This supplement contains the following items:

Protocol & Statistical analysis plan

Version: 1.0

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Impact of a COmprehensive cardiac REhabilitation framework among high cardiovascular risk cancer survivors: the CORE trial

Version history

Version	Version date	Section	Change	Summary
1.0	18/10/2020	All pages	Addition	Document creation

There were no changes to the initial protocol.

PROTOCOL SUMMARY

Title:	**Impact of a COmprehensive cardiac REhabilitation framework among high cardiovascular risk cancer survivors: the CORE trial**
Objectives:	Primary: To compare the impact on cardiorespiratory fitness of a cardiac rehabilitation program model *versus* usual care encompassing a community-based exercise intervention. Secondary: to assess the effects on quality of life, psychosocial outcomes, physical function, fatigue, health literacy, cardiovascular risk factors, inflammatory biomarkers and cost-effectiveness. Adherence, safety and satisfaction will also be assessed.
Study design:	Prospective, single-center, single-blinded, randomized controlled trial with a parallel two-arm group.
Primary outcome measure:	Cardiorespiratory fitness – maximal aerobic capacity as assessed through peak oxygen uptake (VO_{2peak}) on a maximal or symptom-limited cardiopulmonary exercise test, from baseline to the end of the 8-week intervention.
Secondary outcome measures:	Changes in cardiovascular risk factors (e.g. body composition, lipid profile and inflammatory biomarkers, blood pressure, smoking status, physical activity levels), fatigue, physical function, quality of life and psychosocial outcomes, and health literacy from baseline to 8 weeks. Exercise session adherence and safety (adverse events) and cost-effectiveness will be also assessed.

Population: 80 cancer survivors will be recruited and randomized into a cardiac rehabilitation program (CBCR, n=40) or usual care encompassing a community-based exercise intervention (CBET, n=40) groups.

Eligibility Criteria: 1) Adult cancer survivors in follow up after primary treatment with curative intent

1.1) exposed to the following therapies: high-dose anthracycline (eg, doxorubicine ≥ 250mg/m2) or high dose radiotherapy (thoracic wall, (RT≥30Gy); low-dose anthracycline or anti-human Epidermal growth factor Receptor-type 2 drugs (anti-HER2) alone plus ≥ 2 cardiovascular risk factors and / or age ≥ 60 years at cancer treatment; low-dose anthracycline followed by anti-HER2;

and/or

1.2) the following medical background: history of coronary heart disease, moderate valvular disease; Left ventricular ejection fraction <50%.

1.3) Having concluded primary treatment at least 2 months before the inclusion

Screening and Randomization:	After the signing of informed consent, medical screening will include physical examination, biochemical measures, office blood pressure, and exercise testing, prior to a final decision about eligibility. After fulfilling all eligibility criteria, subjects will be randomized 1:1 to receive an exercise training intervention at a community-facility or a center-based cardio-oncology rehabilitation program. Randomization will be stratified according to age and sex.
Description of Intervention:	An 8-week intervention. Group CBCR: in addition to standard medical care, participants will receive the core components of a cardiac rehabilitation program, delivered by a multidisciplinary rehabilitation team on a hospital Cardiac Rehabilitation Unit; Group CBET: in addition to standard medical care, participants will receive on demand psychological and nutritional individual support, and community-based as recommended for cancer survivors.
Study Duration:	The study comprises an 8-week intervention.
Safety:	Adverse events will be summarized for each group. Adverse effects during/after exercise sessions will be recorded.
Funding source:	No funding to declare.

Table of content

1. Background and Rationale

As survival rates for several cancers continue to improve, there is a growing awareness about the increased risk for morbidity and mortality from noncancer causes among cancer survivors, and the pivotal need for holistic and individualized interventions.[1,2] Many of these survivors are at risk for cardiovascular disease (CVD) and have more cardiovascular risk factors (CVRF) compared to those without previous cancer. [3,4]

Data from different reports concurs as to increases in both traditional CVRF incidence as well as cardiovascular (CV) mortality among cancer survivors. [5-7] Indeed, several cancer and CV patients share many common features such as smoking, unbalanced diets and physical inactivity.[4,8] Furthermore, it is recognized that CVD are likely to become more prevalent in oncology settings due to age-related pathologies in conjunction with potential cancer treatment cardiotoxic effects on heart function and structure, as well as on the entire CV, pulmonary and skeletal-muscle systems [9-11].

Heart failure (HF) is one of the most frequent and concerning CV complication of cancer therapy, influencing functional and survival prognosis.[11] In addition, coronary artery disease (CAD) can also be more prevalent in this setting.[12] Chemotherapy can induce myocardial ischemia, while mediastinal radiotherapy may accelerate coronary damage [11,13,14]. The mechanisms associated with these side effects range from endothelial injury to arterial thrombosis, but the effects of CVRF aggravation may also modulated expression of atherosclerotic disease.[13,15,16] The time-point at which potential CV complications set in varies substantially, sometimes appearing early after exposure, or generating late clinical manifestations, making it difficult to predict long-term consequences of cancer treatment side effects, prevent adverse events or establish a specific long-term CV prognosis. [11,17]

These facts highlight the importance of an accurate identification of patients at increased risk for cardiotoxicity, namely those with major CVRF burden or pre-existing CVD, including a

careful baseline risk assessment for developing cardiac complications after cancer treatment .[16,18] As such, the need for designing and implementing individualized interventions that can mitigate the increased risk of CV morbidity and mortality in cancer survivors has progressively gained the spotlight, as the scientific community is now becoming aware of this need.

During the past decade, emerging data supports several benefits of exercise-based interventions in several cancer populations, either during or after primary adjuvant therapy.[19,20] Current recommendations suggest risk assessment and referring for trained personnel instead of simple counselling by health professionals for the practice of physical activity (IIA recommendation). [21] However, these exercise interventions are delivered in various settings (center, home or community-based), regarding different cancer populations and cancer treatments, supervised by different health or sports professionals, and still with limited information about eligibility criteria, assessment for exercise prescription, CVRF control, monitoring or safety.[19,20]

Though over the last years there have been significant advances in this field, the full scope of this exercise interventions and the relative impact of its components in terms of functional capacity, overall health-related quality of life (HRQoL) and CV outcomes as well as the optimal tailored design of these programs across different subgroups of patients, is still not completely assessed.

In a recent statement, the American Heart Association (AHA) proposed a framework to refer certain cancer patients at higher risk of CVD (according to previous therapeutic cancer management) to a cardio-oncology rehabilitation (CORE) program.[22] The development of a comprehensive model of CORE was suggested, identifying patients to deliver a multimodality approach based on Cardiac Rehabilitation (CR), including exercise training (ET), nutritional counselling and CVRF assessment, to prevent CV morbidity and improve cardiorespiratory fitness (CRF). Impaired CRF predisposes to noncancer competing morbidity and mortality observed in cancer survivors, also contributing to symptom burden and poor HRQoL.[23]

According to AHA statement, patients exposed to higher doses of cardiotoxic chemotherapeutic, radiation treatment regimens or patients with cardiac symptoms, multiple CVRF, history of reduced left ventricular ejection fraction (LVEF), valvular disease or CAD, regardless of previous therapeutic approaches, should be considered eligible to CORE.[22]

The significant and global clinical benefits evidenced by contemporary structured CR programs in individuals with CVD, based on a systematic conjunction of medical therapies with ET performed under close monitoring from a multidisciplinary specialized team, can provide the rationale for applying this successful approach in cancer patients as well, potentially questioning the standard of care offered to some cancer survivors. [24,25]

The AHA framework takes into consideration the exercise prescription under special considerations and comorbidities, selecting patients that require close monitoring and medical supervision, in a multimodal comprehensive approach.[22] It also highlights the need for the remaining cancer survivors to be guided to supervised exercise programs, in a community setting.

Since exercise programs are being offered to cancer survivors, including those at higher risk for CVD, the question that arises is what are the additional outcomes in benefits and safety issues that may overcome from a CR model, considering all the costs and resources implied, instead of an exercise intervention added to usual care, as recommended by international guidelines.

Moreover, the effect of this multimodal approach across the CV continuum in cancer survivors, namely in terms of CVRF control and CRF (this latter of recognized clinical importance because of its association with incidence of treatment related toxicity, including CVD, cancer-specific and CV mortality) is still not fully ascertained.[26-28]

In a recent scoping review, the acceptability of CR offered to cancer survivors and the impact on health outcomes was investigated. [29] Authors included 9 studies in final synthesis, though

only one using a randomized controlled trial design (compared to usual care),[30] concluding that many health–related and psychosocial benefits may be associated with CR, suggesting further research to better understand how to integrate cancer survivors in these programs, to improve generalization of findings and its acceptability, according to population characteristics.[29]

Given these data, more studies are needed to investigate outcomes obtained with a comprehensive approach in specific subgroups of cancer survivors, researching physical and psychosocial benefits that may in the future reinforce these interventions in the same way that CR is now recommended in several clinical situations, bringing new perspectives on the continuum of care offered to cancer patients, beyond exercise training.[31]

2. Study objectives

2.1 Primary objective

The primary objective of this trial is to determine the impact of an eight-week center-based cardiac rehabilitation program (CBCR) compared to usual care encompassing community-based exercise (CBET) on cardiorespiratory fitness.

2.2 Secondary objectives

As secondary objectives, we aim to evaluate the effects of CBCR versus CBET in quality of life, psychosocial outcomes, physical function, fatigue, health literacy, cardiovascular risk factors and inflammatory biomarkers. We also aim to evaluate safety (adverse events), satisfaction, adherence and cost-effectiveness of CBCR versus CBET.

The central **hypothesis** of the CORE trial is that a CBCR is more effective than CBET, in terms of cardiorespiratory fitness, cardiovascular risk factors control and quality of life, among cancer survivors at high cardiovascular risk.

3. Study design

This is a prospective, single-center, single-blinded, randomized controlled trial with a parallel two-arm group, to be performed in Portugal. Cancer survivors will be recruited from the hospital Oncology and Hematology departments of the Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia. After successfully completing all screening and baseline procedures, participants will be randomized in a 1:1 ratio to receive either a CBCR program or CBET program. Cancer survivors who meet all inclusion criteria and none of the exclusion criteria will be enrolled; eighty (n=80) participants are planned. Outcomes will be assessed at baseline (M_0) and after the 8-week intervention (M_1), at hospital facility, over two non-consecutive days. The total duration of participant participation is expected to be 2.5 months. The total duration of the study is expected to be two years. Before study initiation and enrollment, all investigators, clinicians and health professionals will complete study-specific training for the topic and the study protocol.

4. Study Population

Cancer survivors followed at the hospitals' Oncology and Hematology departments who meet the inclusion and exclusion criteria will be eligible for participation and will be invited in a clinical consultation to participate in this study. Once a potentially eligible cancer survivor is identified at a clinical consultation, the principal investigator will present the study (purpose, potential risks and benefits, requirements of the study, participant rights) to him/her for consideration. The cancer survivor will be given enough time to carefully consider

participation. If he/she agrees to participate the initial visit will be scheduled (visit V1). Screening assessments will include physical examination, biochemical measures, office blood pressure, and exercise testing, prior to a final decision about eligibility. Reasons for exclusion, declining participation and screening failure will be registered.

4.1 Inclusion criteria

To be eligible to participate in this study, a participant must meet the following criteria:

1) Cancer survivors, aged >18 years, in follow-up after primary treatment with curative intent

1.1) exposed to the following therapies: high-dose anthracycline or high dose radiotherapy (thoracic wall); low-dose anthracycline or anti-human epidermal growth factor receptor-type 2 drugs (anti-HER2) alone plus ≥ 2 CVRF and / or age ≥ 60 years at cancer treatment; low-dose anthracycline followed by anti-HER2

and/or

1.2) prior history of CAD, moderate valvular disease; left ventricular ejection fraction (LVEF) <50%

1.3) Having concluded primary treatment at least 2 months prior to inclusion

4.2 Exclusion criteria

To be eligible to participate in this study, cancer survivors must not meet any of the following criteria:

1) previous participation in a cardiac rehabilitation

2) contraindications to ET (e.g. musculoskeletal or neurologic disorders, unstable *angor pectoris*, decompensated HF, active myocarditis, complex ventricular arrhythmias)

3) active cancer

4) considered unsuitable *as per* principal investigator judgment (namely due to expected inability to fulfil the proposed trial schedule).

4.3 Medication

All participants should be maintained on the previous medications throughout the 8-week intervention period, as medically feasible. Changes in current medication and/or administration of new medication should be registered.

4.4 Randomization procedures

Cancer survivors who successfully complete the screening assessments will be randomized into the study. Eligible patients will be randomly assigned in a 1:1 ratio to undergo an 8-week CBCR (n=40) or CBET (n=40). Computer-based randomization (www.sealedenvelope.com) will be generated using a permutated block design with random block sizes with stratification by two dichotomous variables: sex and age (<65 or ≥65 years old)**,** with outcome communicated by telephone. The two intervention arms will run in a parallel fashion.

Participants will not be blinded owing to the nature of the intervention. Except for those who will deliver the intervention, those assessing outcome measures will be kept blinded to subject allocation.

4.5 Screen failures

Cancer survivors who are ineligible for the study based on screening assessments will be considered screen failures and registered as such. Reason(s) for failing screening, date of screening, and participant identification number will be required.

4.6 Participant withdrawal or discontinuation from study

Participants are free to withdraw from participation in the study at any time upon request (reasons for withdrawal will be recorded). They may decide to discontinue the intervention but

continue to be followed, hence participating in the subsequent assessments. The investigator/clinician may discontinue a participant's participation in case of a clinical adverse event or other medical condition such that continued participation in the study would not be in the best interest of the participant (reasons for withdrawal will be recorded).

4.7 Replacement of participant

Randomized subjects will not be replaced if discontinued.

5. Study endpoints

5.1 Primary outcome measure

- Change in cardiorespiratory fitness assessed by the VO_{2peak}, derived from a symptom-limited CPET performed on a treadmill, using a modified version of the Bruce protocol (from baseline to 8-week)

5.2 Secondary outcome measures

- Change in office arterial blood pressure and heart rate (from baseline to 8-week)
- Change in lipid profile, glycated hemoglobin and inflammatory biomarkers (from baseline to 8-week)
- Change in smoking status (from baseline to 8-week)
- Change in anxiety scores (from baseline to 8-week)
- Change in depression scores (from baseline to 8-week)
- Change in body composition (from baseline to 8-week)
- Change in quality of life (from baseline to 8-week)
- Change in physical activity (from baseline to 8-week)
- Change in fatigue (from baseline to 8-week)

- Change in health literacy (from baseline to 8-week)
- Change in physical function (from baseline to 8-week)
- Adverse events (including adverse events related to the exercise training)
- Participants satisfaction with the intervention
- Feasibility parameters (retention rate, intervention adherence, completion rate)

6. Study intervention

Participants will be randomized to one of two arms.

1) Center-based CR program (CBCR): the intervention will consist of core components of a CR program delivered by a multidisciplinary rehabilitation team in addition to standard medical care:

a) Baseline consultation with a physiatrist, addressing comorbidities, cardiovascular risk factor control, disabilities and rehabilitation needs; case-by-case discussion with a cardiologist specialized in cardiac rehabilitation for tailoring of exercise prescription.

b) Individualized plan, delivered by a nutritionist, addressing dietary goals to improve modifiable cardiovascular risk factor control.

c) Psychological management intervention addressing psychosocial outcomes and motivation for healthy lifestyle habits (weekly group sessions and individualized approach when needed)

d) Educational meeting: monthly group sessions, delivered by a multidisciplinary team, with health education purposes, regarding cardiovascular risk factor control

e) Exercise training – cancer survivors will participate in two combined exercise sessions *per* week, for an eight-week period, performed at hospital facilities, conducted by a physiotherapist under medical supervision, in groups of 4 to 6 participants. Each session will include 5-10 minutes of warm-up (consisting in balance and dynamic range of

motion exercises), 30-40 minutes of aerobic conditioning exercises, 10-15 minutes of strength training and 5-10 minutes of cool-down (including static stretching of major muscle groups). The aerobic exercise component will be performed on a treadmill or cycloergometer at a level of 50-80% of participants initial hear rate reserve (moderate to vigorous exercise intensity, determined at the time of their baseline cardiopulmonary exercise test, rating of perceived exertion 12 to 16 on the Borg scale, with gradual progression of exercise volume according to cardiac rehabilitation guidelines. Resistance training will be performed initially at 40-60% of the 1 repetition maximum, 1 set of 10-15 repetitions, increasing to 2 sets, of 3-5 resistance exercises of the major muscle groups performed with free weights; if free of symptoms, training load will be gradually increased. Participants will be encouraged by the rehabilitation team to perform physical activity on the remaining days of the week, in accordance with the recommendations for cancer survivors and patients with cardiovascular disease. Heart rate will be continuously monitored during sessions.

2) Community-based exercise training (CBET): this arm will consist of standard medical and supportive care provided by the participants' physicians supplemented by an exercise training intervention, as recommended for cancer survivors. Participants will receive nutritional and psychological support on demand, in hospital setting. The exercise program will be performed at a community-based facility (local gym), conducted by an exercise physiologist, certified in exercise for cancer patients (http://canrehab.co.uk/). Each exercise session, in groups of 3 to 5 participants, will include upper and lower limbs callisthenic exercises, with intensity assessed by the participant`s rating of perceived exertion (12 to 16 on the Borg Scale). Resistance training will follow the same characteristics of the exercise program of the CBCR arm. Participants will also be encouraged to achieve the weekly recommended physical activity levels.

6.1 Measures of treatment compliance

Compliance with the exercise program will be assessed as the percentage of expected sessions attended over the training period. The physiotherapist/exercise specialist will be asked to keep a participant diary/exercise log noting the day and date of each exercise session, exercise session parameters, and any adverse events occurring during/after the exercise sessions.

7. Study procedures and guidelines

Written informed consent must be obtained before performing any procedure. The investigator is responsible for ensuring that all assessments are performed according to the protocol and that the appropriate data are recorded in the case report forms. Missed visits or assessments that are not conducted should be reported (stating the reason when appropriate) on the case report forms.

7.1 Clinical assessments

7.1.1 Demographics, medical history, and medication

Demographic information (date of birth, sex, marital status, education level, employment status) and relevant medical history, including history of current disease (type of cancer, cancer treatment, time elapsed since cancer diagnosis and treatment, and co-morbidities), will be recorded. All medical data obtained must be supported in the participant's source documentation (e.g. medical charts or participant notes). A physical examination will be performed by an investigator who is a physician to exclude any limitations to physical activity or other prior or existing medical conditions that may exclude participants from the study. All medication and/or complementary therapies will be documented.

7.1.2 Cardiorespiratory fitness

Cardiorespiratory fitness will be assessed by the VO_{2peak}, derived from a symptom-limited CPET performed on a treadmill,[32] using a modified version of the Bruce protocol. The examiner deriving the VO_2peak, time of exercise, maximal heart rate and other CPET variables will be blinded to the study groups.

7.1.3 Physical function

Physical function will be assessed by measuring muscle strength and neuromuscular function. Muscle strength will be assessed through handgrip isometric maximal strength[33] by a digital hand dynamometer. Neuromuscular function using the one-minute Sit to Stand (STS) test.[34]

7.1.4 Body composition

Height and weight measurements will be attained using a standard wall-mounted stadiometer and scale, respectively. Body mass index will be calculated as weight (kg) divided by squared height (m^2). The percentage of fat mass and fat-free mass will be measured using a body composition analyzer.

7.1.5 Clinical laboratory assessments

A 12-hour fasting blood samples will be obtained for the analysis of total cholesterol, low-density lipoprotein-cholesterol, high-density-lipoprotein cholesterol, triglycerides, hemoglobin A1c (%), high-sensitivity C-reactive protein, and interleukin-6. The laboratory staff processing the samples will be blinded to the study groups.

7.1.6 Blood Pressure and Heart Rate

Office blood pressure and heart rate measurements (office values, in sitting position) will be assessed following current recommendations.[35] Trained staff will measure resting office blood pressure and heart rate with an automatic, validated, sphygmomanometer using appropriate cuffs according to individual-sized arms.

7.1.7 Physical Activity

Physical activity will be objectively measured for 7 consecutive days using an accelerometer. Participants will be asked to wear the accelerometer on the waist using an elastic strap with placement aligned with the right anterior iliac crest during all waking hours (except when bathing or swimming). At the end of the 7-day recording period, participants will return to the lab with their accelerometers and a study investigator will use a reader interface unit to download the accelerometer data into a desktop computer. An investigator blinded to the participant assignment will process the accelerometers data.

When returning the accelerometer, participants will also subjectively assess their physical activity in the previous seven days through the International Physical Activity Questionnaire (IPAQ) – short form.[36]

7.1.8 Smoking status

Cigarette smoking will be quantified to measure exposure to tobacco. The need for specific medication will be registered.

7.1.9 Quality of life and Psychosocial parameters

Quality of life will be assessed by the European Quality of Life 5 Dimensions (EQ-5D-5L) questionnaire. Screening for depression and anxiety will be performed using the Hospital

Anxiety and Depression Score (HADS). An investigator blinded to the participant assignment will process the questionnaires.

7.1.10 Fatigue

Fatigue score will be evaluated by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) questionnaire. An investigator blinded to the participant assignment will process the questionnaires.

7.1.11 Health Literacy

Health Literacy will be assessed by the Newest Vital Sign™.

7.1.12 Safety

Adverse events and exercise-related complications during the intervention will be registered, based on the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). The consequences associated with the adverse event will be recorded as follows: permanent discontinuation of exercise training before week eight or treatment interruption; dose modification (at least one session requiring dose reduction during training) and the total number of sessions requiring dose modification.

7.1.13 Feasibility

The following outcomes will be used to assess the feasibility of key trial parameters:

Consent rate: number of participants who meet inclusion criteria divided by the number who consented in writing to participate. The feasibility of the intervention will be defined as achievement of >25% of referred participants enrolling.[37] Reasons for not participating in the study will be registered.

Retention rate: number of participants who remained in the study.

Intervention adherence: total number of exercise sessions attended by participants allocated to the intervention. Mean adherence rate defined as > 80% at the exercise sessions.[43] Reasons for dropping out will be registered.

Completion rate: number of participants that completed all the evaluations during the defined timeline.

7.1.14 Satisfaction

Participants satisfaction with the intervention will be assessed using a questionnaire (5-item, with a 5-point Likert scale, questionnaire (1 being very dissatisfied and 5 being very satisfied).

7.3 Evaluations by visit

The following table lists the assessment procedures and indicates (X) in which visits they are performed. Written informed consent should be obtained before performing screening procedures. The investigator is responsible for ensuring that all assessments are performed according to the protocol, and that data are recorded in the case report forms. Missed or partial visits/ assessments must be reported on the case report forms (reasons should be provided).

Phase	Screening	Inclusion/Baseline	After intervention
Visit	1	2	3
Month	-1/2	0	2
Day	-8	0	60
Informed consent form	X		
Randomization		X	
Inclusion/exclusion criteria	X	X	

Med history/demography	X	X	
Medication	X	X	X
Physical exam	X		
Cardiorespiratory fitness/exercise testing	X		X
Body composition		X	X
Office BP and heart rate		X	X
Fatigue questionnaire		X	X
Physical function (handgrip strength and STS)		X	X
Blood collection		X	X
Smoking status		X	X
HADS questionnaire		X	X
Quality of life questionnaire		X	X
Physical activity (accelerometer and IPAQ-SF)		X*	X
Health Literacy questionnaire		X	X
Adverse events		X	X
Satisfaction questionnaire			X

* Deliver the accelerometer at visit 1; BP, blood pressure. HADS, Hospital Anxiety and Depression Score. IPAQ-SF, International Physical Activity Questionnaire – short form. STS, one-minute Sit to Stand test.

8. Statistical analysis plan

8.1 Sample size calculation

The study is powered for the primary endpoint of cardiorespiratory fitness ($VO2_{peak}$). The number of participants required for the trial was calculated by a priori power analysis

(G*Power 3.1, University Düsseldorf, Germany). Based on a between-group mean difference of changes induced by cardiac rehabilitation interventions in cardiovascular patients[38,39] compared to exercise-based interventions delivered to cancer patients[40], a total of 36 participants in each group was estimated [38,40] assuming a power of 0.8 and using unpaired t-tests, with a moderate effect (d=0.6) on cardiorespiratory fitness ($VO2_{peak}$). To accommodate for a 10% attrition rate, we will recruit a total of 80 participants (40 in each group).

8.2. General considerations

A study flow chart will be constructed according to the CONSORT statement (http://www.consort-statement.org/). The analyses will be performed based on the intention-to-treat principle. A baseline table with the characterization variables will be summarized by treatment group. For continuous variables, means ± standard deviations if the parameter follows a normal distribution or median [interquartile range] if the distribution is not normal will be presented according to treatment group. Between-group differences at baseline will be tested with Student's independent t-test or nonparametric Mann–Whitney U test. For the categorical variables, the results will be presented as counts and percentages. Between-treatment comparisons at baseline in categorical variables will be tested with chi-square test or Fischer test if appropriated. The assessment of compliance with the intervention and the safety of exercise training will be summarized for both groups. Adverse events, if any, will be reported by treatment group.

8.3 Analysis of the primary outcome

Between-group differences in the change (difference) in cardiorespiratory fitness ($VO2_{peak}$) from baseline to the end of the intervention will be tested with Student's independent t-test or the Mann-Whitney U test. A univariate general linear model will also be performed to ascertain

the differences in the change in the primary outcome between treatments with treatment group as fixed factor and baseline differences in variables of interest as covariate. Mean differences will be expressed with their two-sided 95% confidence interval. Student's paired t-tests or the Wilcoxon signed-rank test will be performed for within-group comparisons from baseline to the end of the intervention.

8.4 Analysis of the secondary outcomes

The change from baseline to the end of the 8-week interventions in the secondary endpoints will be analyzed using the same statistical methods as those used for the primary outcome. Between-group differences in the change from baseline to the end of the intervention will be tested with Student's independent t-test or the Mann-Whitney U test. Student's paired t-tests or the Wilcoxon signed-rank test will be performed for within-group comparisons from baseline to the end of the intervention.

8.5 Subgroup analysis

Subgroup analyses may be considered at the time of the statistical analysis taking into account the results of other studies [e.g. men versus women, age (>65 versus ≤65)].

9. Ethics, data handling, and regulatory obligations

- The investigator is responsible for obtaining written informed consent (in duplicate, the investigator will retain one original and a signed copy must be given to the participant) before performing any screening procedure and after adequate explanation of the study purpose, methods, potential risks and benefits, requirements of the study, and participant rights. The investigator must ensure that all the procedures are conducted according to the Declaration of Helsinki.

- Before study initiation, the hospital ethics committee must grant ethical approval.
- The trial will be registered at ClinicalTrials.gov before study initiation.
- The investigator must ensure that confidentiality is maintained. Data processing will be in accordance with Portuguese law.
- Data will be recorded by the physician (investigator) and clinical researchers on the participants' case report form and verified by the principal investigator according to good clinical practices.
- Data will be taken from different sources (e.g., medical records, laboratory data); supporting copies of source documentation, informed consents, and case report forms will be kept for 5 years after the end of the study.

10. Steering committee

A Steering Committee comprising national (Portuguese) experts in the exercise, oncology and rehabilitation fields will provide oversight and advice to ensure the most efficient conduct and execution of the trial. Steering Committee members may be investigators in the study. The focus of the committee will be on the exercise and rehabilitation intervention, ethical, and scientific integrity of the study.

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