sup>‡</sup></i>	2
Any percutaneous interventions <i>PCI, TAVI, etc.</i>	1
Myocardial infarction <i>According to the third universal definition of myocardial infarction<sup>§</sup></i>	2
Cerebral vascular accident / stroke <i>Acute neurological event of at least 24 hours of duration, with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnosis of stroke requires confirmation by CT, MRI, or pathological confirmation.</i>	2
Sudden death survivor <i>The sudden onset of symptoms, such as chest pain and cardiac arrhythmias, ventricular tachycardia, which lead to the loss of consciousness and cardiac arrest followed by reanimation and does not lead to biological death.</i>	2
Death <i>All-cause mortality</i>	3
Total score = sum of physical status and SAE's at 3 months and 1 year (worst score of each event)	

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<sup>†</sup>Compared with baseline; <sup>‡</sup>According to the definitions of the 'Begeleidingscommissie Hartinterventies Nederland'; <sup>§</sup>Thygesen et al., 2012(44); DOS: Delirium Observation Screening scale(45); CABG: Coronary arterial bypass graft; PCI: Percutaneous coronary intervention; TAVI: Transcathetic aortic valve implantation; In gray: post-operative complications can be scored ones; SAE: Serious adverse event.

Table 2: Discharge criteria of the University Medical Centre Groningen (UMCG)

- 1) no drain, no external pacemaker lead, no infusion, or oxygen present,
- 2) stable clinical conditions (stable lab results, X-ray, and haemodynamic parameters),
- 3) able to perform basic activity of daily living (ADL)-activities (i.e. going independently to the toilet).

Table 3: definitions of the secondary complications and events

Definitions	Time of measure
Atrial fibrillation <i>New onset of atrial fibrillation or atrial flutter requiring medical treatment or cardioversion</i>	Surgery to T3
Prolonged ICU stay <i>When the number of calendar days is two or more from ICU admission to discharge</i>	Initial stay
Readmissions to hospital <i>The number of unplanned hospital stays with different dates of admission and discharge with a medical indication (i.e. clinical signs and symptoms or change of treatment)</i> a) directly related to a cardiac cause b) not directly related to a cardiac cause	Baseline to T6 <sup>§</sup>
Hospitalisation days <i>Total number of days of hospitalisation</i> a) directly related to a cardiac cause b) not directly related to a cardiac cause	Baseline to T6 <sup>§</sup>
Cardiovascular death <i>Any death due to proximate cardiac or cardiovascular cause (e.g. Myocardial infarct, low-output failure, fatal arrhythmia, death secondary to a cerebral vascular accident, pulmonary embolism, ruptured or dissecting aortic aneurysm, or other vascular diseases), un-witnessed death, and death of unknown cause, and all procedure related deaths (e.g. PCI, CABG), including those related to concomitant treatment<sup>†</sup>.</i>	Baseline to 5 years after surgery
Non-cardiovascular death <i>Any death not covered by above definition, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma</i>	Baseline to 5 years after surgery
<b>Concerning safety</b>	
Surgical re-exploration for bleeding/ tamponade <i>Surgical incision into the sternum as a result of a bleeding or tamponade</i> a) acute: presented within 24 hours after surgery b) late: presented after 24 hours after surgery	Surgery to T4
Surgical re-exploration dehiscence <i>Aseptic wound dehiscence</i>	Surgery to T4

<sup>†</sup>Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) will be classified as cardiac death; <sup>§</sup>Not measured between the day of admission before surgery and 30 days after surgery, because of POST-in phase of Heart-ROCQ program; ICU: Intensive care unit; T4: Follow-up at 3 months after surgery; T6: Follow-up at 12 months after surgery.

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### 241 *Questionnaires and physical tests*

242 Table 4 shows the physical tests and questionnaires of the secondary outcomes regarding physical  
243 and psychological health, life style risk factors, and the economic evaluation. Physical tests and  
244 questionnaires are completed at six assessment points (Figure 1). The preoperative measurements  
245 (T1 and T2) are conducted at the start (preoperative consultation) and the end (1 to 8 days before  
246 surgery) of the waiting period. The third measurement (T3) is performed when patients meet the  
247 UMCG discharge criteria (Table 2). The follow-up measurements (T4, T5, and T6) are at 3, 7, and 12  
248 months after surgery. Patients are asked to fill in questionnaires online or when requested on paper,  
249 prior to the visits for the physical tests. All adverse events reported spontaneously by the patient or  
250 observed by the investigator are recorded. In addition, serious adverse events are reported to the  
251 METc. Data are stored in REDCap and on a secure drive at the department CardioResearch in the  
252 UMCG. Two times per year, the study is monitored by a trained research monitor from another  
253 department of the UMCG. Details of procedures, data collection, management and monitoring can be  
254 found in the Trial Master File of the Heart-ROCQ study (can be obtained by the investigators). On the  
255 12<sup>th</sup> of June 2018, the study was audited and certified for the ISO 9001: 2015 independently by DNV  
256 GL.

### 258 Potential moderators

259 Preoperative risk profile (i.e. Euroscore II, medical history, life style risk factors, physical, and mental  
260 status), surgery parameters, and demographics are collected from the medical record and baseline  
261 measurements. The content of the CR program is described in terms of compliance, duration of CR  
262 program, type of treatment, frequency, and training load (i.e. for bicycle training: external workload,  
263 heart rate response, rate of perceived exertion using the Borg scale, and for strength training: sets,  
264 repetitions, and intensity) for both the Heart-ROCQ group as the Standard Care group.

Table 4: Time of measure, physical tests, and questionnaires of the secondary outcomes

Secondary outcomes	Measure	Time of measure
<i>Physical health</i>		
Cardiorespiratory fitness	6MWT(46)	T1-T4, T6
Muscle strength	STS_10, grip & leg strength(47,48)	T1-T4, T6
Independence in ADL	KATZ(49,50)	T1, T4, T6
<i>Psychological health</i>		
General anxiety	GAD-7(51)	T1,T2, T4, T6
Feelings of depression	PHQ-9(52,53)	T1,T2, T4, T6
Health related Quality of Life	Rand-36_v2(42)	T1, T4, T6
<i>Life style risk factors</i>		
Physical activity	iPAQ(54) & Actigraph <sup>†</sup> (55)	T1, T4, T6
Obesity indices	BMI, waist-to-hip ratio	T1, T4, T6
Smoking behaviour	Number of cigarettes per day	T1, T4, T6
<i>Economic evaluation</i>		
Health care use & related medical costs	iMCQ(56)	T1, T4-T6
Work participation <sup>‡</sup>	iPCQ(57)	T1, T4-T6
QALYs	EQ-5D-5L(58)	T1, T4-T6
<i>Potential mediators</i>		
Cardiac self-efficacy	CSE(59)	T1, T2, T4, T6
Illness representations	IPQ-R(60)	T1, T2, T4, T6

<sup>†</sup>Patients are asked to wear the Actigraph during waking hours for 1 consecutive week; <sup>‡</sup>Health-related productivity losses of paid work and unpaid work; T1: Begin of waiting time; T2: 1 to 8 days before surgery; T3: Moment that patients meet the UMCG discharge criteria; T4-T6: Follow-up at 3, 7, and 12 months after surgery; 6MWT: Six minutes walking test; STS\_10: Ten times sit to stand test; ADL: Activities of Daily Living; KATZ: Katz Index of Independence in Activities of Daily Living; GAD-7: Generalized Anxiety Disorder 7-item scale; PHQ-9: Patient Health Questionnaire 9-item scale; iPAQ: International Physical Activity Questionnaire; BMI: Body Mass Index; iMCQ: iMTA Medical Cost Questionnaire; iPCQ: iMTA Productivity Cost Questionnaire; QALY: Quality-adjusted life years; EQ-5D-5L: EuroQol five-dimensional questionnaire; CSE: Cardiac Self-efficacy; IPQ-R: Illness Perception Questionnaire, Revised.

#### Potential mediators

Illness perceptions (i.e. patients mental representations of their illness based on different sources of information) are measured with three subscales (personal control, treatment control, and consequences) of the revised illness perception questionnaire (IPQ-R).(60) These subscales are chosen because of their sensitivity to change and because of their relation to psychological distress(61). The cardiac self-efficacy (CSE) scale(59) is used to measure CSE (i.e. patients confidence to perform a specific task related to cardiac disease).

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### 283 Statistical analyses

#### 284 *Sample size*

285 Assuming a normal distribution, the mean weighted score of the primary end point is estimated on  
286 1.0 with a standard deviation of 0.9 at 1 year after surgery. This estimation is based on historical data  
287 of the UMCG, an unpublished on-going pilot study in the UMCG, the Dutch registration database,(62)  
288 and data reported in literature.(6,63–65) A decrease of 0.3 is expected in the Heart-ROCQ group,  
289 based on previous studies comparing CR with standard care(36,64,66) (i.e. no CR) and is  
290 considered to be clinically relevant (i.e. on average a 30% decrease in complications/events or  
291 worsening in functional status or 10-20% decrease in MACE or death). To detect this decrease and  
292 achieve 80% power (significance level of 5%) a group of 286 patients (143 in the Heart-ROCQ group  
293 and 143 in the Standard Care group) is needed. To incorporate a withdrawal of  $\pm 20\%$  a total sample  
294 size of 350 is needed at baseline.

#### 296 *Interim analysis*

297 An interim analysis will be conducted when 40% of the included patients have had the  
298 measurements one year after surgery. The study will be terminated prematurely when the primary  
299 outcome of one of the CR programs is obviously ( $P < 0.001$ ) different from the other CR program.

#### 301 *Primary and sensitivity analyses*

302 All end points are primary analysed according to the 'intention-to-treat' principles and missing values  
303 are counted as worst-case score (nominal variables) or estimated using Maximum Likelihood  
304 estimation (interval variables). As supplementary analyses, the end points are analysed on a per-  
305 protocol principle with and without using imputation methods for missing values. In all analyses, a  
306 two-sided  $p < 0.05$  is considered statistically significant.

307 Statistical methods and clinical relevance for analysing secondary outcomes are written in the  
308 research protocol (ClinicalTrials.gov : NCT02984449).

### *Economic evaluation*

For the evaluation of health-care utilization, standard prices published in the Dutch costs guidelines are used.<sup>(67)</sup> To compare the costs to quality adjusted life years (QALYs), QALYs are estimated with use of the EQ-5D-5L.<sup>(58)</sup> Utility values for the EQ-5D-5L are calculated based on the new Dutch tariff.<sup>(68)</sup> Results from the analysis are reported as an Incremental Cost Effectiveness Ratio (ICER), dividing the difference in effect, by the difference in costs. Bootstrap re-sampling will be performed, and cost-effectiveness acceptability curves will be plotted, to estimate the probability that the Heart-ROCQ program is cost effective when compared to standard care. A societal perspective is applied.

### Study status

From May 2017 to December 2018, 75 patients were enrolled. In following years we expect that the enrolment will increase to 85 patients per year. The last patient is expected to be included in July 2021.

### Patient and public involvement

In a pilot study (to be submitted) the patient satisfaction and the feasibility (in terms of accessibility, compliance, training load and safety) of the Heart-ROCQ program have been evaluated. Patients were very satisfied with the program and scoring it eight out of ten, therefore we did not change the content of the program. However, patients' rate of perceived exertion was generally quite low and no serious adverse events occurred during the bicycle training. For safety reasons the intensity was not increased. However, in order to estimate the maximum load more accurately and better tailor the program to the individual, we decided to change one of the stop criteria of the preoperative submaximal ergometry test from 70% to 90% of expected maximal heart rate. Furthermore, our outcomes are, among others, based on the reasons why patients recommended the program to other patients. For example, patients reported that their self-efficacy and physical capacity were improved, so we added the CSE questionnaire and physical tests to objectively measure these outcomes. In this way the results were taken into account in the further development of the Heart-ROCQ program and the protocol of this study. The results of this trial will be distributed by various

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338 information channels (e.g. websites of cardiac patient organisations, social media). Two to three  
339 times a year we provide a newsletter about the progress and (in the end) the results of the study are  
340 sent to patients, who are interested.

For peer review only

## DISCUSSION

The Heart-ROCQ study is the first randomised clinical trial evaluating the effect of a combination of pre- and post-operative CR program compared to a post-operative CR program. Unlike the vast majority of CR programs in previous studies, the current program is multidisciplinary targeting different aspects of surgical outcomes in patients undergoing cardiac surgery. Because different aspects are targeted, a composite weighted score will better reflect the treatment benefits than a single outcome. Therefore, the primary end point is a composite end point of functional status, post-operative surgical complications, readmissions to the hospital and MACE. The components of the end point are of clinical importance to patients undergoing cardiac surgery and reflect a comprehensive representation of the recovery of the patient.

Both the ideas of the combined primary end point and the weighting of the individual components were derived from other studies.(41,69,70) Assigning different weights to the components was needed for more accurate comparison. Since the components are not equal in clinical importance, equal weights would lead to inaccurate statistical analysis(70). In the current study, the weighted score of HRQoL is lower (1 point instead of 2 points) to minimize bias due to patients' knowledge of group allocation. Therefore, improvements in quality of life are not counted in the primary end point to prevent bias in a positive direction. This also prevents that a score in quality of life and adverse event cancel each other out (e.g. when a patient experiences an improvement in Quality in Life [+2 points] and has a stroke [-2 points] then the total score is 0). The scores of all-cause mortality, stroke, myocardial infarction and revascularization are in line with the results showed by Tong and colleagues (2013)(70). A disadvantage of composite end points is that the effect may be driven by complications that occur with the greatest frequency.(71) Therefore, post-operative complications which occur frequently, such as atrial fibrillation, are evaluated separately as secondary end point. The primary end point is evaluated by an end-point committee, which is blinded to group allocation and consists of four independent cardiologists and cardio-thoracic surgeons.

Previous preoperative CR studies were primarily focused on short-term effects; only one preoperative CR study and a few post-operative CR studies have determined long-term



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3 368 effects.(23,35,36,72) In contrast to previous preoperative CR studies, the Heart-ROCQ study sets  
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5 369 out to investigate both short- and long term effects of the CR programs.(23,35,36) Due to the trends  
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7 370 in, among others, increasing age, obesity, and physical inactivity, patients undergoing cardiac  
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9 371 surgery are becoming more complex. The Heart-ROCQ program aims to address these issues,  
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11 372 which make the program clinically relevant for all cardiac surgery patients. Therefore, we chose to  
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13 373 include different types of cardiac surgery. Since different moderators and mediators are assessed  
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15 374 before, during and after CR, we can explore which factors are associated with better outcomes and  
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17 375 which working mechanisms contribute to its effectiveness. These findings may provide a more in-  
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19 376 depth understanding of who benefits the most from CR in both the short and long term and the  
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21 377 underlying mechanisms of CR, which are still not fully understood in patients undergoing cardiac  
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23 378 surgery.(35) In addition, the present study is thought to considerably contribute to the evidence to  
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25 379 further develop guidelines for clinical practice, especially regarding the preoperative CR program.(73)  
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29 380 The Heart-ROCQ program is expected to be cost-effective in the long-term, which is also of  
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31 381 interest for policymakers and health care providers. Therefore, an economic evaluation is performed  
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33 382 to assess the cost-effectiveness of CR, since little is known about the cost-effectiveness of CR.(64) A  
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35 383 societal perspective of this economic evaluation is chosen, meaning that not only health-care costs,  
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37 384 but also patient- and productivity related costs and benefits are taken into account. If the Heart-  
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39 385 ROCQ program is proven to be effective, it might be advisable to include a supportive prevention-  
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41 386 oriented waiting period prior to surgery as an integral part of the treatment for patients undergoing  
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43 387 elective cardiac surgery. This implies a paradigm shift from curative care following cardiac surgery to  
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45 388 an additional preventive care attitude before surgery. Extensions of rehabilitation options in, or in the  
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47 389 vicinity of cardiac centres, will then be required.

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49 390 The Heart-ROCQ study is the first randomised clinical trial comparing the effect of a  
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51 391 combined pre- and post-operative CR program to a regular Dutch phase II post-surgery outpatient  
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53 392 rehabilitation CR program in a population undergoing elective cardiac surgery. This study is expected  
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55 393 to provide new understanding of the effectiveness and underlying working mechanisms of CR, and  
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57 394 subsequently to improve value-based health care.  
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### Declaration of interest

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### Authors' contributions

Conception and design of the study: JH, FZ, MJLdJ, MFR, WD, JF, LHVvdW, PvdH, and MAM; Methodology: JH, FB, SD, MJLdJ, MFR, and PvdH; Acquisition of data: JH, FB and SD; Writing – Original draft, tables, and figures: JH; Writing- Reviewing and Editing: FB, SD, MJLdJ, MFR, WD, ICCvdH, JF, LHVvdW, PvdH, and MAM; Supervision: MJLdJ, MFR, WD, JF, ICCvdH, LHVvdW, PvdH, and MAM; Funding Acquisition: JH, SD, JF, LHVvdW, PvdH, and MAM. All authors approved the final version of the manuscript.

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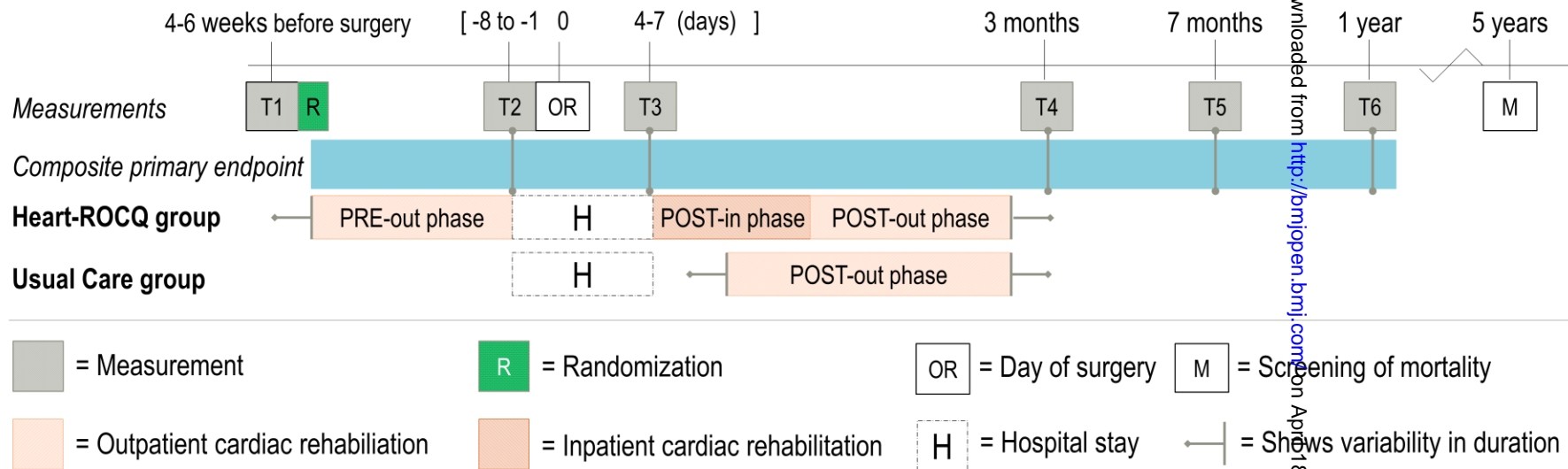
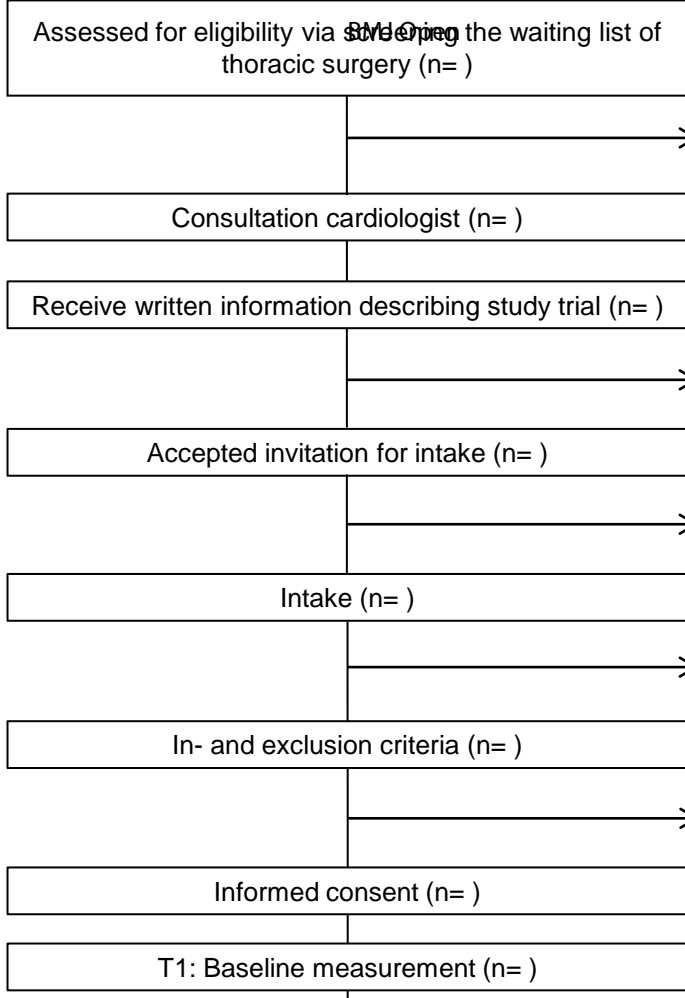


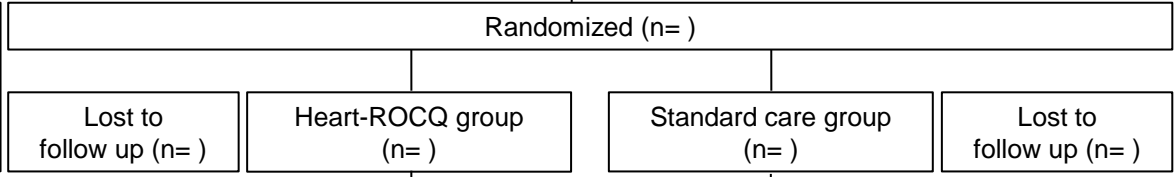
Figure 1: Research design of the Heart-ROCQ PROBE trial. The phases of both cardiac rehabilitation programs and the measurements are shown relative to the moment of surgery.



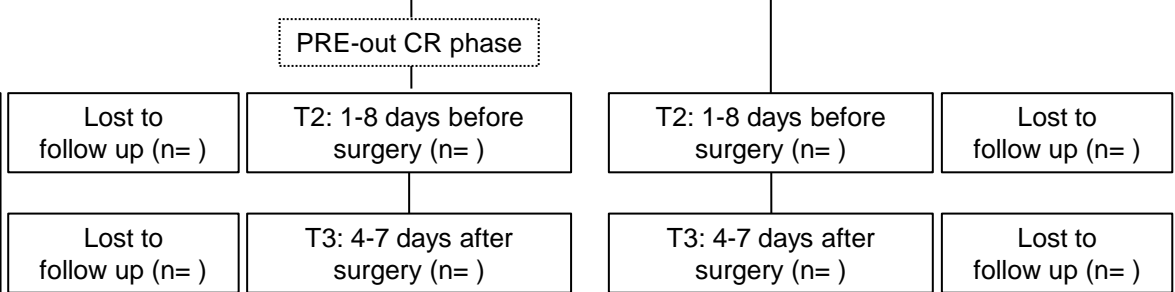
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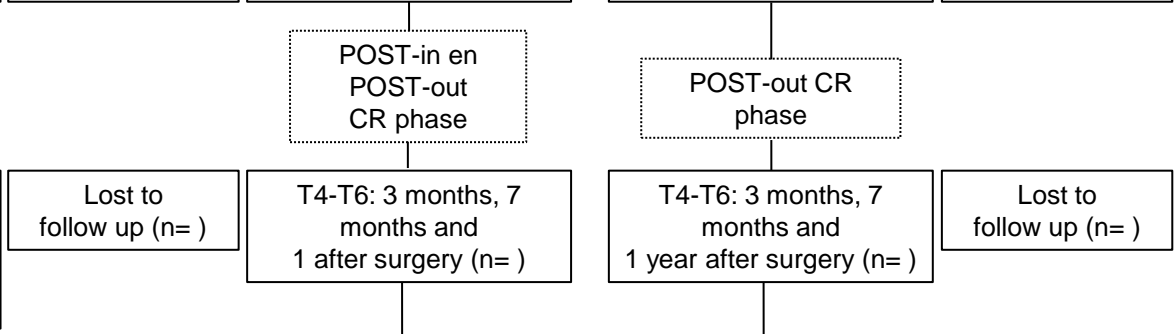
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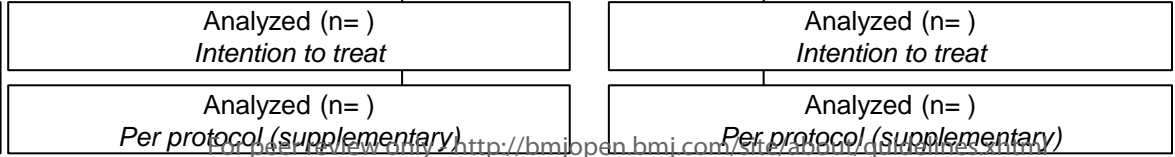
Short-term



Follow-up



Analyses



## SUPPLEMENTARY INFORMATION - DESCRIPTION OF THE HEART-ROCQ PROGRAM

<b>PRE-out phase – An outpatient cardiac rehabilitation phase during the waiting period</b>			
<i>Three times per week, a minimum of three weeks</i>			
<b>Physical therapy</b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients physical capacity before surgery</li> <li>- Patient learns to apply the stress-strain training principles</li> <li>- To optimize pulmonary muscle strength</li> <li>- Patient knows which breathing and coughing techniques should be used after surgery to prevent pulmonary complications</li> </ul>			
When needed:			
<ul style="list-style-type: none"> <li>- Patient learns to recognize body signals and boundaries.</li> <li>- Patient is able to exercise despite of possible kinesiphobia</li> </ul>			
<b>Type of exercise</b>	<b>Frequency</b>	<b>Intensity</b>	<b>Monitoring</b>
IMT	3 x p / wk	<ul style="list-style-type: none"> <li>- 6 cycles of 6 repetitions,</li> <li>- rest periods of resp. 60, 45, 30, 15 and 5 s.</li> <li>- 60-80% of maximal inspiratory pressure<sup>65</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Week 1: each training ↑ intensity with 10%</li> <li>- Intensity ↑ with 5% if RPE &lt;5<sup>1</sup></li> </ul>
Aerobic cycle	3 x p / wk	<ul style="list-style-type: none"> <li>- 25 min. at RPE 3<sup>1</sup></li> <li>- Interval training will be given, if the patient is not able to perform endurance training.</li> </ul>	<ul style="list-style-type: none"> <li>- First training: 50% of POpeak</li> <li>- Load ↑ if RPE &lt; 3<sup>1</sup></li> <li>- Interval training: guided by complaints and RPE of 3</li> </ul>
Resistance training	3 x p / wk	<ul style="list-style-type: none"> <li>- 1-3 cycles of 10-15 repetitions</li> <li>- Rest: 30-60 s.</li> <li>- 50-80% of estimated 1RM</li> <li>- On six fitness apparatus</li> </ul>	<ul style="list-style-type: none"> <li>- First training: 6-10 RM per fitness apparatus</li> </ul>
Body awareness	1 x p / 2 wks	<ul style="list-style-type: none"> <li>- 30 min. breathing and relaxation techniques</li> </ul>	Not Applicable
Group education	Two sessions	<ul style="list-style-type: none"> <li>- Basic training principles</li> <li>- Forced expiration, huff- and cough techniques</li> </ul>	Not Applicable
<b>Dietary advice<sup>2</sup></b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients nutritional status</li> <li>- Patient knows which nutrients are important focusing on the surgery</li> <li>- Patients knows the importance of food in relation to cardiovascular disease and cardiovascular risk management</li> </ul>			
<b>Type</b>	<b>Frequency</b>	<b>Content</b>	
Intake interview	One session	- Anamnesis about nutritional status	
Counselling	On indication	- Individual sessions according to existing guidelines	
Group education	One session	- 60 min., cardiovascular risk factors and dietary intake	
<b>Psychological guidance<sup>2</sup></b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To optimize mental status of the patients before surgery</li> <li>- Patient has made a start with the awareness of cardiovascular risk factors</li> </ul>			
Intake interview	One session	- Anamnesis about mental status	
Counselling	On indication	- Individual sessions according to evidence-based treatment protocols dependent on mental problems of patient <sup>3</sup>	
Group education	One session	- Coping with psychological tension/stress, to process the mental trauma of cardiac surgery, and risk factors	
<b>No-smoking consultation (For patients who smoke)</b>			
<u>Aim</u>			
- Patient gives up smoking during the waiting time before surgery			
Intake interview & counselling	One session per wk	- 30 min., individual session based on existing guidelines	

IMT: Inspiratory muscle training; RPE: Rate perceives exertion; POpeak: Maximum power output achieved during submaximal Ergometry test. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Involvement of partner/relatives during group and individual sessions; <sup>3</sup>like cognitive behavioural therapy, eye movement desensitization and reprocessing (EMDR), acceptance and commitment therapy etc.

<b>POST-in phase – An inpatient cardiac rehabilitation phase</b>			
<i>Starting 4-7 days after surgery, duration of three weeks, weekends at home</i>			
<b>Physical therapy</b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- To recover patients physical capacity</li> <li>- Patient performs breathing and coughing techniques to prevent pulmonary complications</li> <li>- Patient mobilize and can perform activities of daily living independently</li> <li>- Patient knows about risk factors according to physical activity, knows the ACSM recommendations (moderate-intensity cardiorespiratory exercise training for ≥30min/day ≥5 days/week or vigorous-intensity cardiorespiratory exercise training for ≥20 min/day on ≥3 days/week or a combination<sup>66</sup>) and makes a plan to apply the ACSM recommendations in his own life</li> <li>- Patient works on personal goals</li> </ul>			
Type of exercise	Frequency	Intensity	Monitoring
Individual therapy	2 x p / day	<ul style="list-style-type: none"> <li>- Practice at transfers, walking, and climbing stairs</li> <li>- Very light mobilizing exercises for upper extremity</li> </ul>	<ul style="list-style-type: none"> <li>- During the first 2 days of this phase.</li> <li>- Extended, if patient is not able to participate in the group sessions.</li> </ul>
Individual therapy	2 x p / wk	<ul style="list-style-type: none"> <li>- Attention to personal goals</li> </ul>	<ul style="list-style-type: none"> <li>- Week 2 and 3</li> </ul>
IMT <sup>2</sup>	3 x p / wk: 2 x under supervision, 1 x without supervision	<ul style="list-style-type: none"> <li>- 6 cycles of 6 repetitions, - rest periods of resp. 60, 45, 30, 15 and 5 s.</li> <li>- intensity of 60-80% of maximum inspiratory pressure<sup>65</sup></li> </ul>	<ul style="list-style-type: none"> <li>- First training: 50% of resistance of last preoperative training</li> <li>- Intensity ↑ with 5% if RPE &lt;5<sup>1</sup></li> <li>- IMT stops when resistance of preoperative training is reached</li> </ul>
Aerobic cycle <sup>2</sup>	1 x p / day	<ul style="list-style-type: none"> <li>- Week 1: duration of 5-20 min. at light intensity (RPE 2<sup>1</sup>)</li> <li>- Week 2 and 3: Work up to 25 min. at moderate intensity (RPE 3<sup>1</sup>)</li> <li>- Interval training will be given, if the patient is not able to perform endurance training.</li> </ul>	<ul style="list-style-type: none"> <li>- First training: at 50% of power output of last preoperative training</li> <li>- Load ↑ if RPE &lt; 2 à 3<sup>1</sup></li> <li>- Interval training: guided by complaints and RPE of 3.</li> </ul>
Resistance training <sup>2</sup>	3-4 x p / wk	<ul style="list-style-type: none"> <li>- 3 cycles of 15-20 repetitions</li> <li>- Rest periods of 30-60 seconds</li> <li>- On 6 fitness apparatus</li> </ul>	<ul style="list-style-type: none"> <li>- First training: 50% of resistance of last preoperative training for LE and 25% for UE.</li> <li>- Gradual build up to 50-80% van 1RM based on RPE 3<sup>1</sup></li> </ul>
Body awareness <sup>2</sup>	1 x p / wk	<ul style="list-style-type: none"> <li>- 30 min. breathing and relaxation techniques</li> </ul>	Not Applicable
<b>Dietary advice<sup>3</sup></b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients nutritional status</li> <li>- Patient knows which nutrients are important focusing on the recovery of surgery</li> <li>- Patients knows the importance of food in relation to cardiovascular disease and cardiovascular risk management</li> </ul>			
Type	Frequency	Content	
Intake interview	One session	- Anamnesis about nutritional status post-surgery	
Counselling	Sessions on indication	- Treatment according to existing guidelines	
Group education	One session	- 90 min., skills needed to maintain a healthy life style	
<b>Psychological guidance<sup>3</sup></b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- Patient start to process the mental trauma of cardiac surgery and the consequences of it</li> <li>- Patient has self-management competence to maintain a healthy life style</li> <li>- Patient and partner/relatives are able to support each other in the processing process</li> </ul>			
Intake interview	One session	- Anamnesis about mental status post-surgery	
Intake interview & counselling	Sessions on indication	- Individual sessions according to evidence-based treatment protocols dependent on mental problems of patient <sup>4</sup>	
Group education	One session	- 90 min., processing the cardiac surgery: possible reactions en consequences, coping with stress and healthy life style	

IMT: Inspiratory muscle training; RPE: Rate perceives exertion; LE: Lower extremities; UE: Upper extremities. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Group sessions start from day three of the inpatient phase or when patient is able to perform in the group activities; <sup>3</sup>Involvement of partner/relatives during group and individual sessions; <sup>4</sup>like cognitive behavioural therapy, eye movement desensitization and reprocessing (EMDR), acceptance and commitment therapy etc.

<b>POST-in phase – An inpatient cardiac rehabilitation phase (continuation)</b>		
<i>Starting 4-7 days after surgery, duration of three weeks, weekends at home</i>		
<b>No-smoking consultation<sup>1</sup> (For patients who smoke)</b>		
<u>Aim</u>		
- Patient is still motivated to stop smoking or patient is motivated to give up smoking (when patient did not give up smoking before cardiac surgery).		
Intake interview & counseling	1 x p / wk	- 30 min., individual sessions based on
Group education	One session	- 60 min., general information about smoking addiction and support from fellow smokers
<b>Return to work consultation<sup>1</sup> (for patients who are employed)</b>		
<u>Aim</u>		
- Patient is informed about laws and regulation for illness, social security contributions, and medical examinations		
- Patient knows their rights and obligations, the rights and obligations of the employer, the working conditions agency, the employee insurance agency, and re-integration companies		
- Patient received tools to return adequately back to work (knows positive and negative factors that can impact the re-integration)		
Group education	One session	- 60 min., laws and regulation for illness, procedures, roles, rights and obligations of different involved persons, communication to involved persons (e.g. colleagues, employer), working during rehabilitation, positive and negative factors regarding to return to work
Counseling	Sessions on indication	- Individual sessions with labour consultant dependent on problems of patient

<sup>1</sup>Involvement of partner/relatives during group and individual sessions.

**POST-out phase – An outpatient cardiac rehabilitation phase***Starting on Tuesday after discharge of the POST-in phase, two times per week, four weeks***Physical therapy**Aim

- Patient has optimized his/her physical capacity
- Patient knows his/her boundaries and limitations
- Patient knows about cardiovascular risk factors according to physical activity, knows the ACSM recommendations (moderate-intensity cardiorespiratory exercise training for  $\geq 30$  min/day  $\geq 5$  days/week or vigorous-intensity cardiorespiratory exercise training for  $\geq 20$  min/day on  $\geq 3$  days/week or a combination<sup>65</sup>) and makes a plan to apply the ACSM recommendations in his own life
- Patient resumes his/her work or hobbies
- Patient experiences pleasure during exercise
- Patients achieves their personal goals

Type of exercise	Frequency	Intensity	Monitoring
Aerobic cycle	2 x p / wk	Depending on trainability of patient - 25 min. at 50-80% HRR or RPE 5 <sup>1</sup>	- Work up to 25 minutes at moderate intensity (RPE 3 <sup>1</sup> ), when patient was not able to do it in POST-in phase - Load $\uparrow$ if RPE < 5 <sup>1</sup> or HRR < 50-80%
Resistance training	2 x p / wk	UE: - 3-4 cycles of 10-15 repetitions - Rest: 30-60 s. - 50-80% of estimated 1RM - On six fitness apparatus LE: - Focus on mobilization in week 1 & 2 - Focus on strength and endurance in week 3 & 4	- UE: Load $\uparrow$ if RPE < 5 <sup>1</sup> - LE: Under guidance of complaints
Sport and games	1 x p / wk	Focus on: - Experiencing pleasure during exercise, regaining trust and handling boundaries. - Exploring different types of sports and knowing the possibilities after CR	
Swimming	1 x p / wk		
Education	1 x p / wk	- Training principles of POST-out phase and a repetition of ACSM recommendations - Awareness of exercise after CR; making a plan to exercise after CR - Explanation of the results of the exercise test - Discussing the plan to exercise, share experiences to expand exercise in home situation	

**Dietary advice, psychological guidance, no-smoking consultation, and return to work consultation**

Individual sessions are continued when aims are not achieved

RPE: Rate perceives exertion; HRR: Heart rate reserve; LE: Lower extremities; UE: Upper extremities; ACSM: American College of Sports Medicine; CR: Cardiac Rehabilitation. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Involvement of partner/relatives during group and individual sessions.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 3, 6 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ 3, 6 ___
Protocol version	3	Date and version identifier	___ 6 ___
Funding	4	Sources and types of financial, material, and other support	___ 7 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1, 19 ___
	5b	Name and contact information for the trial sponsor	___ 1 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 7 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ 7, 8, 10, 13 ___

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1	<b>Introduction</b>			
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3	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___ 4, 5 ___
4				
5				
6		6b	Explanation for choice of comparators	___ 4, 5 ___
7				
8	Objectives	7	Specific objectives or hypotheses	___ 5 ___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___ 6, 7, ___
11				
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14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___ 6 ___
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18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___ 7 ___
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___ 9 ___
23				
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___ NA ___
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___ 13 ___
27				
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 7 ___
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___ 10-14 ___
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34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___ 6-14 ___
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___15___
2				
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___7, 8, 16___
5				

### 6 **Methods: Assignment of interventions (for controlled trials)**

#### 7 Allocation:

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10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___7, 8___
11				
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___7, 8___
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___7, 8___
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23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___7, 8___
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___NA___
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### 31 **Methods: Data collection, management, and analysis**

32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___11-14___
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___NA___
40				
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13__
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__15, 16__
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__15__
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10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__15__
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14	<b>Methods: Monitoring</b>			
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16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__13__
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__15__
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__13__
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__13__
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32	<b>Ethics and dissemination</b>			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__6__
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36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__6__
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___7, 8___
2				
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___7, 8___
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___13___
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___19___
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___13___
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16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___13___
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___6___
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	___6___
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___NA___
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29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___13___
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	___NA___
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license.

# BMJ Open

## HEART Rehabilitation in patients awaiting Open-heart surgery targeting to prevent Complications and to improve Quality of life (Heart-ROCQ): Study protocol for a Prospective Randomised Open Blinded End-point (PROBE) trial

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Manuscripts

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9 4 **HEART** Rehabilitation in patients awaiting **Open**-heart surgery targeting to prevent **Complications**  
10 and to improve **Quality of life** (Heart-ROCQ) - Study protocol for a **Prospective Randomised Open**  
11 **Blinded End-point** (PROBE) trial  
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## 31 ABSTRACT

### 32 Introduction

33 The rising prevalence of modifiable risk factors (e.g. obesity, hypertension, and physical inactivity) is  
34 causing an increase in possible avoidable complications in patients undergoing cardiac surgery. This  
35 study aims to assess whether a combined pre- and postoperative multidisciplinary cardiac  
36 rehabilitation (CR) program (Heart-ROCQ program) can improve functional status and reduce  
37 surgical complications, readmissions and major adverse cardiac events (MACE) as compared to  
38 standard care.

### 39 Methods and analysis

40 Patients (n=350) are randomised to the Heart-ROCQ program or standard care. The Heart-ROCQ  
41 program consists of a preoperative optimization phase whilst waiting for surgery (3 times p/week,  
42 minimum 3 weeks), a post-operative inpatient phase (3 weeks) and an outpatient CR phase (2 times  
43 p/week, 4 weeks). Patients receive multidisciplinary treatment (e.g. physical therapy, dietary advice,  
44 psychological sessions, and smoking cessation). Standard care consists of 6 weeks post-surgery  
45 outpatient CR with education and physical therapy (2 times p/week). The primary outcome is a  
46 composite weighted score of functional status, surgical complications, readmissions, and MACE and  
47 is evaluated by a blinded end-point committee. Secondary outcomes are length of stay, physical, and  
48 psychological functioning, life style risk factors, and work participation. Finally, an economic  
49 evaluation is performed. Data is collected at six time points: at baseline (start of the waiting period),  
50 the day before surgery, at discharge from the hospital, and at 3, 7, and 12 months post-surgery.

### 51 Ethics and dissemination

52 This study will be conducted according to the principles of the Declaration of Helsinki (version 8,  
53 October 2013). The protocol has been approved by the Medical Ethical Review Board (METc) of the  
54 UMCG (No. 2016/464). Results of this study will be submitted to a peer-reviewed scientific journal  
55 and can be presented at national and international conferences.

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2  
3 56 **Registration:** The Heart-ROCQ study has been registered at ClinicalTrials.gov (No. NCT02984449).  
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6 57 **Data sharing statement:** Data are available upon reasonable request after the results have been  
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8 58 published.  
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### 10 11 59 **Strength and limitations of this study** 12

- 13
- 14 60 • A prospective randomised open, blinded end-point (PROBE) trial
- 15
- 16 61 • Comparison of a unique multidisciplinary pre- and post-operative CR program with a standard  
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18 62 care post-operative outpatient CR program
- 19
- 20 63 • Patient-oriented: primary and secondary outcomes provide a comprehensive and clinically  
21  
22 64 relevant evaluation of patients' recovery from surgery (e.g. on physical, psychological, social  
23  
24 65 domains)
- 25
- 26 66 • Both short- and long term effects of the CR programs are included
- 27
- 28 67 • Single centre study, albeit that patients are referred from four hospitals
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## 68 INTRODUCTION

69 The leading cause of death in Western countries is ischemic heart disease.(1) One of the treatments  
70 for severe ischemic heart disease is cardiac surgery. The risk of post-operative complications related  
71 to cardiac surgery is substantial; pulmonary complications (up to 33%), delirium (~26%), and  
72 arrhythmias (~30%) have been reported to occur.(2–4) These complications are associated with  
73 prolonged hospitalisation, increased adverse events (i.e. readmission, stroke, myocardial infarction,  
74 and mortality), reduced health related quality of life (HRQoL), and higher health care costs.(5–10)  
75 Patients with poor dietary habits (present in ~80% of the candidates for cardiac surgery), who are  
76 physically inactive (~45%), who smoke (22%), or who experience depression and/or anxiety  
77 disorders (~30%) are at higher risk for post-operative complications and are at risk for lack of  
78 functional benefits after cardiac surgery.(8,11–19)

79 Over the last decades risk factors such as age, obesity, diabetes, hypertension and  
80 dyslipidemia have steadily increased in patients undergoing cardiac surgery.(20,21) Despite their  
81 adverse effects on treatment outcomes, reducing the burden of modifiable risk factors are currently  
82 not part of standard clinical care before and after cardiac surgery. Before cardiac surgery, patients  
83 often have a preoperative period of several weeks on the waiting list in which they receive little or no  
84 guidance. This waiting period has been associated with increased psychological stress, feelings of  
85 anxiety and reduced functional status.(22,23) With respect to inactivity during hospitalisation after  
86 cardiac surgery, research has shown that during the 8 to 11 days of hospitalisation, patients spent  
87 the majority of their time sitting or in a supine position.(24,25) In-hospital physical inactivity is a  
88 predictor of a longer hospital stay and re-hospitalisation.(24,26,27) It causes a decrease in muscle  
89 strength and aerobic capacity, both fundamental in the performance of activities of daily living.(28,29)  
90 This reduced physical capacity may seriously impact independence, especially since these patients  
91 are often elderly and the functioning of their entire physiological system is already reduced.(30)

92 The goal of Cardiac rehabilitation (CR) is to improve the pre- and post-operative status of  
93 patients undergoing cardiac surgery. CR aims “to favourably influence the underlying cause of  
94 cardiovascular disease, as well as to provide the best possible physical, mental, and social



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3 95 conditions".(31) Post-operative CR is already an essential part of standard care in the Netherlands,  
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5 96 although many hospitals in the Netherlands provide a phase II outpatient CR program, starting 3 to 6  
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7 97 weeks after cardiac surgery.(32,33) Benefits of post-operative CR are reported for a variety of  
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9 98 cardiac patients,(34) however the evidence in patients undergoing cardiac surgery is still lacking with  
10  
11 99 regard to patient-relevant outcomes and mortality.(35) In addition to post-operative CR, small trials  
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14 100 suggested that preoperative CR is effective in reducing post-operative pulmonary complications,  
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16 101 duration of hospital stay, improving HRQoL, physical fitness and increasing the compliance to post-  
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18 102 operative CR.(23,36,37) However, long-term effects and the effects on other complications remain  
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20 103 unclear. Furthermore, most studies investigated the effect of preoperative CR or post-operative CR,  
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22 104 but not the effect of both CR methods combined. The hypothesis is that a combined pre- and post-  
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24 105 operative CR program is more beneficial when compared to a separate preoperative CR program or  
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26 106 a single post-operative CR program.

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29 107 The aim of the Heart-ROCQ study is to determine the effect of a comprehensive pre- and  
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31 108 post-operative CR program (the Heart-ROCQ program) on functional status, post-operative surgical  
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33 109 complications, readmissions to hospital, and major adverse cardiac events (MACE) compared to a  
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35 110 regular Dutch post-operative outpatient CR program (the Standard Care CR program).(32) In  
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37 111 addition, the effect of the Heart-ROCQ program on physical and psychological functioning, including  
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39 112 HRQoL, life style risk factors, work participation, and cost-effectiveness are evaluated in comparison  
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41 113 to the Standard Care CR program. To assess who will benefit from CR and why the CR programs  
42  
43 114 are effective, moderator and mediator analyses are performed.

## METHODS AND ANALYSIS

### Study design and organization

This investigator-initiated prospective randomised open, blinded end-point (PROBE) trial is executed in a single Centre (University Medical Centre Groningen [UMCG]). Patients from three referral hospitals (Ommelander Hospital Groningen [OZG], Martini Hospital Groningen [MZH], and Wilhelmina Hospital Assen [WZA]) who are accepted for cardiac surgery at the UMCG are also approached to participate. Patients are randomly assigned to a combined pre- and post-operative multidisciplinary CR program (the Heart-ROCQ group) or a regular phase II outpatient CR program after surgery (the Standard Care group).<sup>(32)</sup> Figure 1 provides an overview of the study design.

### Ethical considerations and dissemination

This study is conducted according to the principles of the Declaration of Helsinki (version 8, October 2013) and according to the research code of the UMCG. It has been registered at ClinicalTrials.gov (No. NCT02984449) and the protocol (version 2, 2016-Dec-19) has been approved by the Medical Ethical Review Board (METc) of the UMCG (No. 2016/464). If applicable, substantial amendments will be notified to the METc for approval and changes will be written into articles describing the results of the study. Results of this study will be submitted to a peer-reviewed scientific journal and can be presented at national and international conferences.

### Funding

The Heart-ROCQ study is financially supported by Edwards Lifesciences SA, Abbott (former St. Jude Medical Nederland B.V.) and 'Stichting Beatrixoord Noord-Nederland'. The sponsors are not involved in the design or execution of the study.

### Participants

Patients ( $\geq 18$  years) admitted to elective coronary artery bypass grafting (CABG), valve surgery, aortic surgery, or combined procedures are eligible. Patients accepted for congenital procedures,

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3 142 transcatheter aortic valve implantations (TAVI), aortic dissections, or aortic descending repair are  
4  
5 143 excluded. Other exclusion criteria are: inability to participate in all program elements of the Heart-  
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7 144 ROCQ program due to disorders of the nervous or musculoskeletal system that limits exercise  
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10 145 capacity, chronic obstructive pulmonary disease (COPD) with Global Initiative for Chronic  
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12 146 Obstructive Lung Disease (GOLD) criteria classification 3 or 4,(38) addiction to alcohol or drugs, a  
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14 147 serious psychiatric illness (i.e. recently experienced psychosis, bipolar disorder, diagnosis of  
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16 148 schizophrenia, serious cognitive, or neurological problems, and acute suicidal ideations or  
17  
18 149 behaviour), or when it is undesirable to exercise (i.e. hypertrophic cardiomyopathy, unstable angina,  
19  
20 150 advice from cardiologist); any treatment which is planned during one of the CR programs and which  
21  
22 151 is expected to interrupt attendance to the CR program (e.g. planned organ transplantation,  
23  
24 152 preoperative endocarditis, or planned chemotherapy etc.); playing a sport at (inter)national level;  
25  
26 153 being unable to read, write, or understand Dutch.  
27

#### 28 29 154 30 31 155 Study enrolment, randomization and registry

32  
33 156 Figure 2 shows the flow chart of the Heart-ROCQ study. Patients on the waiting list of the thoracic  
34  
35 157 surgery department and meeting the study criteria for type of surgery are asked to participate by their  
36  
37 158 cardiologist. The cardiologist provides the patients with study information and an invitation to meet  
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39 159 the researcher at the preoperative consultation. At the preoperative consultation, the researcher will  
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41 160 obtain informed consent and conduct the baseline measurements. Eligible patients who have signed  
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43 161 informed consent and performed the baseline measurements, are randomised to the Heart-ROCQ  
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45 162 group or Standard Care group. Randomization (concealed group allocation in REDCap, random  
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47 163 blocks of 2-4, 1:1 ratio) is stratified for weight of the surgery (isolated CABG, single non-CABG [i.e.  
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49 164 replacement or repair of part of aortic or valve], 2 procedures or 3 procedures), gender, and age ( $\geq 65$   
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51 and  $< 65$  years). Prior to the start of the study, the randomization lists were created (using the 'ralloc'  
52 165  
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54 166 function of Stata/SE, version 13.0) and imported into the secure data collection tool REDCap  
55  
56 167 (version 7.3.2), by an independent researcher. Medical staff and researchers are not blinded to  
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58 168 group allocation, because of logistic reasons. The primary end point is evaluated by an independent  
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60 169 end-point committee, blinded for group allocation.

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3 170 Patients who are not willing to participate are asked to give written consent for using data that  
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5 171 are collected during routine care. The data are collected in the Heart-ROCQ study registry to  
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7 172 increase insight into-potential differences between patients who participated in the study and patients  
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10 173 who did not. The Heart-ROCQ registry will thus provide more insight into the generalizability of the  
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12 174 results. Data from this registry are not used for the primary statistical analyses.  
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## 14 175 15 16 176 Intervention

### 17 18 177 *Heart-ROCQ group*

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20 178 The Heart-ROCQ group receives a CR program at the Centre of Rehabilitation of the UMCG  
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22 179 (location Beatrixoord, which is located 6 km from the hospital of the UMCG) consisting of 3 phases.  
23  
24 180 The first phase is an outpatient preoperative optimization phase during the waiting period (3 times  
25  
26 181 per week, minimum of 3 weeks). The second phase is a post-operative inpatient CR phase (3 weeks,  
27  
28 182 weekdays only) followed by the third phase, an outpatient CR phase (2 times per week, for 4 weeks).  
29  
30  
31 183 During each phase, all participants receive physical therapy including group sessions of inspiratory  
32  
33 184 muscle training (IMT),(39) strength training, aerobic cycling, breathing, coughing and relaxation. In  
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35 185 addition, patients have an assessment with a dietician and a psychologist and take part, when  
36  
37 186 indicated, in individual sessions to optimize their health. In addition, different group education  
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39 187 sessions are organized regarding coping with stress, awareness of risk factors, and maintaining a  
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41 188 healthy life style. Two additional modules, namely coaching to stop smoking and to return to work,  
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43 189 are available for patients who respectively smoke or are employed. A detailed description of the CR  
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45 190 program is given in the supplementary information.  
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### 47 191 48 49 192 *Standard Care group*

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52 193 In the Netherlands, the current standard of care consists of a phase II outpatient CR program, which  
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54 194 is conducted at the referred hospital.(32,33) In general, this CR program starts 3 to 6 weeks after  
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56 195 discharge from the hospital and lasts for 6 weeks. The program consists of four educational sessions  
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58 196 (regarding risk factors and retaining a healthy life style) and physical therapy (2 times per week: 30  
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60 197 min. cycling together with 30 min. sports and games, relaxation therapy, or strength training).

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3 198 Furthermore, patients can be referred to a psychologist or a dietician when needed. The content of  
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5 199 this CR program is based on the Dutch CR guidelines.(40)

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10 201 Composite primary end point: functional status, complications and events

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12 202 The primary outcome is a composite weighted score of functional status, post-operative surgical  
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14 203 complications, readmissions to the hospital, and MACE. Each event is scored (ranging from 1 to 3  
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16 204 points), separately. Table 1 shows an overview of the primary outcome and the scoring system.

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18 205 The scores of all events are combined to calculate a total score. Only the most serious complication  
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20 206 is counted per event (e.g. when a percutaneous coronary intervention [score 1] is complicated by a  
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22 207 stroke [score 2], the score will be 2 and not 3 [1 + 2]).

23  
24 208 The concept of the composite weighted score is adapted from the African-American Heart  
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26 209 Failure Trial (A-HeFT).(41) Functional status is assessed through two health domains of the Medical  
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28 210 Outcome Study 36-item General Health Survey (RAND-36 version 2)(42): physical functioning and  
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30 211 physical health problems. The primary end point is evaluated at 3 months (T4) and 1 year (T6) after  
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32 212 surgery (Figure 1). Deep wound infections and surgical re-explorations are screened up to 120 days,  
33  
34 213 after surgery. Other post-operative surgical complications are measured in the period between the  
35  
36 214 surgery and when a patient meets the UMCG discharge criteria (Table 2). Hospital admissions are  
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38 215 checked between baseline and one year after surgery. To prevent bias (since the Heart-ROCC  
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40 216 group follows the in-patient CR phase after surgery) hospital admissions between the day of  
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42 217 admission before surgery and 30 days after surgery are not included when determining the  
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44 218 (calculated) primary end point.

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50 220 Secondary outcomes

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52 221 *Complications and events*

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54 222 All individual components of the composite end point regarding the complications and events will be  
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56 223 analysed separately as secondary outcomes. Table 3 summarizes the definitions of the secondary  
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58 224 complications and events, including at the time of screening.

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All documents concerning the composite primary end point and the secondary complications are encrypted and subsequently adjudicated by the independent end-point committee. The end-point committee consists of four members (cardiologists and cardiothoracic surgeons), who are not employed in the UMCG and are blinded for group allocation.

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Table 1: definitions and score of the components of the composite primary end point

Functional status	Score
Worsening in physical functioning ( <i>domain score of health related quality of life, rand36_v2</i> ) <sup>†</sup>	1
No change or improvement in physical functioning <sup>†</sup>	0
Worsening in physical problem ( <i>domain score of health related quality of life, rand36_v2</i> ) <sup>†</sup>	1
No change or improvement in physical problem <sup>†</sup>	0
A clinical relevant worsening is classified as minimal change according to <i>Wyrwich et al., 2004</i> (43)	
<b>(Serious) Adverse Events</b>	
No serious adverse event	0
Prolonged mechanical ventilation <i>Mechanical ventilation longer than 24 hours</i>	1
Lung infection 1) A new lung radiographic infiltrate AND 2) two signs that the infiltrate is infectious origin (i.e. a) fever - body temperature >38°C or <36°C -, b) leukocytosis - white blood cells >10,000 or <4000, c) positive sputum culture AND/OR d) decline in oxygenation	1
Delirium 1) A DOS score ≥ 3 at hospital ward AND/OR 2) Diagnosis confirmed by a psychiatrist, geriatrist, or supervising specialist according to the DSM-IV criteria resulting in treatment with medication	1
Readmissions to intensive care unit <i>Unrelated to a secondary end point</i>	1
Deep wound infection <i>Deeper tissues are affected (muscle, sternum, and mediastinum) and must include: 1) surgical drainage / re-fixation OR 2) an organism is isolated from culture of mediastina tissue or fluid, OR 3) antibiotic treatment, because of sternum wound</i>	2
Readmissions to hospital <i>An unplanned hospital stay with different dates of admission and discharge with a medical indication (i.e. clinical signs and symptoms or change of treatment)</i>	1
Any cardiothoracic surgical interventions <i>Graft- or valve failure, CABG, valve, aortic, or other cardiac surgery<sup>‡</sup></i>	2
Any percutaneous interventions <i>PCI, TAVI, etc.</i>	1
Myocardial infarction <i>According to the third universal definition of myocardial infarction<sup>§</sup></i>	2
Cerebral vascular accident / stroke <i>Acute neurological event of at least 24 hours of duration, with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnosis of stroke requires confirmation by CT, MRI, or pathological confirmation.</i>	2
Sudden death survivor <i>The sudden onset of symptoms, such as chest pain and cardiac arrhythmias, ventricular tachycardia, which lead to the loss of consciousness and cardiac arrest followed by reanimation and does not lead to biological death.</i>	2
Death <i>All-cause mortality</i>	3
Total score = sum of physical status and SAE's at 3 months and 1 year (worst score of each event)	

<sup>†</sup>Compared with baseline; <sup>‡</sup>According to the definitions of the 'Begeleidingscommissie Hartinterventies Nederland'; <sup>§</sup>Thygesen et al., 2012(44); DOS: Delirium Observation Screening scale(45); CABG: Coronary arterial bypass graft; PCI: Percutaneous coronary intervention; TAVI: Transcathetic aortic valve implantation; In gray: post-operative complications can be scored ones; SAE: Serious adverse event.

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60236 *Table 2: Discharge criteria of the University Medical Centre Groningen (UMCG)*

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- 1) no drain, no external pacemaker lead, no infusion, or oxygen present,  
 2) stable clinical conditions (stable lab results, X-ray, and haemodynamic parameters),  
 3) able to perform basic activity of daily living (ADL)-activities (i.e. going independently to the toilet).
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237  
238 *Table 3: definitions of the secondary complications and events*

Definitions	Time of measure
Atrial fibrillation <i>New onset of atrial fibrillation or atrial flutter requiring medical treatment or cardioversion</i>	Surgery to T3
Prolonged ICU stay <i>When the number of calendar days is two or more from ICU admission to discharge</i>	Initial stay
Readmissions to hospital <i>The number of unplanned hospital stays with different dates of admission and discharge with a medical indication (i.e. clinical signs and symptoms or change of treatment)</i> a) directly related to a cardiac cause b) not directly related to a cardiac cause	Baseline to T6 <sup>§</sup>
Hospitalisation days <i>Total number of days of hospitalisation</i> a) directly related to a cardiac cause b) not directly related to a cardiac cause	Baseline to T6 <sup>§</sup>
Cardiovascular death <i>Any death due to proximate cardiac or cardiovascular cause (e.g. Myocardial infarct, low-output failure, fatal arrhythmia, death secondary to a cerebral vascular accident, pulmonary embolism, ruptured or dissecting aortic aneurysm, or other vascular diseases), un-witnessed death, and death of unknown cause, and all procedure related deaths (e.g. PCI, CABG), including those related to concomitant treatment<sup>†</sup>.</i>	Baseline to 5 years after surgery
Non-cardiovascular death <i>Any death not covered by above definition, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma</i>	Baseline to 5 years after surgery
<b>Concerning safety</b>	
Surgical re-exploration for bleeding/ tamponade <i>Surgical incision into the sternum as a result of a bleeding or tamponade</i> a) acute: presented within 24 hours after surgery b) late: presented after 24 hours after surgery	Surgery to T4
Surgical re-exploration dehiscence <i>Aseptic wound dehiscence</i>	Surgery to T4

<sup>†</sup>Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) will be classified as cardiac death; <sup>§</sup>Not measured between the day of admission before surgery and 30 days after surgery, because of POST-in phase of Heart-ROCC program; ICU: Intensive care unit; T4: Follow-up at 3 months after surgery; T6: Follow-up at 12 months after surgery.



### Questionnaires and physical tests

Table 4 shows the physical tests and questionnaires of the secondary outcomes regarding physical and psychological health, life style risk factors, and the economic evaluation. Physical tests and questionnaires are completed at six assessment points (Figure 1). The preoperative measurements (T1 and T2) are conducted at the start (preoperative consultation) and the end (1 to 8 days before surgery) of the waiting period. The third measurement (T3) is performed when patients meet the UMCG discharge criteria (Table 2). The follow-up measurements (T4, T5, and T6) are at 3, 7, and 12 months after surgery. Patients are asked to fill in questionnaires online or when requested on paper, prior to the visits for the physical tests. All adverse events reported spontaneously by the patient or observed by the investigator are recorded. In addition, serious adverse events are reported to the METc. Data are stored in REDCap and on a secure drive at the department CardioResearch in the UMCG. Two times per year, the study is monitored by a trained research monitor from another department of the UMCG. Details of procedures, data collection, management and monitoring can be found in the Trial Master File of the Heart-ROCQ study (can be obtained by the investigators). On the 12<sup>th</sup> of June 2018, the study was audited and certified for the ISO 9001: 2015 independently by DNV GL.

### Potential moderators

Preoperative risk profile (i.e. Euroscore II, medical history, life style risk factors, physical, and mental status), surgery parameters, and demographics are collected from the medical record and baseline measurements. The content of the CR program is described in terms of compliance, duration of CR program, type of treatment, frequency, and training load (i.e. for bicycle training: external workload, heart rate response, rate of perceived exertion using the Borg scale, and for strength training: sets, repetitions, and intensity) for both the Heart-ROCQ group as the Standard Care group.

Table 4: Time of measure, physical tests, and questionnaires of the secondary outcomes

Secondary outcomes	Measure	Time of measure
<i>Physical health</i>		
Cardiorespiratory fitness	6MWT(46)	T1-T4, T6
Muscle strength	STS_10, grip & leg strength(47,48)	T1-T4, T6
Independence in ADL	KATZ(49,50)	T1, T4, T6
<i>Psychological health</i>		
General anxiety	GAD-7(51)	T1,T2, T4, T6
Feelings of depression	PHQ-9(52,53)	T1,T2, T4, T6
Health related Quality of Life	Rand-36_v2(42)	T1, T4, T6
<i>Life style risk factors</i>		
Physical activity	iPAQ(54) & Actigraph <sup>†</sup> (55)	T1, T4, T6
Obesity indices	BMI, waist-to-hip ratio	T1, T4, T6
Smoking behaviour	Number of cigarettes per day	T1, T4, T6
<i>Economic evaluation</i>		
Health care use & related medical costs	iMCQ(56)	T1, T4-T6
Work participation <sup>‡</sup>	iPCQ(57)	T1, T4-T6
QALYs	EQ-5D-5L(58)	T1, T4-T6
<i>Potential mediators</i>		
Cardiac self-efficacy	CSE(59)	T1, T2, T4, T6
Illness representations	IPQ-R(60)	T1, T2, T4, T6

<sup>†</sup>Patients are asked to wear the Actigraph during waking hours for 1 consecutive week; <sup>‡</sup>Health-related productivity losses of paid work and unpaid work; T1: Begin of waiting time; T2: 1 to 8 days before surgery; T3: Moment that patients meet the UMCG discharge criteria; T4-T6: Follow-up at 3, 7, and 12 months after surgery; 6MWT: Six minutes walking test; STS\_10: Ten times sit to stand test; ADL: Activities of Daily Living; KATZ: Katz Index of Independence in Activities of Daily Living; GAD-7: Generalized Anxiety Disorder 7-item scale; PHQ-9: Patient Health Questionnaire 9-item scale; iPAQ: International Physical Activity Questionnaire; BMI: Body Mass Index; iMCQ: iMTA Medical Cost Questionnaire; iPCQ: iMTA Productivity Cost Questionnaire; QALY: Quality-adjusted life years; EQ-5D-5L: EuroQol five-dimensional questionnaire; CSE: Cardiac Self-efficacy; IPQ-R: Illness Perception Questionnaire, Revised.

#### Potential mediators

Illness perceptions (i.e. patients mental representations of their illness based on different sources of information) are measured with three subscales (personal control, treatment control, and consequences) of the revised illness perception questionnaire (IPQ-R).(60) These subscales are chosen because of their sensitivity to change and because of their relation to psychological distress(61). The cardiac self-efficacy (CSE) scale(59) is used to measure CSE (i.e. patients confidence to perform a specific task related to cardiac disease).

## 285 Statistical analyses

### 286 *Sample size*

287 Assuming a normal distribution, the mean weighted score of the primary end point is estimated on  
288 1.0 with a standard deviation of 0.9 at 1 year after surgery. This estimation is based on historical data  
289 of the UMCG, an unpublished on-going pilot study in the UMCG, the Dutch registration database,(62)  
290 and data reported in literature.(6,63–65) A decrease of 0.3 is expected in the Heart-ROCQ group,  
291 based on previous studies comparing CR with standard care(36,64,66) (i.e. no CR) and is  
292 considered to be clinically relevant (i.e. on average a 30% decrease in complications/events or  
293 worsening in functional status or 10-20% decrease in MACE or death). To detect this decrease and  
294 achieve 80% power (significance level of 5%) a group of 286 patients (143 in the Heart-ROCQ group  
295 and 143 in the Standard Care group) is needed. To incorporate a withdrawal of  $\pm 20\%$  a total sample  
296 size of 350 is needed at baseline.

### 297 298 *Interim analysis*

299 An interim analysis will be conducted when 40% of the included patients have had the  
300 measurements one year after surgery. The study will be terminated prematurely when the primary  
301 outcome of one of the CR programs is obviously ( $P < 0.001$ ) different from the other CR program.

### 302 303 *Primary and sensitivity analyses*

304 All end points are primary analysed according to the 'intention-to-treat' principles and missing values  
305 are counted as worst-case score (nominal variables) or estimated using Maximum Likelihood  
306 estimation (interval variables). As supplementary analyses, the end points are analysed on a per-  
307 protocol principle with and without using imputation methods for missing values. In all analyses, a  
308 two-sided  $p < 0.05$  is considered statistically significant.

309 The total score of the primary endpoint will be handled as a continuous variable. All  
310 continuous variables will be analysed using linear mixed models to determine 'time x group'  
311 differences. Significant interactions will be further explored using the Bonferroni post-hoc test to  
312 determine differences between each time point. Non-parametric tests will be used if the assumptions

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3 313 of normal distribution are violated. More information about the statistical methods and clinical  
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5 314 relevance are written in the research protocol (ClinicalTrials.gov : NCT02984449).

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10 316 *Economic evaluation*

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12 317 For the evaluation of health-care utilization, standard prices published in the Dutch costs guidelines  
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14 318 are used.(67) To compare the costs to quality adjusted life years (QALYs), QALYs are estimated with  
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16 319 use of the EQ-5D-5L.(58) Utility values for the EQ-5D-5L are calculated based on the new Dutch  
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18 320 tariff.(68) Results from the analysis are reported as an Incremental Cost Effectiveness Ratio (ICER),  
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20 321 dividing the difference in effect, by the difference in costs. Bootstrap re-sampling will be performed,  
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22 322 and cost-effectiveness acceptability curves will be plotted, to estimate the probability that the Heart-  
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24 323 ROCQ program is cost effective when compared to standard care. A societal perspective is applied.

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29 325 Study status

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31 326 From May 2017 to December 2018, 75 patients were enrolled. In following years we expect that the  
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33 327 enrolment will increase to 85 patients per year. The last patient is expected to be included in July  
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39 330 Patient and public involvement

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41 331 In a pilot study (to be submitted) the patient satisfaction and the feasibility (in terms of accessibility,  
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43 332 compliance, training load and safety) of the Heart-ROCQ program have been evaluated. Patients  
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45 333 were very satisfied with the program and scoring it eight out of ten, therefore we did not change the  
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47 334 content of the program. However, patients' rate of perceived exertion was generally quite low and no  
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49 335 serious adverse events occurred during the bicycle training. For safety reasons the intensity was not  
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51 336 increased. However, in order to estimate the maximum load more accurately and better tailor the  
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53 337 program to the individual, we decided to change one of the stop criteria of the preoperative  
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55 338 submaximal ergometry test from 70% to 90% of expected maximal heart rate. Furthermore, our  
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57 339 outcomes are, among others, based on the reasons why patients recommended the program to  
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59 340 other patients. For example, patients reported that their self-efficacy and physical capacity were

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3 341 improved, so we added the CSE questionnaire and physical tests to objectively measure these  
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5 342 outcomes. In this way the results were taken into account in the further development of the Heart-  
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7 343 ROCQ program and the protocol of this study. The results of this trial will be distributed by various  
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10 344 information channels (e.g. websites of cardiac patient organisations, social media). Two to three  
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12 345 times a year we provide a newsletter about the progress and (in the end) the results of the study are  
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14 346 sent to patients, who are interested.  
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For peer review only

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3 347 DISCUSSION  
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6 348 The Heart-ROCQ study is the first randomised clinical trial evaluating the effect of a combination of  
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8 349 pre- and post-operative CR program compared to a post-operative CR program. Unlike the vast  
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10 350 majority of CR programs in previous studies, the current program is multidisciplinary targeting  
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12 351 different aspects of surgical outcomes in patients undergoing cardiac surgery. Because different  
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14 352 aspects are targeted, a composite weighted score will better reflect the treatment benefits than a  
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16 353 single outcome. Therefore, the primary end point is a composite end point of functional status, post-  
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18 354 operative surgical complications, readmissions to the hospital and MACE. The components of the  
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21 355 end point are of clinical importance to patients undergoing cardiac surgery and reflect a  
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23 356 comprehensive representation of the recovery of the patient.

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25 357 Both the ideas of the combined primary end point and the weighting of the individual  
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27 358 components were derived from other studies.(41,69,70) Assigning different weights to the  
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29 359 components was needed for more accurate comparison. Since the components are not equal in  
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31 360 clinical importance, equal weights would lead to inaccurate statistical analysis(70). In the current  
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33 361 study, the weighted score of HRQoL is lower (1 point instead of 2 points) to minimize bias due to  
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35 362 patients' knowledge of group allocation. Therefore, improvements in quality of life are not counted in  
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37 363 the primary end point to prevent bias in a positive direction. This also prevents that a score in quality  
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40 364 of life and adverse event cancel each other out (e.g. when a patient experiences an improvement in  
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42 365 Quality in Life [+2 points] and has a stroke [-2 points] then the total score is 0). The scores of all-  
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44 366 cause mortality, stroke, myocardial infarction and revascularization are in line with the results  
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46 367 showed by Tong and colleagues (2013)(70). A disadvantage of composite end points is that the  
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48 368 effect may be driven by complications that occur with the greatest frequency.(71) Therefore, post-  
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50 369 operative complications which occur frequently, such as atrial fibrillation, are evaluated separately as  
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52 370 secondary end point. The primary end point is evaluated by an end-point committee, which is blinded  
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54 371 to group allocation and consists of four independent cardiologists and cardio-thoracic surgeons.

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56 372 Previous preoperative CR studies were primarily focused on short-term effects; only one  
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58 373 preoperative CR study and a few post-operative CR studies have determined long-term  
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3 374 effects.(23,35,36,72) In contrast to previous preoperative CR studies, the Heart-ROCQ study sets  
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5 375 out to investigate both short- and long term effects of the CR programs.(23,35,36) Due to the trends  
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7 376 in, among others, increasing age, obesity, and physical inactivity, patients undergoing cardiac  
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9 377 surgery are becoming more complex. The Heart-ROCQ program aims to address these issues,  
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11 378 which make the program clinically relevant for all cardiac surgery patients. Therefore, we chose to  
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13 379 include different types of cardiac surgery. Since different moderators and mediators are assessed  
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16 380 before, during and after CR, we can explore which factors are associated with better outcomes and  
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18 381 which working mechanisms contribute to its effectiveness. These findings may provide a more in-  
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20 382 depth understanding of who benefits the most from CR in both the short and long term and the  
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22 383 underlying mechanisms of CR, which are still not fully understood in patients undergoing cardiac  
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24 384 surgery.(35) In addition, the present study is thought to considerably contribute to the evidence to  
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26 385 further develop guidelines for clinical practice, especially regarding the preoperative CR program.(73)

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28 386 The Heart-ROCQ program is expected to be cost-effective in the long-term, which is also of  
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30 387 interest for policymakers and health care providers. Therefore, an economic evaluation is performed  
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32 388 to assess the cost-effectiveness of CR, since little is known about the cost-effectiveness of CR.(64) A  
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34 389 societal perspective of this economic evaluation is chosen, meaning that not only health-care costs,  
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36 390 but also patient- and productivity related costs and benefits are taken into account. If the Heart-  
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38 391 ROCQ program is proven to be effective, it might be advisable to include a supportive prevention-  
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40 392 oriented waiting period prior to surgery as an integral part of the treatment for patients undergoing  
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42 393 elective cardiac surgery. This implies a paradigm shift from curative care following cardiac surgery to  
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44 394 an additional preventive care attitude before surgery. Extensions of rehabilitation options in, or in the  
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46 395 vicinity of cardiac centres, will then be required.

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48 396 The Heart-ROCQ study is the first randomised clinical trial comparing the effect of a  
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50 397 combined pre- and post-operative CR program to a regular Dutch phase II post-surgery outpatient  
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52 398 rehabilitation CR program in a population undergoing elective cardiac surgery. This study is expected  
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54 399 to provide new understanding of the effectiveness and underlying working mechanisms of CR, and  
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56 400 subsequently to improve value-based health care.

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22 410 Declaration of interest

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33 415  
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35 416 Authors' contributions

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37 417 Conception and design of the study: JH, FB, MJLdJ, MFR, WD, JF, LHVvdW, PvdH, and MAM;  
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39 418 Methodology: JH, FB, SD, MJLdJ, MFR, and PvdH; Acquisition of data: JH, FB and SD; Writing –  
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41 419 Original draft, tables, and figures: JH; Writing- Reviewing and Editing: FB, SD, MJLdJ, MFR, WD,  
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43 420 ICCvdH, JF, LHVvdW, PvdH, and MAM; Supervision: MJLdJ, MFR, WD, JF, ICCvdH, LHVvdW,  
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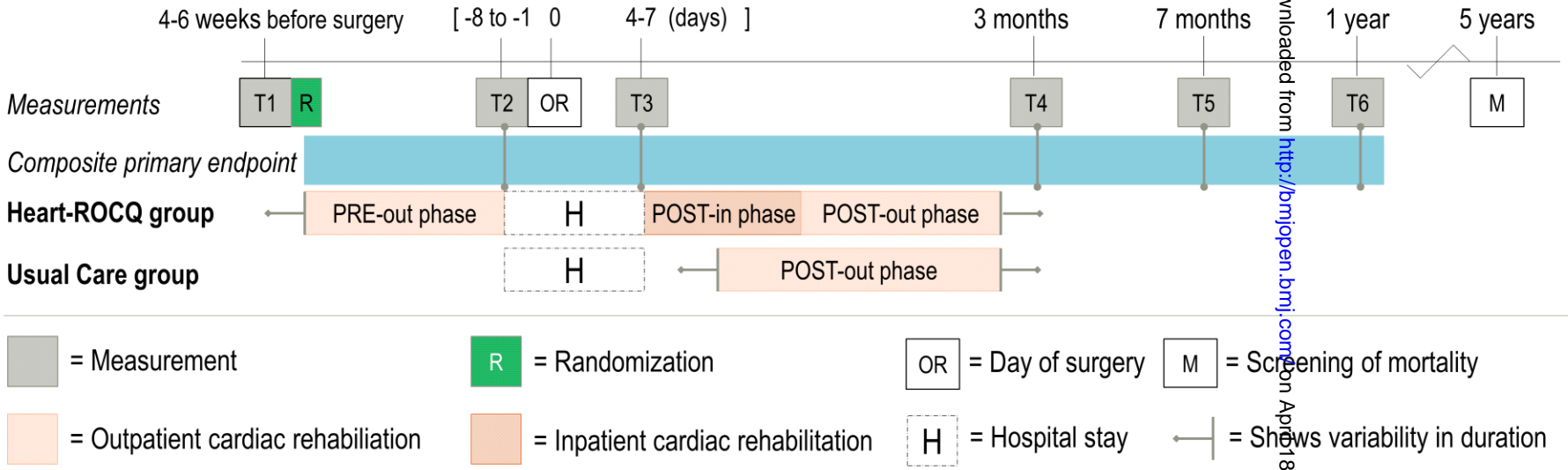
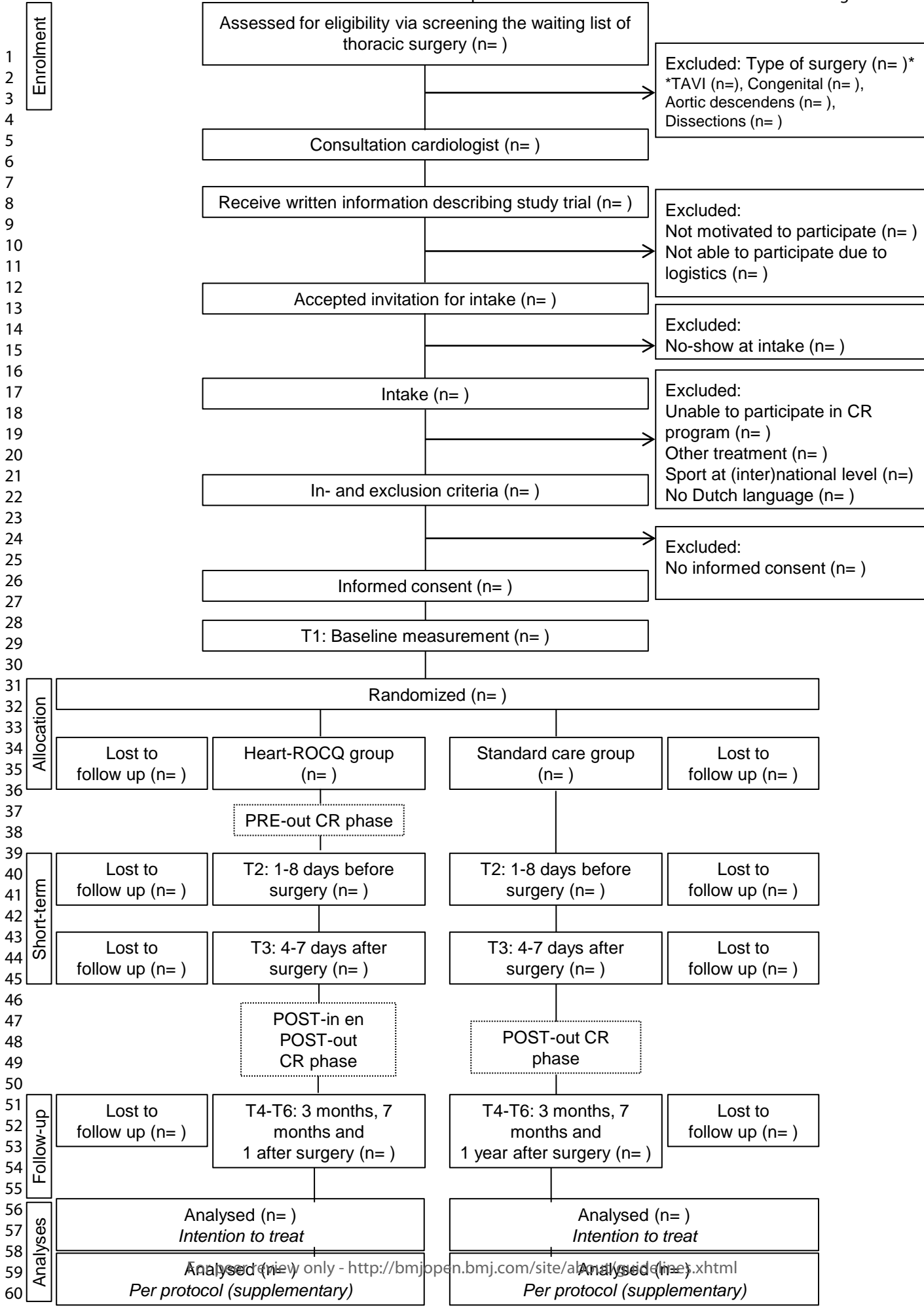


Figure 1: Research design of the Heart-ROCQ PROBE trial. The phases of both cardiac rehabilitation programs and the measurements are shown relative to the moment of surgery.



## SUPPLEMENTARY INFORMATION - DESCRIPTION OF THE HEART-ROCQ PROGRAM

<b>PRE-out phase – An outpatient cardiac rehabilitation phase during the waiting period</b>			
<i>Three times per week, a minimum of three weeks</i>			
<b>Physical therapy</b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients physical capacity before surgery</li> <li>- Patient learns to apply the stress-strain training principles</li> <li>- To optimize pulmonary muscle strength</li> <li>- Patient knows which breathing and coughing techniques should be used after surgery to prevent pulmonary complications</li> </ul>			
When needed:			
<ul style="list-style-type: none"> <li>- Patient learns to recognize body signals and boundaries.</li> <li>- Patient is able to exercise despite of possible kinesiophobia</li> </ul>			
<b>Type of exercise</b>	<b>Frequency</b>	<b>Intensity</b>	<b>Monitoring</b>
IMT	3 x p / wk	<ul style="list-style-type: none"> <li>- 6 cycles of 6 repetitions,</li> <li>- rest periods of resp. 60, 45, 30, 15 and 5 s.</li> <li>- 60-80% of maximal inspiratory pressure<sup>65</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Week 1: each training ↑ intensity with 10%</li> <li>- Intensity ↑ with 5% if RPE &lt;5<sup>1</sup></li> </ul>
Aerobic cycle	3 x p / wk	<ul style="list-style-type: none"> <li>- 25 min. at RPE 3<sup>1</sup></li> <li>- Interval training will be given, if the patient is not able to perform endurance training.</li> </ul>	<ul style="list-style-type: none"> <li>- First training: 50% of POpeak</li> <li>- Load ↑ if RPE &lt; 3<sup>1</sup></li> <li>- Interval training: guided by complaints and RPE of 3</li> </ul>
Resistance training	3 x p / wk	<ul style="list-style-type: none"> <li>- 1-3 cycles of 10-15 repetitions</li> <li>- Rest: 30-60 s.</li> <li>- 50-80% of estimated 1RM</li> <li>- On six fitness apparatuses</li> </ul>	<ul style="list-style-type: none"> <li>- First training: 6-10 RM per fitness apparatus</li> </ul>
Body awareness	1 x p / 2 wks	<ul style="list-style-type: none"> <li>- 30 min. breathing and relaxation techniques</li> </ul>	Not Applicable
Group education	Two sessions	<ul style="list-style-type: none"> <li>- Basic training principles</li> <li>- Forced expiration, huff and cough techniques</li> </ul>	Not Applicable
<b>Dietary advice<sup>2</sup></b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients nutritional status</li> <li>- Patient knows which nutrients are important focusing on the surgery</li> <li>- Patients knows the importance of food in relation to cardiovascular disease and cardiovascular risk management</li> </ul>			
<b>Type</b>	<b>Frequency</b>	<b>Content</b>	
Intake interview	One session	- Anamnesis about nutritional status	
Counselling	On indication	- Individual sessions according to existing guidelines	
Group education	One session	- 60 min., cardiovascular risk factors and dietary intake	
<b>Psychological guidance<sup>2</sup></b>			
<u>Aims</u>			
<ul style="list-style-type: none"> <li>- To optimize mental status of the patients before surgery</li> <li>- Patient has made a start with the awareness of cardiovascular risk factors</li> </ul>			
Intake interview	One session	- Anamnesis about mental status	
Counselling	On indication	- Individual sessions according to evidence-based treatment protocols dependent on mental problems of patient <sup>3</sup>	
Group education	One session	- Coping with psychological tension/stress, to process the mental trauma of cardiac surgery, and risk factors	
<b>No-smoking consultation (For patients who smoke)</b>			
<u>Aim</u>			
- Patient gives up smoking during the waiting time before surgery			
Intake interview & counselling	One session per wk	- 30 min., individual session based on existing guidelines	

IMT: Inspiratory muscle training; RPE: Rate perceives exertion; POpeak: Maximum power output achieved during submaximal Ergometry test. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Involvement of partner/relatives during group and individual sessions; <sup>3</sup>like cognitive behavioural therapy, eye movement desensitization and reprocessing (EMDR), acceptance and commitment therapy etc.



<b>POST-in phase – An inpatient cardiac rehabilitation phase</b>			
<i>Starting 4-7 days after surgery, duration of three weeks, weekends at home</i>			
<b>Physical therapy</b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- To recover patients physical capacity</li> <li>- Patient performs breathing and coughing techniques to prevent pulmonary complications</li> <li>- Patient mobilize and can perform activities of daily living independently</li> <li>- Patient knows about risk factors according to physical activity, knows the ACSM recommendations (moderate-intensity cardiorespiratory exercise training for <math>\geq 30</math> min/day <math>\geq 5</math> days/week or vigorous-intensity cardiorespiratory exercise training for <math>\geq 20</math> min/day on <math>\geq 3</math> days/week or a combination<sup>66</sup>) and makes a plan to apply the ACSM recommendations in his own life</li> <li>- Patient works on personal goals</li> </ul>			
Type of exercise	Frequency	Intensity	Monitoring
Individual therapy	2 x p / day	<ul style="list-style-type: none"> <li>- Practice at transfers, walking, and climbing stairs</li> <li>- Very light mobilizing exercises for upper extremity</li> </ul>	<ul style="list-style-type: none"> <li>- During the first 2 days of this phase.</li> <li>- Extended, if patient is not able to participate in the group sessions.</li> </ul>
Individual therapy	2 x p / wk	<ul style="list-style-type: none"> <li>- Attention to personal goals</li> </ul>	<ul style="list-style-type: none"> <li>- Week 2 and 3</li> </ul>
IMT <sup>2</sup>	3 x p / wk: 2 x under supervision, 1 x without supervision	<ul style="list-style-type: none"> <li>- 6 cycles of 6 repetitions, - rest periods of resp. 60, 45, 30, 15 and 5 s.</li> <li>- intensity of 60-80% of maximum inspiratory pressure<sup>65</sup></li> </ul>	<ul style="list-style-type: none"> <li>- First training: 50% of resistance of last preoperative training</li> <li>- Intensity <math>\uparrow</math> with 5% if RPE <math>&lt; 5</math><sup>1</sup></li> <li>- IMT stops when resistance of preoperative training is reached</li> </ul>
Aerobic cycle <sup>2</sup>	1 x p / day	<ul style="list-style-type: none"> <li>- Week 1: duration of 5-20 min. at light intensity (RPE 2<sup>1</sup>)</li> <li>- Week 2 and 3: Work up to 25 min. at moderate intensity (RPE 3<sup>1</sup>)</li> <li>- Interval training will be given, if the patient is not able to perform endurance training.</li> </ul>	<ul style="list-style-type: none"> <li>- First training: at 50% of power output of last preoperative training</li> <li>- Load <math>\uparrow</math> if RPE <math>&lt; 2</math> à 3<sup>1</sup></li> <li>- Interval training: guided by complaints and RPE of 3.</li> </ul>
Resistance training <sup>2</sup>	3-4 x p / wk	<ul style="list-style-type: none"> <li>- 3 cycles of 15-20 repetitions</li> <li>- Rest periods of 30-60 seconds</li> <li>- On six fitness apparatuses</li> </ul>	<ul style="list-style-type: none"> <li>- First training: 50% of resistance of last preoperative training for LE and 25% for UE.</li> <li>- Gradual build up to 50-80% van 1RM based on RPE 3<sup>1</sup></li> </ul>
Body awareness <sup>2</sup>	1 x p / wk	<ul style="list-style-type: none"> <li>- 30 min. breathing and relaxation techniques</li> </ul>	Not Applicable
<b>Dietary advice<sup>3</sup></b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- To maintain or improve patients nutritional status</li> <li>- Patient knows which nutrients are important focusing on the recovery of surgery</li> <li>- Patients knows the importance of food in relation to cardiovascular disease and cardiovascular risk management</li> </ul>			
Type	Frequency	Content	
Intake interview	One session	- Anamnesis about nutritional status post-surgery	
Counselling	Sessions on indication	- Treatment according to existing guidelines	
Group education	One session	- 90 min., skills needed to maintain a healthy life style	
<b>Psychological guidance<sup>3</sup></b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- Patient start to process the mental trauma of cardiac surgery and the consequences of it</li> <li>- Patient has self-management competence to maintain a healthy life style</li> <li>- Patient and partner/relatives are able to support each other in the processing process</li> </ul>			
Intake interview	One session	- Anamnesis about mental status post-surgery	
Intake interview & counselling	Sessions on indication	- Individual sessions according to evidence-based treatment protocols dependent on mental problems of patient <sup>4</sup>	
Group education	One session	- 90 min., processing the cardiac surgery: possible reactions en consequences, coping with stress and healthy life style	

IMT: Inspiratory muscle training; RPE: Rate perceives exertion; LE: Lower extremities; UE: Upper extremities. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Group sessions start from day three of the inpatient phase or when patient is able to perform in the group activities; <sup>3</sup>Involvement of partner/relatives during group and individual sessions; <sup>4</sup>like cognitive behavioural therapy, eye movement desensitization and reprocessing (EMDR), acceptance and commitment therapy etc.

<b>POST-in phase – An inpatient cardiac rehabilitation phase (continuation)</b>		
<i>Starting 4-7 days after surgery, duration of three weeks, weekends at home</i>		
<b>No-smoking consultation<sup>1</sup> (For patients who smoke)</b>		
<u>Aim</u>		
- Patient is still motivated to stop smoking or patient is motivated to give up smoking (when patient did not give up smoking before cardiac surgery).		
Intake interview & counseling	1 x p / wk	- 30 min., individual sessions based on
Group education	One session	- 60 min., general information about smoking addiction and support from fellow smokers
<b>Return to work consultation<sup>1</sup> (for patients who are employed)</b>		
<u>Aim</u>		
- Patient is informed about laws and regulation for illness, social security contributions, and medical examinations		
- Patient knows their rights and obligations, the rights and obligations of the employer, the working conditions agency, the employee insurance agency, and re-integration companies		
- Patient received tools to return adequately back to work (knows positive and negative factors that can impact the re-integration)		
Group education	One session	- 60 min., laws and regulation for illness, procedures, roles, rights and obligations of different involved persons, communication to involved persons (e.g. colleagues, employer), working during rehabilitation, positive and negative factors regarding to return to work
Counseling	Sessions on indication	- Individual sessions with labour consultant dependent on problems of patient

<sup>1</sup>Involvement of partner/relatives during group and individual sessions.

<b>POST-out phase – An outpatient cardiac rehabilitation phase</b>			
<i>Starting on Tuesday after discharge of the POST-in phase, two times per week, four weeks</i>			
<b>Physical therapy</b>			
<u>Aim</u>			
<ul style="list-style-type: none"> <li>- Patient has optimized his/her physical capacity</li> <li>- Patient knows his/her boundaries and limitations</li> <li>- Patient knows about cardiovascular risk factors according to physical activity, knows the ACSM recommendations (moderate-intensity cardiorespiratory exercise training for <math>\geq 30</math>min/day <math>\geq 5</math> days/week or vigorous-intensity cardiorespiratory exercise training for <math>\geq 20</math> min/day on <math>\geq 3</math> days/week or a combination<sup>65</sup>) and makes a plan to apply the ACSM recommendations in his own life</li> <li>- Patient resumes his/her work or hobbies</li> <li>- Patient experiences pleasure during exercise</li> <li>- Patients achieves their personal goals</li> </ul>			
Type of exercise	Frequency	Intensity	Monitoring
Aerobic cycle	2 x p / wk	Depending on trainability of patient - 25 min. at 50-80% HRR or RPE 5 <sup>1</sup>	- Work up to 25 minutes at moderate intensity (RPE 3 <sup>1</sup> ), when patient was not able to do it in POST-in phase - Load $\uparrow$ if RPE < 5 <sup>1</sup> or HRR < 50-80%
Resistance training	2 x p / wk	UE: - 3-4 cycles of 10-15 repetitions - Rest: 30-60 s. - 50-80% of estimated 1RM - On six fitness apparatuses LE: - Focus on mobilization in week 1 & 2 - Focus on strength and endurance in week 3 & 4	- UE: Load $\uparrow$ if RPE < 5 <sup>1</sup> - LE: Under guidance of complaints
Sport and games	1 x p / wk	Focus on: - Experiencing pleasure during exercise, regaining trust and handling boundaries. - Exploring different types of sports and knowing the possibilities after CR	
Swimming	1 x p / wk		
Education	1 x p / wk	- Training principles of POST-out phase and a repetition of ACSM recommendations - Awareness of exercise after CR; making a plan to exercise after CR - Explanation of the results of the exercise test - Discussing the plan to exercise, share experiences to expand exercise in home situation	
<b>Dietary advice, psychological guidance, no-smoking consultation, and return to work consultation</b>			
Individual sessions are continued when aims are not achieved			

RPE: Rate perceives exertion; HRR: Heart rate reserve; LE: Lower extremities; UE: Upper extremities; ACSM: American College of Sports Medicine; CR: Cardiac Rehabilitation. <sup>1</sup>On a Borgscale 0-10; <sup>2</sup>Involvement of partner/relatives during group and individual sessions.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

## SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 3, 6 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ 3, 6 ___
Protocol version	3	Date and version identifier	___ 6 ___
Funding	4	Sources and types of financial, material, and other support	___ 7 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1, 19 ___
	5b	Name and contact information for the trial sponsor	___ 1 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 7 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ 7, 8, 10, 13 ___

## 1 Introduction

2			
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
4	rationale		_____ 4, 5 _____
5			
6		6b	Explanation for choice of comparators
7			_____ 4, 5 _____
8	Objectives	7	Specific objectives or hypotheses
9			_____ 5 _____
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
11			_____ 6, 7, _____
12			

## 14 Methods: Participants, interventions, and outcomes

15			
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
17			_____ 6 _____
18			
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
20			_____ 7 _____
21			
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
23			_____ 9 _____
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
25			_____ NA _____
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
27			_____ 13 _____
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
29			_____ 7 _____
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
31			_____ 10-14 _____
32			
33	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
34			_____ 6-14 _____
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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 15

2  
3  
4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 7, 8, 16

5  
6 **Methods: Assignment of interventions (for controlled trials)**

7  
8 Allocation:

9  
10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions 7, 8

11  
12 generation  
13  
14 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned 7, 8

15  
16 concealment  
17 mechanism  
18  
19 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions 7, 8

20  
21 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how 7, 8

22  
23 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial NA

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31 **Methods: Data collection, management, and analysis**

32  
33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of methods 11-14

34  
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol  
36  
37  
38  
39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols NA

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13__
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__15, 16__
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__15__
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__15__
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__13__
17				
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__15__
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__13__
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__13__
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__6__
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__6__
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___7, 8___
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___7, 8___
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___13___
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___19___
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___13___
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___13___
17				
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19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___6___
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	___6___
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___NA___
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___13___
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	___NA___
35				
36				

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
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