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

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Abstract

**Background:** Cancer survivors are challenging patients, as they often present increased cardiovascular risk. In this background, cardio-oncology rehabilitation frameworks for specific cancer patients have been proposed. However, optimal program designs, as well as their overall safety and efficacy in different subsets of patients, are not fully ascertained.

**Design:** Single-center, pragmatic, prospective, randomized controlled trial performed in Portugal aiming to evaluate the impact of a center-based cardiac rehabilitation program, consisting of exercise training, nutritional counselling, psychosocial management and lifestyle behavior change, compared to community-based exercise training, in cancer survivors.

**Methods:** Adult cancer survivors (N=80) exposed to cardiotoxic cancer treatment and/or with previous cardiovascular disease will be randomized (1:1) to receive either an eight-week cardiac rehabilitation program or community-based exercise training. Primary endpoint is cardiorespiratory fitness; secondary endpoints are physical activity, psychosocial parameters, blood pressure, body composition, lipids and inflammatory parameters. Physical function, quality of life, fatigue, health literacy, and feasibility will be assessed; a cost-effectiveness evaluation will also be performed. Between-group differences at baseline and in the change from baseline to the end of the study will be tested with unpaired t tests or Mann-Whitney U test. Paired t tests or Wilcoxon signed-rank test will be performed for within-group comparisons.

**Conclusion:** This trial will address the overall impact of a contemporary cardiac rehabilitation program framework in cancer survivors, as compared to a community-based exercise training. Given the higher cardiovascular risk in several groups of cancer patients, our results could provide novel insights into optimized preventive strategies in this complex patient population.

**Keywords:** cancer survivors; cardiac rehabilitation; cardiorespiratory fitness; cardiovascular risk factors; exercise training.
Introduction

As survival rates for several cancers continue to improve, there is a growing awareness about the increased risk of morbidity and mortality from non-cancer causes among cancer survivors.\textsuperscript{1,2} Many of these individuals can be at risk for cardiovascular disease (CVD), a concept which has been related (at least partially) to increases in the burden of cardiovascular risk factors (CVRF), aging, cancer-related therapies, as well as their dynamic interactions.\textsuperscript{3-6} Data from different reports concurs as to increases in both CVRF as well as cardiovascular (CV) mortality among cancer survivors.\textsuperscript{7-9} Indeed, several cancers and CVD share common risk factors such as smoking, unbalanced diets and physical inactivity.\textsuperscript{4,10,11} Psychological factors such as personality traits, stressors and trauma, chronic anxiety and depression are also common risk factors for cancer and CVD.\textsuperscript{10}

Heart failure (HF) is one of the most concerning CV complications of cancer therapy.\textsuperscript{6} In addition, coronary artery disease (CAD) can also be more prevalent in this setting.\textsuperscript{12} In this regard, chemotherapy can induce myocardial ischemia, while mediastinal radiotherapy may accelerate coronary damage.\textsuperscript{6,13} The mechanisms associated with these side effects range from endothelial injury to arterial thrombosis, but the effects of CVRF aggravation may also mediate the expression of atherosclerotic disease.\textsuperscript{12} Given these issues, the potential importance of preventive strategies in patients at increased risk for cardiotoxicity such as those with major CVRF burden or pre-existing CVD has progressively gained the spotlight.\textsuperscript{14-16}

Over the years, data have emerged concerning several potential benefits of exercise-based interventions, across different stages of the cancer continuum.\textsuperscript{15-17} Current recommendations highlight the relevance of risk assessment and referral for physical activity (PA) and exercise training (ET).\textsuperscript{15,18} However, exercise programs are delivered across various settings, and encompass different characteristics (e.g., supervision, composition, patient characteristics).\textsuperscript{15,16,19,20} In this setting, and although there have been major advances in this field, the full scope of these exercise-based interventions, as well as their optimal design across diverse subgroups of patients, is still not fully ascertained.

The American Heart Association (AHA) has proposed a framework to refer cancer patients at higher risk of CVD to a comprehensive cardio-oncology rehabilitation
program, including different facets ranging from ET to nutritional and psychological counselling, as well as overall CVRF optimization.\textsuperscript{21,22} The overall benefits associated with contemporary cardiac rehabilitation programs in individuals with CVD provide the rationale for applying this approach in cancer patients as well.\textsuperscript{23-25} The AHA framework takes into consideration the exercise prescription under special considerations and comorbidities, while also highlighting the need for the remaining cancer survivors to be guided to supervised exercise programs, in a community setting.\textsuperscript{21} Since exercise programs are being offered to cancer survivors, including those at higher risk for developing cardiotoxicity,\textsuperscript{19} there could be great relevance in addressing the possible additional benefits associated with a cardiac rehabilitation model, while also considering the costs and resources needed in comparison to usual care.\textsuperscript{22} Moreover, the effect of this multimodal approach across the CV continuum in cancer survivors, namely in terms of CVRF control and cardiorespiratory fitness (CRF) is still not fully ascertained.\textsuperscript{26-29} Importantly, the overall effects of a center-based cardiac rehabilitation program (CBCR) have not been extensively evaluated in cancer survivors with previous CVD and/or exposed to cardiotoxic cancer treatment.\textsuperscript{9,30} While preliminary data suggests that ET may be effective to improve CRF in cancer survivors,\textsuperscript{25,29} there is still a need for clinical trials investigating the feasibility, cost-effectiveness and efficacy of a comprehensive approach – encompassing ET as a central component - in specific subgroups of cancer survivors, examining physical, psychological (e.g. anxiety and depression) and psychosocial benefits, that may in the future reinforce these interventions in the same way that cardiac rehabilitation (CR) is now recommended in several clinical conditions,\textsuperscript{31,32} bringing new perspectives across the span of the cancer care. The present trial aims to determine the impact of an eight-week CBCR compared to a community-based exercise training (CBET) on CRF, CVRF control, quality of life (QoL) and physical function, in a population of cancer survivors at high CV risk.

Methods

Study Design

CORE is a single-center, prospective, two-arm randomized controlled trial (RCT; Clinicaltrials.gov: NCT05132998) performed in Portugal. In addition to evaluating the
primary endpoint of CRF (as assessed by VO$_{2peak}$), the study will also assess effects on QoL, physical function, fatigue, health literacy, along with a constellation of CVD risk factors and biomarkers. Healthcare costs and QoL will be considered for a cost-effectiveness evaluation. A diagram of the study protocol is shown in figure 1.

**Study Population**

Patients who meet the following criteria will be eligible for this study:

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

Exclusion criteria: 1) previous participation in a cardiac rehabilitation; 2) contraindications to ET (e.g. musculoskeletal or neurologic disorders, unstable angina pectoris, decompensated HF, active myocarditis, complex ventricular arrhythmias); 3) active cancer; 4) considered unsuitable as per principal investigator (PI) judgment (namely due to expected inability to fulfil the proposed trial schedule).

**Recruitment and Screening Procedures for the CORE Trial**

All potentially eligible participants will be recruited via direct referral from medical oncologists and hematologists. Eligible patients will provide written informed consent to undergo medical screening and physical examination after verbal discussion with the PI. Screening assessments will also include 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.

**Randomization and blinding**

After baseline testing, eligible patients will be randomly assigned in a 1:1 ratio to
undergo an eight-week CBCR (CBCR group, n=40) or a CBET with on-demand diet/nutritional counselling and psychosocial management (CBET group, 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: gender and age (<65 or ≥65 years old), with outcome communicated by telephone. The two intervention arms will run in a parallel fashion. Patients 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.

Interventions

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\(^{31-33}\) delivered by a multidisciplinary rehabilitation team in addition to standard medical care:

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

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

e) Exercise training – patients 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 (HR) reserve (moderate to vigorous exercise
intensity, determined at the time of their baseline cardiopulmonary exercise test (CPET), rating of perceived exertion (RPE) 12 to 16 on the Borg scale, \cite{34} with gradual progression of exercise volume according to CR guidelines.\cite{32,35} Resistance training will be performed initially at 40-60% of the 1 repetition maximum (1RM), 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.\cite{32} Patients will be encouraged by the rehabilitation team to perform PA on the remaining days of the week, in accordance with the recommendations for cancer patients and CVD.\cite{15,18,31,36} HR 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 patients’ physicians supplemented by a CBET, as recommended for cancer survivors.\cite{2} Patients 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 patient’s rating of perceived exertion (RPE 12 to 16 on the Borg Scale).\cite{34} Resistance training will follow the same characteristics of the exercise program of the CPCP arm. Patients will also be encouraged to achieve the weekly recommended PA levels.\cite{15,18}

Assessments
Demographical data and medical history (including comorbidities, medication, time elapsed since cancer diagnosis and treatment, as well as oncological treatments performed) will be collected from the electronic medical records. Primary and secondary outcome measures will be collected at the baseline assessment and after the eight-week intervention period, performed at hospital facilities, over two non-consecutive days.

Primary endpoint
The primary outcome measure will be the CRF, assessed by the \( \text{VO}_{2\text{peak}} \), derived from a symptom-limited CPET performed on a treadmill,\cite{37,38} using a modified version of the
Bruce protocol.

**Secondary endpoints**

**Physical function**

*Muscle strength* - Upper limb strength will be assessed through handgrip isometric maximal strength by a digital hand dynamometer.

*Neuromuscular function* - Functional performance resembling activities of daily living will be evaluated using the one-minute Sit to Stand (STS) test. The STS test has shown high reliability and good criterion related validity with other exercise capacity tests such as the six-minute walk test.

**CVRF control**

*Body Composition* – Height, weight, and waist circumference measurements will be performed and body mass index (BMI) calculated. The percentage of body fat mass and lean mass will be assessed by electrical bioimpedance.

*Lipid profile and inflammatory markers* – 12-hour fasting blood samples will be obtained for the analysis of total cholesterol, low-density lipoprotein-cholesterol (LDLc), high-density-lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein (hsCRP), and interleukin-6. Lipid control will be considered by LDLc levels, in accordance with the current guidelines.

*Diabetes mellitus* - Glycated hemoglobin (HbA1c) will be assessed, in patients with diabetes. Normal values will be defined as HbA1c <7%.

Office *Blood pressure* and HR measurements (office values, in sitting position) will be assessed following current recommendations.

*Physical activity* – will be measured for seven consecutive days using an accelerometer. When returning the accelerometer, patients will also subjectively assess their PA in the previous seven days through the International Physical Activity Questionnaire (IPAQ) – short form.

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

*Quality of Life and Psychosocial outcomes* – QoL will be assessed by the European Quality of Life 5 Dimensions (EQ-5D-5L) questionnaire (the Portuguese version of the questionnaire have been validated and showed high test-re-test reliability, and good
acceptability and validity in health state measuring).\textsuperscript{45,46} Screening for depression and anxiety will be performed using the Hospital Anxiety and Depression Score (HADS); the Portuguese version of HADS is a reliable and valid instrument for screening anxiety and depression in medical settings.\textsuperscript{47}

**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.\textsuperscript{48} The Portuguese version of the QLQ-C30 showed good metric properties, and measures the same constructs, the same way, in cancer setting, as versions from other languages and cultures.\textsuperscript{48}

**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).\textsuperscript{49} The consequences associated with the adverse event will be recorded as follows: permanent discontinuation of ET 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.

**Feasibility**

Outcomes used to assess the feasibility of key trial parameters are defined below:

- **Consent rate:** number of patients 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 patients enrolling.\textsuperscript{50} 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.\textsuperscript{50} Reasons for dropping out will be registered.
- **Completion rate** – number of patients that completed all the evaluations during the defined timeline.

**Health Literacy**
Health Literacy\textsuperscript{51} will be assessed by the Newest Vital Sign\textsuperscript{TM}, an assessment tool available in Portuguese language and validated in Portuguese population.\textsuperscript{52,53}

**Cost-effectiveness analysis**

Costs will be calculated from the provider perspective, which includes the costs incurred by the health institution providing health services; from the patient perspective, the costs associated with the access to the service, therapeutic activities and outpatient visits; and from a wide societal perspective, which is the aggregation of both previous perspectives.\textsuperscript{54,55} Costs are incurred in a period less than 1 year and so no discounting is considered. QoL will be measured using the EQ-5D-5L.\textsuperscript{45,46} The indicator quality-adjusted life-year (QALY) will be measured in a scale 0 to 1, where 0 means worst health and 1 means best health. The average cost per rehabilitated patient will be computed. Additionally, the incremental cost effectiveness ratio per QALY will be calculated, comparing both interventions.\textsuperscript{54,55} Information on participants’ resources will be assessed with an interviewer administered questionnaire after the eight-week intervention. Data will be extrapolated beyond this period, to explore potential lifetime cost-effectiveness. The model used will link the changes obtained in CFR to the CVD mortality, for estimate the cost-per-QALY associated with each intervention arm.\textsuperscript{55}

**Patients’ perspective**

A questionnaire constructed to survey patient satisfaction with the CBCR and with the CBET will be delivered at the end of the intervention for both groups (5-item, with a 5-point Likert scale).

**Sample size Calculation**

The study is powered for the primary endpoint of CRF (VO\textsubscript{2 peak}). The number of patients required for the trial was calculated by a priori power analysis (G*Power 3.1, University Düsseldorf, Germany), based on the between-group mean difference of changes induced by the interventions using unpaired t-tests, with a moderate effect (\textit{d}=0.6) on CRF induced by CR interventions in CV patients\textsuperscript{56,57} compared to exercise-based interventions delivered to cancer patients,\textsuperscript{58} assuming a power of 0.8, which gives a total of 36 patients in each group.\textsuperscript{56,58} To accommodate for a 10% attrition rate, we will recruit a total of 80 participants (40 in each group).
**Data analysis**

To analyse outcomes for all participants based on their assigned intervention, the intention-to-treat principle will be applied. Data distribution will be assessed through the Shapiro-Wilk test. Between-group differences in the change (difference) in primary and secondary outcomes from baseline to the end of the intervention will be tested with the 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. The significance level will be set a priori at $p < 0.05$. Data will be analysed using the SPSS statistical software version 24.0 (SPSS Inc., USA).

**Discussion**

This pragmatic study will be, to our knowledge, the first RCT to compare a contemporary CR program with a CBET, in cancer survivors. Given the data supporting the potential benefits of exercise (particularly in settings such as breast cancer),\textsuperscript{19} in terms of functional improvements and QoL, cancer survivor support care must consider ET as an adjuvant therapy (besides PA recommendations)\textsuperscript{15,18} which makes tailoring of this intervention an area of major interest.\textsuperscript{17,22} ET safety, especially in high risk CV patients, constitutes a particular concern, in order to determine the appropriate level of medical supervision advised, according to clinical determinants. The AHA statement,\textsuperscript{21} endorsed by the American Cancer Society, includes a framework suggestion for a wide variety of clinical situations, from patients undergoing cardiotoxic therapy (regardless their age group or CVRF burden), as well as patients with different cancer types with known CVD. Thus, data pertaining to optimal program designs and components, in terms of safety and efficacy, are of paramount contemporary importance.

CR frameworks have the potential to become an important pillar in the support of certain subgroups of cancer patients.\textsuperscript{20,21,24,59} Interestingly, data have shown that in CV patients these programs have a pivotal role, as attested by their impact in terms of morbidity, QoL and mortality.\textsuperscript{23,31,36}

Exercise-based CR programs for cancer survivors have gained increased interest.\textsuperscript{24,59,60}
However, most studies focused on specific cancer subtypes and considered only chemotherapy treatment with regard to the risk for developing cardiotoxicity, mainly with heart function related variables as primary endpoints. Differences in terms of design (e.g. CBET group) should also be acknowledged. In the CORE trial, patients with various types of cancer and undergoing several treatments options (regarding cardiotoxicity), and with different cardiac comorbidities will be eligible, reproducing the clinical practice heterogeneity, with the goal of mitigating future CV morbidity, through improvement of physical function and CVRF burden reduction, without depriving any cancer patient of a guided exercise intervention.

Variables such as CRF or gains in muscle strength have an important prognostic value. In fact, CRF (the primary endpoint in this trial) is recognized as an important parameter in overall health assessment across different settings, having been associated with the incidence of treatment related toxicity and symptom burden as well as CVD, cancer-specific and CV mortality. Special focus will be given to CVRF control, an important target of CR comprehensive approach. CV risk management together with lifestyle counselling, provided by a multidisciplinary specialized team, may prove to be fundamental in reducing CVRF burden and CV morbidity among cancer survivors.

Inflammation is also a recognized strong predictor of CVD and research has suggested that inflammatory markers, such as hsCRP, provide an alternative method for global assessment of CV risk. Prospective studies reported marked reductions in levels of inflammatory plasma biomarkers in patients with metabolic syndrome following CR. In cancer patients, exercise may decrease inflammatory cytokines, mitigating systemic inflammation, and reducing cancer and treatment side-effects.

Another important variable considered in this study, health literacy, has been defined as people’s knowledge, motivation and competences to access, understand, appraise, and apply health information to make judgments and take decisions concerning healthcare, disease prevention and health promotion to maintain or improve QoL. In Portugal, health literacy has started being addressed through national policies, but research on the topic is still scarce, whereby literature on this subject can potentially be practice changing in clinical setting, considering CVRF burden.

Multiple barriers have been suggested to explain the relative low adherence to CR programs. Given this background, we will assessed the feasibility and acceptability of the CORE trial to provide detailed information concerning some of the hindrances to
program application in this patient population. Given the lack of data on this topic, particularly in a Portuguese setting, the findings derived from this study will be of great value, by presenting an overview of some of the challenges to program implementation, and thus providing a potentially useful framework for further studies on this field. Identifying the most efficient use of limited resources available in health care national system is a big challenge for health professionals and policy makers. The cost-effectiveness economic evaluation will provide the economic savings for each health gain obtained in CBCR, measured in QoL, and it will also provide the average cost per rehabilitated patient, comparing the two interventions considered in this trial. This analysis is innovative since, to our knowledge, no previous study focused on cost-effectiveness in the context of CR for cancer survivors, despite the extrapolated data from the international literature regarding this multidisciplinary approach.  

Limitations
Some limitations should be acknowledged. Firstly, patients will be derived from a single center. Secondly, due to the impossibility of blinding patients and those who will deliver the intervention, the open design of this study may influence the retention rate of the community ET group. Thirdly, although patients will be stratified according to age and gender, the heterogeneity of the population in terms of cancer type and comorbidities, prior staging and cancer treatment should also be noted.

Conclusion
CORE trial will provide data on the overall role of a CR program framework among cancer survivors, focusing those with increased CV risk. The findings will add novel data on the potential impact of this intervention and may thus reinforce the role of a multilayered approach, in this challenging subset of patients, just as CR is currently recommended in many other clinical settings, beyond ET.

Trial status
Recruitment for this study commenced in September 2021 and is expected to be completed in September 2022, being the estimated completion date December 2022.

Abbreviations
AHA: American Heart Association; BMI: body mass index; CAD: coronary artery disease; CBCR: center-based cardiac rehabilitation program; CBET: community-based exercise training;
CR: cardiac rehabilitation; CRF: cardiorespiratory fitness; CTCAE: Common Terminology Criteria for Adverse Events; CV: cardiovascular; CVD: cardiovascular diseases; CVRF: cardiovascular risk factors; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EQ-5D: European Quality of Life 5 Dimensions; ET: exercise training; HADS: Hospital Anxiety and Depression Scale; HbA1c: glycated hemoglobin; HER2: human epidermal growth factor receptor 2; HF: heart failure; HR: heart rate; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukine-6; IPAQ: International Physical Activity Questionnaire; LDLc: low-density lipoprotein-cholesterol; LVEF: left ventricular ejection fraction; PA: physical activity; QoL: quality of life; RCT: randomized controlled trial; STS: sit-to-stand.

**Ethical approval**

Ethical approval for this study was obtained from the Centro Hospitalar Vila Nova de Gaia /Espinho Ethics Committee (reference number 168/2020).

**Authors Declarations of Interests:** none

**Authors’ contribution**

Sofia Viamonte, Ana Joaquim, Alberto Alves, Andreia Capela, Eduardo Vilela and Fernando Ribeiro conceived the idea for the study, contributed to the revision of the protocol, improved upon the design of this study and approved the final manuscript. Barbara Duarte, Cristina Ferreira and Nuno Dias Rato contributed for investigation, formal analysis and data curation. Aida Tavares and Mario Santos contributed to the revision of the protocol, read and approved the final manuscript.

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**References** (references 51 to 67 can be found in Supplement file)


49. Common Terminology Criteria for Adverse Events (CTCAE) version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute

Figure 1. Study flowchart
Highlights

- Exercise training should be part of any survivorship program for cancer patients
- Impact of cardiac rehabilitation vs community exercise in cancer patients is unknown
- First trial comparing a cardiac rehabilitation setting with community exercise
- Its results can be practice changing
- Cardiac rehabilitation might be beneficial in certain cancer survivor’s subgroups