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Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

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ABSTRACT

Introduction Androgen deprivation therapy (ADT) and radiotherapy (RT) increase survival in selected patients with prostate cancer (PCa). Nevertheless, the side effects of these therapies are associated with an increased risk of accidental falls and fractures and a decreased quality of life. Preliminary evidence suggests that physical exercise (PE) can be a valid strategy to reduce the side effects of ADT and RT in men with PCa. Despite this knowledge, most patients with PCa are insufficiently active, and there is a lack of data on the safety and adherence to the recommended dose of PE. This study protocol is designed to examine the feasibility and safety of a multicomponent experimental PE intervention targeting psychophysical and cognitive functions and the quality of life in this population.

Methods and analysis This is a pilot feasibility study. Twenty-five men currently treated with ADT and RT for PCa will be invited to participate in a 20-week, multicomponent PE intervention, including supervised and unsupervised exercise sessions and meeting the current recommendation for exercise in cancer. The primary outcomes are PE feasibility (recruitment, adherence, and drop-out rates) and safety (adverse events related and unrelated to the intervention). The secondary outcomes are muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life, and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up.

Ethics and dissemination The study has received ethics approval from The Area Vasta Nord Local Ethics Committee (Province of Reggio Emilia, June 23, 2020, Number 520/2020/SPER/IRCCSRE). Recruitment began in September 2020 and will be completed in September 2021. The results will be disseminated through scientific journals and conference presentations.

Trial registration ClinicalTrial.gov (NCT04500080)

Keywords Prostatic neoplasms, Accidental falls, Bone fractures, Exercise, Androgen deprivation therapy, Radiotherapy.

Strengths and limitations of this study

- This pilot study thoroughly assesses the feasibility and safety of a multicomponent experimental PE intervention for individuals with PCa receiving ADT and RT.
- Preliminary data regarding the efficacy of structured, supervised, and unsupervised aerobic, resistance, neuromotor, and impact-loading exercise on the bone health of this population will be provided.

- Both the ecological setting, a community sport facility, and the step-down approach, from supervised to unsupervised PE intervention, should foster the adoption of exercise as daily habits, promoting healthy behaviour.
- The single-group design does not allow for assessment of the efficacy of the multicomponent experimental PE intervention on the bone health outcomes of interest.

INTRODUCTION

Prostate cancer (PCa) affects approximately 3.7 million people worldwide, ranking first among the most prevalent cancers in the male population.[1] Curative treatment of locally advanced PCa usually entails radiotherapy (RT) frequently associated with androgen deprivation therapy (ADT).[2] This type of multimodal treatment is unfortunately associated with a large number of side effects.[3,4] Previous studies have demonstrated a significant increase in cancer-related fatigue in patients receiving RT, which not only decreases physical well-being but also affects daily activities, cognitive function, and quality of life.[5—7] Furthermore, it is well known that the cardiovascular, metabolic, cognitive, and musculoskeletal adverse effects of ADT lead to an increased number of accidental falls and fractures in this population.[8] Furthermore, since PCa incidence increases with age,[1] older patients are normally already at a greater risk of frailty due to the presence of other comorbidities that can dramatically affect physical function.[9] Exercise interventions can prevent a large number of these complications, improving the health and quality of life of individuals with PCa.[10,11] These exercise programmes should include moderate-high intensity activities that must be performed regularly to maintain exercise-related benefits.[12,13] A recent systematic review of randomized controlled trials (RCTs) showed that to counteract the negative effects of ADT on bone, multicomponent PE interventions involving aerobic, resistance and impact-loading exercise have been performed.[14] Although these interventions were feasible for most participants in the RCT, those study protocols did not systematically record the adherence rate or adverse events associated with the experimented PE interventions (Cagliari M et al. Feasibility and Safety of Physical Exercise to Preserve Bone Health in Men with Prostate Cancer Undergoing Androgen Deprivation Therapy: a Systematic Review. Unpublished material).[12,13] However, these data are fundamental to fostering individual compliance with the recommended dose of exercise.[12] In fact, despite the well-known benefits of PE for cancer survivors,[15,16] this population is frequently unactive[17] and reports several common barriers to exercise, such as the location or distance to facilities.[18—20] Furthermore, hospital-based supervised PE interventions can be challenging to implement because they requires the use of complex hospital resources,[18,21,22] and this modality does not promote long-term adherence to PE or changes towards a healthier lifestyle.

Therefore, based on previous research and our current descriptive study (Bressi et al. Physical exercise and lifestyle behaviours among men with prostate cancer: a cross sectional study. Unpublished Material), we developed a structured

experimental PE intervention that combines supervised and unsupervised exercise with a step-down approach. This PE intervention is implemented in a community sports facility and is currently being tested in a small group of patients with PCa receiving ADT and RT for feasibility and safety. Secondary outcomes include muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up. This study protocol describes the experimental PE intervention in detail, with related outcomes, to allow for reproducibility and adaptation to other contexts.

METHODS AND ANALYSIS

Patients and study design

This single group feasibility pilot study was approved by the Area Vasta Nord Local Ethics Committee of Azienda USL-IRCCS of Reggio Emilia (June 23, 2020, Number 520/2020/SPER/IRCCSRE) and was registered with ClinicalTrials.gov (Identifier NCT04500080). This study protocol adheres to the recommendation for clinical trials (SPIRIT) guidelines (additional file 1), and the study registration data set is shown in Table 1.[23] Eligible patients are adult men (≥18 years) with a histological diagnosis of PCa who are currently treated with ADT and RT and are able to communicate in the Italian language. Participants with musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate exercise will be excluded. Written informed consent will be obtained from all participants, who will be invited to participate in a 20-week structured, supervised and unsupervised, multicomponent PE programme. Patients will be assessed at baseline (T0), at the end of the intervention (T1), and at follow-up, which will occur 12 months from recruitment (T2).

Recruitment strategies

Between September 2020 and September 2021, eligible patients treated by the Radiotherapy Unit of Santa Maria Nuova Hospital of Reggio Emilia (Italy) will be given brief, written information about the study by their attending physician (radiotherapist or oncologist). Upon written consent, patients willing to receive more information will be referred to the Physical Medicine and Rehabilitation Unit and will receive a phone call by a research staff member (physiotherapist), who describes the study aim and modalities to them in detail. Patients who confirm their interest in participating will receive written information and consent forms to participate in the study to be filled out and signed. They will also make the first appointment to provide written consent and to perform the baseline assessment. The patient recruitment process is shown in Figure 1.

Baseline assessment

In the baseline assessment, demographic, anthropometric, clinical data, and physical function data will be collected. Clinical data include the date of diagnosis, tumour stage, time since receiving ADT and RT, and the presence of comorbidities assessed through the Charlson Comorbidity Index (CCI).[24] Physical function will be measured using a six-minute walk test (6MWT)[25] to calculate the intensity of aerobic exercise (AE).

Experimental PE intervention

The multicomponent experimental PE intervention will last 20 weeks and consists of supervised and unsupervised PE sessions held three times per week. Following a step-down approach, during the first eight weeks, all PE sessions will be supervised by a physiotherapist, while during the following four weeks, only one weekly session will be supervised, whereas the other two will be unsupervised; finally, during the last eight weeks of experimental PE, all sessions will be unsupervised. Supervised sessions will be conducted in small groups or individually at the Municipal Athletics Field in Reggio Emilia according to scheduled appointments, whereas the unsupervised sessions can be completed by participants in times, modalities and places of their convenience, providing for them the possibility to access the Municipal Athletics Field.

The multicomponent PE intervention meets the dictates for exercise components, posology (frequency, sets, repetitions, intensity) and progression recommended for healthy adults.[26] Its components are aerobic, resistance, core muscle stabilization, and neuromotor exercises associated with cognitive tasks. In addition, PE intervention will include impact-loading exercise to provide an effective bone osteogenic stimulus. This type of exercise has been considered an effective strategy to prevent loss of bone mineral density (BMD) in elderly patients[27,28] and has been applied in patients with PCa receiving ADT in previous studies.[14] Altogether, the components of this intervention should preserve muscle strength and improve fatigue, balance, and cognitive function,[26] and eventually, it should prevent accidental falls and fractures.

The intervention is tailored to individual general health, functional capacity and, as far as possible, preferences.

Supervised PE sessions

Supervised sessions last one hour and 15 minutes and include a period of warm up and cool-down and a combination of the following PE components:

- Aerobic exercise (AE) consists of 20-30 minutes of aerobic activity at moderate-high intensity, from 60 to 80% of maximum heart rate (% HRmax), previously determined through the 6MWT.[25] To obtain the greatest effects on bone health, the proposed AE activities are walking or jogging, depending on individual capacity and habitual or previous experiences of physical activity.
- Progressive resistance exercise (PRE) consists of strength activity of the major lower and upper extremity muscle groups, using body weight as a load and free weights (resistance bands, dumbbells, anklets with weight, medicine ball). During each session, the goal is to perform four to eight exercises targeting different muscle groups by performing two

to four sets of 8-15 repetitions for each exercise. The progression of intensity will be tailored to the individual using the Borg RPE scale,[29] starting with body weight and gradually increasing the load using free weights.[30] Adjustments to load will be made when participants can complete the highest number of specified repetitions (8 to 15, see also Table 2). Thus, the number of exercises, dose progression (sets, repetitions) and related difficulties (e.g., squat depth and/or duration, double task exercises) will be changed during the weeks based on the patient's compliance and performance (see also Table 2). For isometric exercises, dose will be incrementally increased by adding free weights, further limb exercise or asking for double task exercise, and/or increasing the duration of exercise from 20 to 60 seconds.

• Core muscle stabilization exercise (CSE) consists of postural and trunk stability exercises (e.g., strengthening of transverse abdominis and pelvic floor muscles). Participants will perform two core exercises per session in two-four sets of 8-15 repetitions. Sets, repetitions, additional free weights, additional upper body and/or lower body movements and time of exercise from 20 to 60 seconds will be used to increase the intensity of exercises.

• Neuromotor exercise (NE) consists of balance and functional (coordination) exercises associated with cognitive tasks (e.g., counting, adding, subtracting, saying day of weeks) and includes fit ball exercises (e.g., knee and contralateral upper limb extension sitting on fit ball), standing balance activities (e.g., stand on one leg) and dynamic functional tasks (e.g., stop walking balanced on one foot, walking backward). Participants will be asked to complete two to four static and dynamic exercises per session. Static exercises are performed in two-four sets of 20-60 seconds, while dynamic exercises are performed in two-four sets of 8-15 repetitions. To provide progression, exercises are modified by introducing difficulties (e.g., closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task).

• Impact-loading exercise (IE) consists of jumping, leaping, jumping rope, hopping on one leg, going up and down steps, etc., in other words, exercises that provide impact with the ground using the body weight as a load. Two to four exercises per session will be performed. Training intensity is increased by adding repetitions, additional free weights, introducing multidirectional movement, and raising the exercise speed. To provide a large number of stimuli, several tools will be used.

A detailed description of exercises, posology, tools, and progressivity is available in Table 2. Altogether, PRE, CSE, NE and IE are performed for 30-40 minutes each session.

Unsupervised PE sessions

Unsupervised sessions also consist of AE, PRE, CSE, NE, and IE. In addition to walking or jogging, AE can also be performed using bikes, stationary bikes, or other aerobic activities based on individual availability and preferences. Regarding the PRE, CSE, NE and IE components, exercises that trade on body weight or with resistance bands that will be provided to patients are taught and suggested to overcome the possible unavailability of appropriate tools. Each activity

and exercise will be explained to participants and practised by them during the supervised sessions. Furthermore, written educational material with instructions and pictures of the exercises will be provided to maximize accuracy of the unsupervised execution. The physiotherapist provides individualised indications regarding the activities to be performed during unsupervised sessions but also supports participants in progressively increasing the exercise workload when the individual perceives an improvement in their functional capacity.

Outcome measures

Primary outcome

Feasibility will be measured through recruitment, adherence, and dropout rates.

The recruitment rate is the proportion of eligible individuals referred to the Physical Medicine and Rehabilitation Unit by their treating physician included in the study.

Protocol adherence is the proportion of exercise sessions that are attempted and completed by each participant. The percentage of patients who withdraw from the study and their reason for withdrawal will also be registered.

Safety is measured through the recording of any adverse events related and not related to exercise and its grading for seriousness,[31] causality and health consequences by the researcher during the study.

Feasibility and safety are monitored by the physiotherapist through direct inquiry during the first 12 weeks of the programme when supervised sessions are implemented and through a weekly phone call during the last eight weeks of unsupervised sessions.

Secondary outcomes

Secondary outcome measures include changes in muscle strength, fatigue, cognitive function, balance, quality of life, symptoms of anxiety and depression, number of accidental falls and associated fractures, and participant satisfaction.

Muscle strength

The strength of the major lower and upper extremity muscle groups will be measured with the 10-RM test (extensor muscle group). The 10-RM test assesses the maximum weight that can be lifted for ten repetitions while maintaining the correct technique. Prior to attempting this test, participants will complete five minutes of aerobic warm-up and 1-2 sets of 15-20 repetitions with a light load. Then, the load will be progressively increased while the number of repetitions will decrease accordingly until only ten repetitions can be completed. A recovery period of two minutes will be provided between each set.[32,33]

Fatigue

Fatigue will be measured using the Fatigue Severity Scale (FSS), a 9-item questionnaire on how fatigue interferes with activities and that rates its severity. The item is scored on a 7-point Likert scale with 1 = strongly disagree and 7 = strongly agree. The minimum score = 9, and the maximum score = 63. A higher score indicates greater fatigue severity.[34]

Cognitive function

Cognitive function will be measured using the Mini Mental State Examination (MMSE), a brief cognitive test designed to assess the overall cognitive status of patients. The MMSE tests five areas of mental status (orientation; registration; attention and calculation; recall; language) and is scored on a scale of 30, with adequate cognition for most adults indicated by scores from 24 to 30.[35]

Balance

Balance will be measured using the Tinetti Performance Oriented Mobility Assessment (POMA). The Tinetti POMA scale is a clinical test used to measure balance and gait abilities. The balance section (POMA-B) consists of 9 items, while the gait section (POMA-G) consists of 8 items. Each item can receive an ordinal score from 0 to 2, where "0" indicates the highest level of impairment and "2" indicates individual independence. The maximum possible total score for POMA-T is 28, for POMA-B is 16, and for POMA-G is 12. A POMA-T cut-off score < 24 indicates a risk of falling.[36]

Quality of life

Quality of life will be measured using the Short Form-12 questionnaire (SF-12), which consists of twelve items measuring different physical and mental health parameters. Higher scores indicate better physical and mental health.[37]

Anxiety and depression level

Anxiety and depression level will be measured using the Hospital Anxiety and Depression Scale (HADS), a fourteen-item scale equally distributed across anxiety and depression states. The total score ranges from 0-21, with higher scores indicating greater levels of mood disturbances. In patients with cancer, a cut-off score of > 9 for the HADS-A and > 7 for the HADS-D indicates clinically relevant anxiety and depression levels, respectively.[38]

Accidental falls and fractures

During the intervention, accidental falls and fractures were recorded directly by the physiotherapist who supervised the sessions and performed the weekly phone call and thereafter at the 12-month follow-up.

Participant satisfaction

Patient satisfaction will be assessed through a simple structured interview. At the end of the intervention, each participant will be invited to answer the following four open-ended questions that investigate its acceptability:

• How do you assess the overall experience you have had by participating in this study?

• Which activities did you like the most?

• Which activities did you like least?

• What can to be improved in your opinion, or what would you have liked to have been offered?

A summary of the outcome measures and their assessments at follow-up is shown in Table 3.

Sample size calculation

No formal sample size requirement is needed for this single-group, pilot, feasibility study. At the Santa Maria Nuova Hospital of Reggio Emilia, nearly 30 patients/year undergo ADT and RT, and we aim to recruit 25 patients during the 12-month recruitment period.

Data analysis

All statistical analyses will be performed by the local Research and Statistics Unit of the AUSL-IRCCS of Reggio Emilia. The SAS System or R software will be used according to their availability at the time of data analyses. Descriptive statistics will be reported for feasibility and safety outcomes. For each percentage, the exact two-sided confidence interval will be calculated according to the Clopper-Pearson approach, ensuring a confidence level of at least 95%. In fact, since it is an exact technique, the confidence level typically does not coincide with 95%. Adverse events will be described and grouped into homogeneous classes. The data regarding patient satisfaction will be analysed to identify patterns of response and grouped into categories emerging from the data.

Descriptive statistics for secondary outcomes will be reported to inform potential future studies in terms of clinical health outcome measures. For all variables, percentiles, minimum, maximum, mean, and SD will be calculated. For the mean, a 95% two-sided confidence interval will be calculated assuming a t distribution.

Concerning the number of accidental falls and fractures, as counts, the confidence interval for the mean will be calculated according to the Poisson distribution.

Data management and archiving

The dataset will be stored on a password-protected computer and managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia to protect patient privacy.

Patient and public involvement

Patients will participate in the study design so that the time and spaces necessary for the home-based intervention can be adapted according to their availability and discretion. Participants may suggest changes related to the frequency and intensity of the sessions and inform the study team about which type of exercises they prefer.

ETHICS AND DISSEMINATION

This study was approved by the Area Vasta Nord Local Ethics Committee of Azienda USL-IRCCS of Reggio Emilia (June 23, 2020, Number 520/2020/SPER/IRCCSRE), which will also review potential modifications, if any. All patients will provide consent prior to participation. Results will be disseminated through scientific peer-reviewed journals and conference presentations. The expected impact for this study is the development of a useful and acceptable PE programme for patients with PCa receiving ADT and RT integrated into the daily routine of patients with PCa.

These results will inform which type of PE is required to improve adherence to the recommended PE guidelines for cancer survivors and will help researchers plan feasible PE interventions whose efficacy on bone health is to be verified through well-designed RCTs.

Author contributions BB, CI, MC, SC, SF and SCo contributed to study conceptualization and design and provided input into the development of the protocol. BB, MC and SCo drafted the manuscript, and all authors revised it critically and approved the final version for publication.

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Table 1 Study registration data set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04500080
Date of registration in primary registry	August 5, 2020
Secondary identifying numbers	520/2020/SPER/IRCCSRE
Source of monetary or material support	Manodori Foundation
Primary sponsor	Azienda USL-IRCCS di Reggio Emilia
Secondary sponsor	NA
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Contact for scientific queries	SC [stefania.costi@unimore.it], BB [barbara.bressi@ausl.re.it]
Public title	Feasibility and Safety of Physical Exercise in Men With Prostate Cancer (PCa_Ex)
Scientific title	"The Feasibility and Safety of Physical Exercise Programme in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol"
Countries of recruitment	Italy
Health conditions or problems studied	Prostate cancer, androgen deprivation therapy and radiotherapy
Intervention	Physical exercise intervention
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: man Accepts healthy volunteers: no
	Inclusion criteria: Adult male patient (≥ 18 years) Histologically documented diagnosis of PCa Undergoing ADT and RT during the study period Willing and able to give written informed consent Able to read and understand Italian Language Exclusion criteria: Any musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate physical exercise

Study type	Interventional Allocation: single group assignment Primary purpose: supportive care
Date of first enrolment	September 2020
Target sample size	25 patients
Recruitment status	Recruiting
Primary outcomes	Feasibility: recruitment, adherence, and drop-out rates Safety: any adverse events related and not related to the intervention
Key secondary outcomes	Muscle strength, fatigue, cognitive function, balance, quality of life, anxiety and depression level, and number of falls and fractures. Patient's satisfaction: patient feedback via interview with open-ended question

Table 2 Description of exercise programme and dose progression

Weeks		**1-4**	**5-8**	**9-12**	**13-16**	**17-20**
Component	**Dose**					
AE	Intensity (% HRmax)	60-80%	60-80%	60-80%	60-80%	60-80%
	Duration	15-20 min	20 min	20 min	25 min	30 min
PRE	Sets	2	2	3	3	4
	Repetitions	8-12	12-15	8-12	12-15	8-12
	Difficulties	Additional free weights, range of motion, number and time* of exercise, additional upper body and/or lower body movements				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), step				
CSE	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, additional upper body and/or lower body movements and time* of exercise				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), fit ball				
NE	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Time* of exercise, closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), fit ball, balance board				
IE	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, introducing multi-directional movement, and raising the exercise speed				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), hurdles/hoops/training cone markers, rope, steps				

Abbreviations: AE, aerobic exercise; HRmax, maximum heart rate; PRE, progressive resistance exercise, CSE; core muscle stabilization exercise, NE; neuromotor exercise. IE, impact-loading exercise; % HRmax, percent maximum heart rate.

*varies from 20 to 60 seconds and regards isometric exercise and static balance exercise

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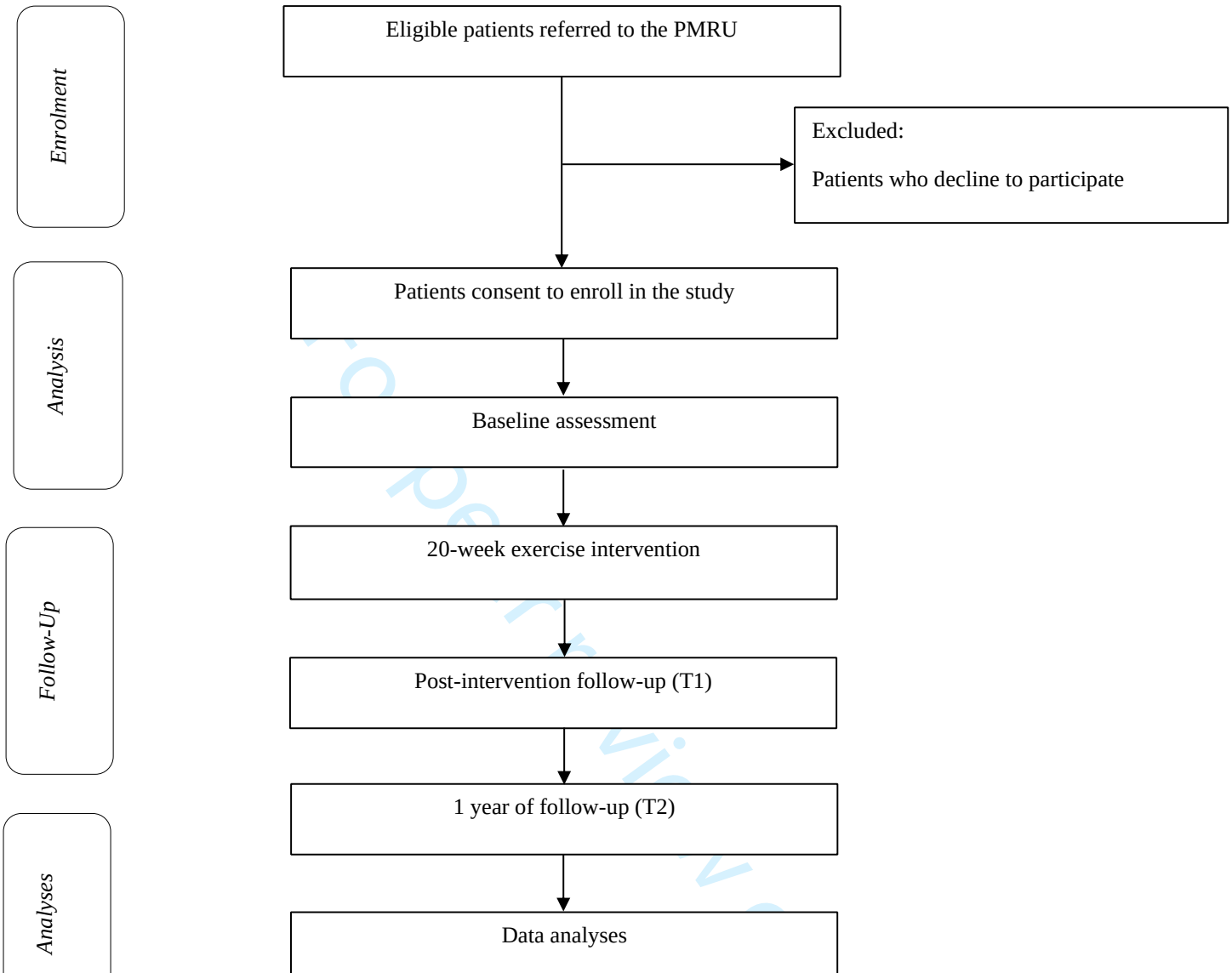
Table 3 Data collected

Variables	Data collection method	Data collection points		
		Baseline	T1 (10 weeks*)	T2 (1 year*)
Primary outcome measures				
Feasibility	Recruitment rate	x		
	Adherence rate		x	
	Drop-out rate		x	
Safety	Number and type of AEs related and not related to intervention		x	
Secondary outcome measures				
Muscle strength	Ten repetitions maximum (10-RM) Test	x	x	
Fatigue	Fatigue Severity Scale (FSS)	x	x	
Cognitive function	Mini mental State examination (MMSE)	x	x	
Balance	Tinetti Performance Oriented Mobility Assessment (POMA)	x	x	
Quality of life	Short form-12 questionnaire (SF-12)	x	x	
Anxiety and depression level	Hospital Anxiety and Depression Scale (HADS)	x	x	
Numbers of fall and fractures	Recorded directly by the physiotherapist during the supervised sessions and with weekly phone call during unsupervised session	x	x	x
Participant satisfaction	Patient satisfaction		x	
Additional measures	Anthropometry (height, weight, BMI)	x	x	
	Demographic data	x		
	Clinical data	x		
	Functional capacity (6MWT)	x		

Abbreviations: AEs, adverse events; BMI, body mass index; 6MWT, six minutes walking test.
*from baseline.

Fig 1 Schematic study flow diagram[23]



Legend: PMRU= Physical Medicine and Rehabilitation Unit

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 3
	2b	All items from the World Health Organization Trial Registration Data Set	3, Table 1
Protocol version	3	Date and version identifier	3, Table 1
Funding	4	Sources and types of financial, material, and other support	Title page
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	Title page, Table 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	Title page, Table 1
	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)	NA
Introduction			
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	2, 3
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4, 5, Table 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	4, 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
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)	3, Fig. 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	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., 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	3, 6-8
	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	5-8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
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	7, 8
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	NA
Methods: Monitoring			
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	NA
	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	NA
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	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 8
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Title page
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	Title page
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	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1, 8
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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

*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" license.

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Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

prepared by the authors

Barbara Bressi, Cinzia Iotti, Maribel Cagliari, Silvio Cavuto, Stefania Fugazzaro, Stefania Costi

was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at AJE.

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Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine, Sports and exercise medicine
Keywords:	REHABILITATION MEDICINE, SPORTS MEDICINE, PUBLIC HEALTH

TITLE PAGE

Title: Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

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Declarations

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Conflicts of interest/competing interest: Barbara Bressi, Cinzia Iotti, Maribel Cagliari, Silvio Cavuto, Stefania Fugazzaro, and Stefania Costi declare that they have no conflicts of interest.

Ethics approval and consent to participate: This study was approved by the Comitato Etico dell'Area Vasta Emilia Nord (23/06/2020, number 520/2020/SPER/IRCCSRE, protocol version number 1, amendment number 0). Each patient provided informed consent to participate in this study.

Patient consent for publication: not required.

Availability of data and material: Data collected in the current study are stored on a password-protected computer and managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia to protect patient privacy. Data are available from the corresponding author upon reasonable request.

Author contributions: BB, CI, MC, SC, SF and SCo contributed to study conceptualization and design and provided input into the development of the protocol. BB, MC and SCo drafted the manuscript, and all authors revised it critically and approved the final version for publication.

Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

ABSTRACT

Introduction Androgen deprivation therapy (ADT) and radiotherapy (RT) increase survival in selected patients with prostate cancer. Nevertheless, the side effects of these therapies are associated with an increased risk of accidental falls and fractures and a decreased quality of life. Preliminary evidence suggests that physical exercise can be a valid strategy to reduce the side effects of ADT and RT in men with prostate cancer. Despite this knowledge, most patients with prostate cancer are insufficiently active, and there is a lack of data on the safety and adherence to the recommended dose of physical exercise. This study protocol is designed to examine the feasibility and safety of a multicomponent experimental physical exercise intervention targeting psychophysical and cognitive functions and the quality of life in this population.

Methods and analysis This is a pilot feasibility study. Twenty-five men currently treated with ADT and RT for prostate cancer will be invited to participate in a 20-week, multicomponent physical exercise intervention, including supervised and unsupervised exercise sessions and meeting the current recommendation for exercise in cancer. The primary outcomes are physical exercise feasibility (recruitment, adherence, and drop-out rates) and safety (adverse events related and unrelated to the intervention). The secondary outcomes are muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life, and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up.

Ethics and dissemination The study has received ethics approval from The Area Vasta Nord Local Ethics Committee (Province of Reggio Emilia, June 23, 2020, Number 520/2020/SPER/IRCCSRE). Recruitment began in September 2020 and will be completed in September 2021. The results will be disseminated through scientific journals and conference presentations.

Trial registration ClinicalTrial.gov (NCT04500080)

Keywords Prostatic neoplasms, Accidental falls, Bone fractures, Exercise, Androgen deprivation therapy, Radiotherapy.

Strengths and limitations of this study

- This pilot study thoroughly assesses the feasibility and safety of a multicomponent experimental physical exercise intervention for individuals with prostate cancer receiving ADT and RT.
- Preliminary data regarding the efficacy of structured, supervised, and unsupervised aerobic, resistance, neuromotor, and impact-loading exercise on the bone health of this population will be provided.

- Both the ecological setting, a community sport facility, and the step-down approach, from supervised to unsupervised physical exercise intervention, should foster the adoption of exercise as daily habits, promoting healthy behaviour.
- The single-group design does not allow for assessment of the efficacy of the multicomponent experimental physical exercise intervention on the bone health outcomes of interest.

INTRODUCTION

Prostate cancer affects approximately 3.7 million people worldwide, ranking first among the most prevalent cancers in the male population.[1] Curative treatment of locally advanced prostate cancer usually entails radiotherapy (RT) frequently associated with androgen deprivation therapy (ADT).[2] This type of multimodal treatment is unfortunately associated with a large number of side effects.[3,4] Previous studies have demonstrated a significant increase in cancer-related fatigue in patients receiving RT, which not only decreases physical well-being but also affects daily activities, cognitive function, and quality of life.[5—7] Furthermore, it is well known that the cardiovascular, metabolic, cognitive, and musculoskeletal adverse effects of ADT lead to an increased number of accidental falls and fractures in this population.[8] Furthermore, since prostate cancer incidence increases with age,[1] older patients are normally already at a greater risk of frailty due to the presence of other comorbidities that can dramatically affect physical function.[9] Exercise interventions can prevent a large number of these complications, improving the health and quality of life of individuals with prostate cancer.[10,11] These exercise programmes should include moderate-high intensity activities that must be performed regularly to maintain exercise-related benefits.[12,13] A recent systematic review of randomized controlled trials (RCTs) showed that to counteract the negative effects of ADT on bone, multicomponent physical exercise interventions involving aerobic, resistance and impact-loading exercise have been performed.[14] Although these interventions were feasible for most participants in the RCT, those study protocols did not systematically record the adherence rate or adverse events associated with the experimented physical exercise interventions (Cagliari M et al. Feasibility and Safety of Physical Exercise to Preserve Bone Health in Men with Prostate Cancer Undergoing Androgen Deprivation Therapy: a Systematic Review. Unpublished material).[12,13] However, these data are fundamental to fostering individual compliance with the recommended dose of exercise.[12] In fact, despite the well-known benefits of physical exercise for cancer survivors,[15,16] this population is frequently unactive[17] and reports several common barriers to exercise, such as the location or distance to facilities.[18—20] Furthermore, hospital-based supervised physical exercise interventions can be challenging to implement because they requires the use of complex hospital resources.[18,21,22] This modality does not promote long-term adherence to physical exercise or changes towards a healthier lifestyle, which are considered contemporary health priorities for physical therapy practice.[23,24]

In this regard, we are investigating the lifestyle of patients recently diagnosed of prostate cancer, their perceived barriers and facilitators to physical exercise, and motivation to change towards healthier lifestyle (Bressi et al. Physical exercise and lifestyle behaviours among men with prostate cancer: a cross sectional study. Unpublished Material). Therefore, based on previous research and our current descriptive study, we developed a structured experimental physical exercise intervention that combines supervised and unsupervised exercise with a step-down approach. This physical exercise intervention is implemented in a community sports facility and is currently being tested in a small group of patients with prostate cancer receiving ADT and RT for feasibility and safety. Secondary outcomes include muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up. This study protocol describes the experimental physical exercise intervention in detail, with related outcomes, to allow for reproducibility and adaptation to other contexts.

METHODS AND ANALYSIS

Patients and study design

This single group feasibility pilot study was approved by the Comitato Etico dell'Area Vasta Emilia Nord (June 23, 2020, Number 520/2020/SPER/IRCCSRE) and was registered with ClinicalTrials.gov (Identifier NCT04500080). This study protocol adheres to the recommendation for clinical trials (SPIRIT) guidelines (additional file 1), and the study registration data set is shown in Table 1.[25] Eligible patients are adult men (≥18 years) with a histological diagnosis of prostate cancer who are currently treated with ADT and RT and are able to communicate in the Italian language. Participants with musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate exercise will be excluded. All patients referred to RT which are also candidate to receive ADT will be assessed for eligibility. If confirmed, written informed consent will be obtained from all participants, who will be invited to participate in a 20-week structured, supervised and unsupervised, multicomponent physical exercise programme. Patients will be assessed at baseline (T0), at the end of the intervention (T1), and at follow-up, which will occur 12 months from recruitment (T2).

So, the experimental physical exercise intervention will start concomitantly with RT, which lasts about two months. As regard to ADT, its duration can vary from six to thirty-six months and it can begin up to three months before patient's enrolment in this study and RT commencement.

Recruitment strategies

Between September 2020 and September 2021, eligible patients treated by the Radiotherapy Unit of Santa Maria Nuova Hospital of Reggio Emilia (Italy) will be given brief, written information about the study by their attending physician (radiotherapist or oncologist). Upon written consent, patients willing to receive more information will be referred to the

Physical Medicine and Rehabilitation Unit and will receive a phone call by a research staff member (physiotherapist), who describes the study aim and modalities to them in detail. Patients who confirm their interest in participating will receive written information and consent forms to participate in the study to be filled out and signed. They will also make the first appointment to provide written consent and to perform the baseline assessment. The patient recruitment process is shown in Figure 1.

Baseline assessment

In the baseline assessment, demographic, anthropometric, clinical data, and physical function data will be collected. Clinical data include the date of diagnosis, tumour stage, time since receiving ADT and RT, and the presence of comorbidities assessed through the Charlson Comorbidity Index (CCI).[26] Physical function will be measured using a six-minute walk test (6MWT)[27] to calculate the intensity of aerobic exercise.

Experimental physical exercise intervention

The multicomponent experimental physical exercise intervention will last 20 weeks and consists of supervised and unsupervised exercise sessions held three times per week. Following a step-down approach, during the first eight weeks, all physical exercise sessions will be supervised by a physiotherapist, while during the following four weeks, only one weekly session will be supervised, whereas the other two will be unsupervised; finally, during the last eight weeks of experimental physical exercise, all sessions will be unsupervised. Supervised sessions will be conducted in small groups or individually at the Municipal Athletics Field in Reggio Emilia according to scheduled appointments, whereas the unsupervised sessions can be completed by participants in times, modalities and places of their convenience, providing for them the possibility to access the Municipal Athletics Field.

The multicomponent physical exercise intervention meets the dictates for exercise components, posology (frequency, sets, repetitions, intensity) and progression recommended for healthy adults.[28] Its components are aerobic, resistance, core muscle stabilization, and neuromotor exercises associated with cognitive tasks. In addition, exercise intervention will include impact-loading exercise to provide an effective bone osteogenic stimulus. This type of exercise has been considered an effective strategy to prevent loss of bone mineral density (BMD) in elderly patients[29,30] and has been applied in patients with prostate cancer receiving ADT in previous studies.[14] Altogether, the components of this intervention should preserve muscle strength and improve fatigue, balance, and cognitive function,[28] and eventually, it should prevent accidental falls and fractures.

The intervention is tailored to individual general health, functional capacity and, as far as possible, preferences.

Supervised physical exercise sessions

Supervised sessions last one hour and 15 minutes and include a period of warm up and cool-down and a combination of the following physical exercise components:

• Aerobic exercise consists of 20-30 minutes of aerobic activity at moderate-high intensity, from 60 to 80% of maximum heart rate (% HRmax), previously determined through the 6MWT.[27] To obtain the greatest effects on bone health, the proposed aerobic exercise activities are walking or jogging, depending on individual capacity and habitual or previous experiences of physical activity. The exercise intensity will be monitored by the Borg's Rate of Perceived Exertion-Scale (RPE), in order to maintain it between moderate to high, that correspond to RPE scores 11 to 16.[31] To ensure that participants reach the target HR we will use the HR monitors.

• Progressive resistance exercise consists of strength activity of the major lower and upper extremity muscle groups, using body weight as a load and free weights (resistance bands, dumbbells, anklets with weight, medicine ball). During each session, the goal is to perform four to eight exercises targeting different muscle groups by performing two to four sets of 8-15 repetitions for each exercise. The progression of intensity will be tailored to the individual using the Borg RPE scale[32] (score between 11 and 16), starting with body weight and gradually increasing the load using free weights.[33] Adjustments to load will be made when participants can complete the highest number of specified repetitions (≥ 15 repetitions, see also Table 2). Thus, the number of exercises, dose progression (sets, repetitions) and related difficulties (e.g., squat depth and/or duration, double task exercises) will be changed during the weeks based on the patient's compliance and performance (see also Table 2). For isometric exercises, dose will be incrementally increased by adding free weights, further limb exercise or asking for double task exercise, and/or increasing the duration of exercise from 20 to 60 seconds.

• Core muscle stabilization exercise consists of postural and trunk stability exercises (e.g., strengthening of transverse abdominis and pelvic floor muscles). Participants will perform two core exercises per session in two-four sets of 8-15 repetitions. Sets, repetitions, additional free weights, additional upper body and/or lower body movements and time of exercise from 20 to 60 seconds will be used to increase the intensity of exercises.

• Neuromotor exercise consists of balance and functional (coordination) exercises associated with cognitive tasks (e.g., counting, adding, subtracting, saying day of weeks) and includes fit ball exercises (e.g., knee and contralateral upper limb extension sitting on fit ball), standing balance activities (e.g., stand on one leg) and dynamic functional tasks (e.g., stop walking balanced on one foot, walking backward). Participants will be asked to complete two to four static and dynamic exercises per session. Static exercises are performed in two-four sets of 20-60 seconds, while dynamic exercises are performed in two-four sets of 8-15 repetitions. To provide progression, exercises are modified by introducing difficulties (e.g., closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task).

• Impact-loading exercise consists of jumping, leaping, jumping rope, hopping on one leg, going up and down steps, etc., in other words, exercises that provide impact with the ground using the body weight as a load. Two to four exercises

per session will be performed. Training intensity is increased by adding repetitions, additional free weights, introducing multidirectional movement, and raising the exercise speed. To provide a large number of stimuli, several tools will be used.

Also, for core muscle stabilization, neuromotor, and impact-loading exercises, adjustments to load will be made when participants can complete the highest number of repetitions (≥15 repetitions) at the target exercise intensity (RPE score between 11 and 16).

A detailed description of exercises, posology, tools, and progressivity is available in Table 2. Altogether, progressive resistance, core muscle stabilization, neuromotor, and impact-loading exercises are performed for 30-40 minutes each session.

Unsupervised physical exercise sessions

Unsupervised sessions also consist in all exercise components. In addition to walking or jogging, aerobic exercise can also be performed using bikes, stationary bikes, or other aerobic activities based on individual availability and preferences. Regarding the progressive resistance, core muscle stabilization, neuromotor, and impact-loading exercise components, exercises that trade on body weight or with resistance bands that will be provided to patients are taught and suggested to overcome the possible unavailability of appropriate tools. Each activity and exercise will be explained to participants and practised by them during the supervised sessions. Furthermore, written educational material with instructions and pictures of the exercises will be provided to maximize accuracy of the unsupervised execution. The physiotherapist provides individualised indications regarding the activities to be performed during unsupervised sessions but also supports participants in progressively increasing the exercise workload when the individual perceives an improvement in their functional capacity.

Outcome measures

Primary outcome

Feasibility will be measured through recruitment, adherence, and dropout rates.

The recruitment rate is the proportion of eligible individuals referred to the Physical Medicine and Rehabilitation Unit by their treating physician included in the study.

Protocol adherence is the proportion of exercise sessions that are attempted and completed by each participant. The percentage of patients who withdraw from the study and their reason for withdrawal will also be registered.

Safety is measured through the recording of any adverse events related and not related to exercise and its grading for seriousness,[34] causality and health consequences by the researcher during the study.

Feasibility and safety are monitored by the physiotherapist through direct inquiry during the first 12 weeks of the programme when supervised sessions are implemented and through a weekly phone call during the last eight weeks of unsupervised sessions.

Secondary outcomes

Secondary outcome measures include changes in muscle strength, fatigue, cognitive function, balance, quality of life, symptoms of anxiety and depression, number of accidental falls and associated fractures, and participant satisfaction.

Muscle strength

The strength of the major lower and upper extremity muscle groups will be measured with the 10-RM test (extensor muscle group). The 10-RM test assesses the maximum weight that can be lifted for ten repetitions while maintaining the correct technique. Prior to attempting this test, participants will complete five minutes of aerobic warm-up and 1-2 sets of 15-20 repetitions with a light load. Then, the load will be progressively increased while the number of repetitions will decrease accordingly until only ten repetitions can be completed. A recovery period of two minutes will be provided between each set.[35,36]

Fatigue

Fatigue will be measured using the Fatigue Severity Scale (FSS), a 9-item questionnaire on how fatigue interferes with activities and that rates its severity. The item is scored on a 7-point Likert scale with 1 = strongly disagree and 7 = strongly agree. The minimum score = 9, and the maximum score = 63. A higher score indicates greater fatigue severity.[37]

Cognitive function

Cognitive function will be measured using the Mini Mental State Examination (MMSE), a brief cognitive test designed to assess the overall cognitive status of patients. The MMSE tests five areas of mental status (orientation; registration; attention and calculation; recall; language) and is scored on a scale of 30, with adequate cognition for most adults indicated by scores from 24 to 30.[38]

Balance

Balance will be measured using the Tinetti Performance Oriented Mobility Assessment (POMA). The Tinetti POMA scale is a clinical test used to measure balance and gait abilities. The balance section (POMA-B) consists of 9 items, while the gait section (POMA-G) consists of 8 items. Each item can receive an ordinal score from 0 to 2, where "0" indicates the highest level of impairment and "2" indicates individual independence. The maximum possible total score for POMA-T is 28, for POMA-B is 16, and for POMA-G is 12. A POMA-T cut-off score < 19 indicates a high risk of falling.[39,40]

Quality of life

Quality of life will be measured using the Short Form-12 questionnaire (SF-12), which consists of twelve items measuring different physical and mental health parameters. Higher scores indicate better physical and mental health.[41]

Anxiety and depression level

Anxiety and depression level will be measured using the Hospital Anxiety and Depression Scale (HADS), a fourteen-item scale equally distributed across anxiety and depression states. The total score ranges from 0-21, with higher scores indicating greater levels of mood disturbances. In patients with cancer, a cut-off score of > 9 for the HADS-A and > 7 for the HADS-D indicates clinically relevant anxiety and depression levels, respectively.[42]

Accidental falls and fractures

During the intervention, accidental falls and fractures were recorded directly by the physiotherapist who supervised the sessions and performed the weekly phone call and thereafter at the 12-month follow-up.

Participant satisfaction

Patient satisfaction will be assessed through a simple structured interview. At the end of the intervention, each participant will be invited to answer the following four open-ended questions that investigate its acceptability:

• How do you assess the overall experience you have had by participating in this study?

• Which activities did you like the most?

• Which activities did you like least?

• What can to be improved in your opinion, or what would you have liked to have been offered?

A summary of the outcome measures and their assessments at follow-up is shown in Table 3.

Sample size calculation

No formal sample size requirement is needed for this single-group, pilot, feasibility study. At the Santa Maria Nuova Hospital of Reggio Emilia, nearly 30 patients/year undergo ADT and RT, and we aim to recruit 25 patients during the 12-month recruitment period.

Data analysis

All statistical analyses will be performed by the local Clinical Trials and Statistics Unit of the AUSL-IRCCS of Reggio Emilia. The SAS System or R software will be used according to their availability at the time of data analyses. Descriptive statistics will be reported for feasibility and safety outcomes. For each percentage, the exact two-sided confidence interval will be calculated according to the Clopper-Pearson approach, ensuring a confidence level of at least 95%. In fact, since it is an exact technique, the confidence level typically does not coincide with 95%, the discrepancy for small samples being more noticeable. Adverse events will be described and grouped into homogeneous classes. The data regarding patient satisfaction will be analysed to identify patterns of response and grouped into categories emerging from the data. Descriptive statistics for secondary outcomes will be reported to inform potential future studies in terms of clinical health outcome measures. For all variables, percentiles, minimum, maximum, mean, and SD will be calculated. For the mean, a

95% two-sided confidence interval will be calculated assuming a t distribution. The changing over time of the secondary outcomes will be studied by the analysis of variance for repeated measures.

Concerning the number of accidental falls and fractures, as counts, the confidence interval for the mean will be calculated according to the Poisson distribution. No missing data imputation techniques have been planned, therefore only the available data will be analyzed. However, missing data will be appropriately described in their distributional aspects of relevance.

Data management and archiving

The dataset will be stored on a password-protected computer and managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia to protect patient privacy and data.

Patient and public involvement

Patients will participate in the study design so that the time and spaces necessary for the home-based intervention can be adapted according to their availability and discretion. Participants may suggest changes related to the frequency and intensity of the sessions and inform the study team about which type of exercises they prefer.

ETHICS AND DISSEMINATION

This study was approved by the Area Vasta Nord Local Ethics Committee of Azienda USL-IRCCS of Reggio Emilia (June 23, 2020, Number 520/2020/SPER/IRCCSRE), which will also review potential modifications, if any. All patients will provide consent prior to participation. Results will be disseminated through scientific peer-reviewed journals and conference presentations. The expected impact for this study is the development of a useful and acceptable physical exercise programme integrated into the daily routine of patients with prostate cancer receiving ADT and RT.

These results will inform which type of physical exercise is required to improve adherence to the recommended exercise guidelines for cancer survivors and will help researchers plan feasible physical exercise interventions whose efficacy on bone health is to be verified through well-designed RCTs.

Author contributions BB, CI, MC, SC, SF and SCo contributed to study conceptualization and design and provided input into the development of the protocol. BB, MC and SCo drafted the manuscript, and all authors revised it critically and approved the final version for publication.

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2522inc%2522%253Afalse%252C%2522mort%2522%253Afalse%252C%2522prev%2522%253Atrue%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D&population_group_globocan_id= Date accessed: Dec 29, 2020.

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43.

Table 1 Study registration data set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04500080
Date of registration in primary registry	August 5, 2020
Secondary identifying numbers	520/2020/SPER/IRCCSRE
Source of monetary or material support	Manodori Foundation
Primary sponsor	Azienda USL-IRCCS di Reggio Emilia
Secondary sponsor	NA
Contact for public queries	BB [barbara.bressi@ausl.re.it], SC [stefania.costi@unimore.it]
Contact for scientific queries	SC [stefania.costi@unimore.it], BB [barbara.bressi@ausl.re.it]
Public title	Feasibility and Safety of Physical Exercise in Men With Prostate Cancer (PCa_Ex)
Scientific title	"The Feasibility and Safety of Physical Exercise Programme in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol"
Countries of recruitment	Italy
Health conditions or problems studied	Prostate cancer, androgen deprivation therapy and radiotherapy
Intervention	Physical exercise intervention
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: man Accepts healthy volunteers: no
	Inclusion criteria: Adult male patient (≥ 18 years) Histologically documented diagnosis of PCa Undergoing ADT and RT during the study period Willing and able to give written informed consent Able to read and understand Italian Language Exclusion criteria: Any musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate physical exercise

Study type	Interventional Allocation: single group assignment Primary purpose: supportive care
Date of first enrolment	September 2020
Target sample size	25 patients
Recruitment status	Recruiting
Primary outcomes	Feasibility: recruitment, adherence, and drop-out rates Safety: any adverse events related and not related to the intervention
Key secondary outcomes	Muscle strength, fatigue, cognitive function, balance, quality of life, anxiety and depression level, and number of falls and fractures. Patient's satisfaction: patient feedback via interview with open-ended question

Table 2 Description of exercise programme and dose progression

Weeks		**1-4**	**5-8**	**9-12**	**13-16**	**17-20**
Component	**Dose**					
Aerobic exercise	Intensity (% HRmax)	60-80%	60-80%	60-80%	60-80%	60-80%
	Duration	15-20 min	20 min	20 min	25 min	30 min
Progressive resistance exercise	Sets	2	2	3	3	4
	Repetitions	8-12	12-15	8-12	12-15	8-12
	Difficulties	Additional free weights, range of motion, number and time* of exercise, additional upper body and/or lower body movements				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), step				
Core muscle stabilization exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, additional upper body and/or lower body movements and time* of exercise				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), fit ball				
Neuromotor exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Time* of exercise, closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), fit ball, balance board				
Impact-loading exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, introducing multi-directional movement, and raising the exercise speed				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), hurdles/hoops/training cone markers, rope, steps				

Abbreviations: % HRmax, percent maximum heart rate.

*varies from 20 to 60 seconds and regards isometric exercise and static balance exercise

Table 3 Data collected

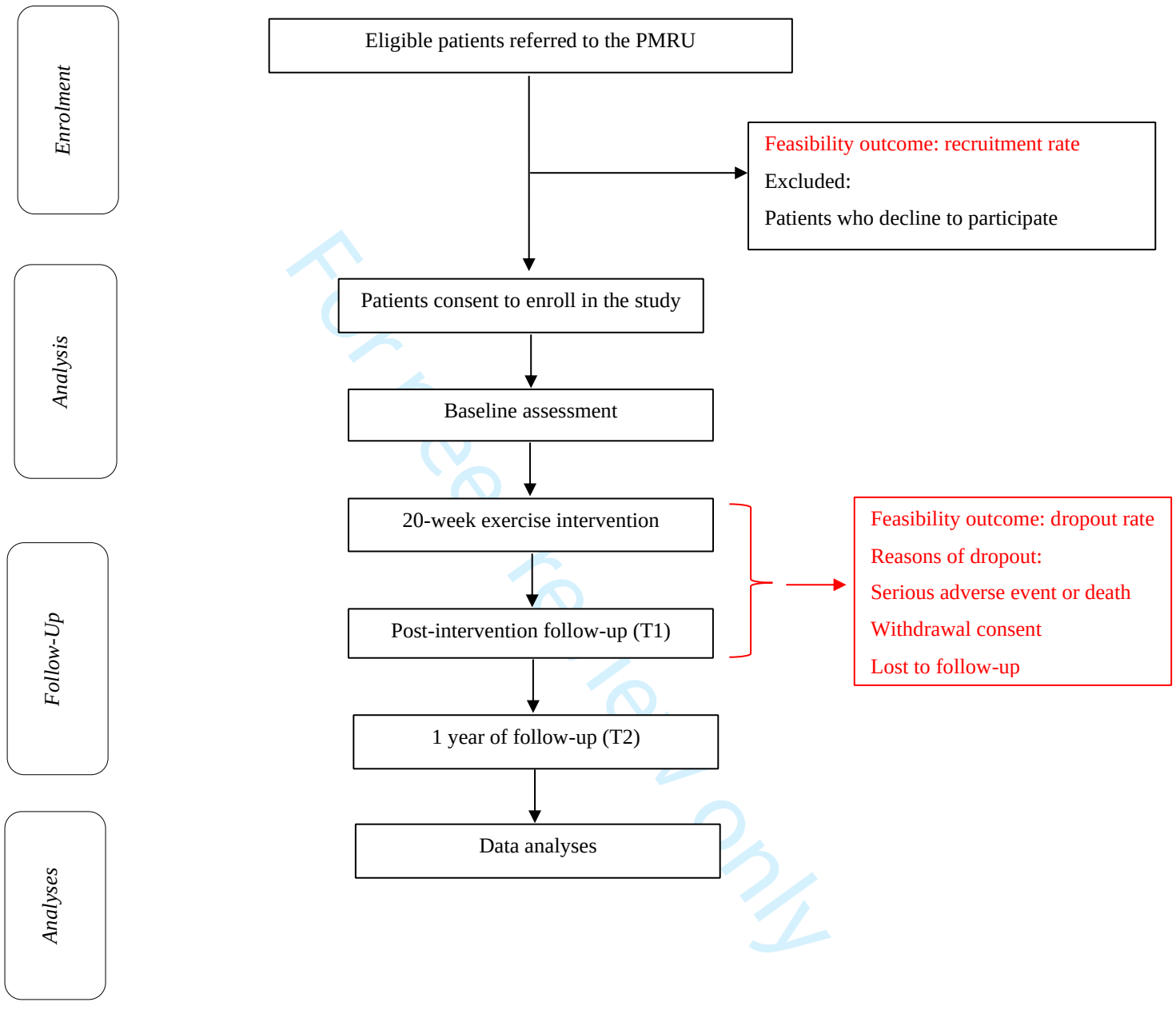
Variables	**Data collection method**	**Data collection points**		
		Baseline	T1 (20 weeks*)	T2 (1 year*)
Primary outcome measures				
Feasibility	Recruitment rate	x		
	Adherence rate		x	
	Drop-out rate		x	
Safety	Number and type of AEs related and not related to intervention		x	
Secondary outcome measures				
Muscle strength	Ten repetitions maximum (10-RM) Test	x	x	
Fatigue	Fatigue Severity Scale (FSS)	x	x	
Cognitive function	Mini mental State examination (MMSE)	x	x	
Balance	Tinetti Performance Oriented Mobility Assessment (POMA)	x	x	
Quality of life	Short form-12 questionnaire (SF-12)	x	x	
Anxiety and depression level	Hospital Anxiety and Depression Scale (HADS)	x	x	
Numbers of fall and fractures	Recorded directly by the physiotherapist during the supervised sessions and with weekly phone call during unsupervised session	x	x	x
Participant satisfaction	Patient satisfaction		x	
Additional measures	Anthropometry (height, weight, BMI)	x	x	
	Demographic data	x		
	Clinical data	x		
	Functional capacity (6MWT)	x		

Abbreviations: AEs, adverse events; BMI, body mass index; 6MWT, six minutes walking test.
*from baseline.

Figure legend

Fig 1 Schematic study flow diagram

Fig 1 Schematic study flow diagram[25]



Abbreviations: PMRU= Physical Medicine and Rehabilitation Unit

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 3
	2b	All items from the World Health Organization Trial Registration Data Set	3, Table 1
Protocol version	3	Date and version identifier	3, Table 1
Funding	4	Sources and types of financial, material, and other support	Title page
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	Title page, Table 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	Title page, Table 1
	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)	NA
Introduction			
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	2, 3
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4, 5, Table 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	4, 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
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)	3, Fig. 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	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., 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	3, 6-8
	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	5-8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
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	7, 8
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	NA
Methods: Monitoring			
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	NA
	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	NA
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	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 8
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Title page
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	Title page
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	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1, 8
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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

*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" license.

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Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

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TITLE PAGE

Title: Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

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Declarations

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Ethics approval and consent to participate: This study was approved by the Comitato Etico dell'Area Vasta Emilia Nord (23/06/2020, number 520/2020/SPER/IRCCSRE, protocol version number 1, amendment number 0). Each patient provided informed consent to participate in this study.

Patient consent for publication: not required.

Availability of data and material: Data collected in the current study are stored on a password-protected computer and managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia to protect patient privacy. Data are available from the corresponding author upon reasonable request.

Author contributions: BB, CI, MC, SC, SF and SCo contributed to study conceptualization and design and provided input into the development of the protocol. BB, MC and SCo drafted the manuscript, and all authors revised it critically and approved the final version for publication.

Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

ABSTRACT

Introduction Androgen deprivation therapy (ADT) and radiotherapy (RT) increase survival in selected patients with prostate cancer. Nevertheless, the side effects of these therapies are associated with an increased risk of accidental falls and fractures and a decreased quality of life. Preliminary evidence suggests that physical exercise can be a valid strategy to reduce the side effects of ADT and RT in men with prostate cancer. Despite this knowledge, most patients with prostate cancer are insufficiently active, and there is a lack of data on the safety and adherence to the recommended dose of physical exercise. This study protocol is designed to examine the feasibility and safety of a multicomponent experimental physical exercise intervention targeting psychophysical and cognitive functions and the quality of life in this population.

Methods and analysis This is a pilot feasibility study. Twenty-five men currently treated with ADT and RT for prostate cancer will be invited to participate in a 20-week, multicomponent physical exercise intervention, including supervised and unsupervised exercise sessions and meeting the current recommendation for exercise in cancer. The primary outcomes are physical exercise feasibility (recruitment, adherence, and drop-out rates) and safety (adverse events related and unrelated to the intervention). The secondary outcomes are muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life, and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up.

Ethics and dissemination The study has received ethics approval from The Area Vasta Nord Local Ethics Committee (Province of Reggio Emilia, June 23, 2020, Number 520/2020/SPER/IRCCSRE). Recruitment began in September 2020 and will be completed in September 2021. The results will be disseminated through scientific journals and conference presentations.

Trial registration ClinicalTrial.gov (NCT04500080)

Keywords Prostatic neoplasms, Accidental falls, Bone fractures, Exercise, Androgen deprivation therapy, Radiotherapy.

Strengths and limitations of this study

- This pilot study thoroughly assesses the feasibility and safety of a multicomponent experimental physical exercise intervention for individuals with prostate cancer receiving ADT and RT.
- Preliminary data regarding the efficacy of structured, supervised, and unsupervised aerobic, resistance, neuromotor, and impact-loading exercise on the bone health of this population will be provided.

- Both the ecological setting, a community sport facility, and the step-down approach, from supervised to unsupervised physical exercise intervention, should foster the adoption of exercise as daily habits, promoting healthy behaviour.
- The single-group design does not allow for assessment of the efficacy of the multicomponent experimental physical exercise intervention on the bone health outcomes of interest.

INTRODUCTION

Prostate cancer affects approximately 3.7 million people worldwide, ranking first among the most prevalent cancers in the male population.[1] Curative treatment of locally advanced prostate cancer usually entails radiotherapy (RT) frequently associated with androgen deprivation therapy (ADT).[2] This type of multimodal treatment is unfortunately associated with a large number of side effects.[3,4] Previous studies have demonstrated a significant increase in cancer-related fatigue in patients receiving RT, which not only decreases physical well-being but also affects daily activities, cognitive function, and quality of life.[5—7] Furthermore, it is well known that the cardiovascular, metabolic, cognitive, and musculoskeletal adverse effects of ADT lead to an increased number of accidental falls and fractures in this population.[8] Furthermore, since prostate cancer incidence increases with age,[1] older patients are normally already at a greater risk of frailty due to the presence of other comorbidities that can dramatically affect physical function.[9] Exercise interventions can prevent a large number of these complications, improving the health and quality of life of individuals with prostate cancer.[10,11] These exercise programmes should include moderate-high intensity activities that must be performed regularly to maintain exercise-related benefits.[12,13] A recent systematic review of randomized controlled trials (RCTs) showed that to counteract the negative effects of ADT on bone, multicomponent physical exercise interventions involving aerobic, resistance and impact-loading exercise have been performed.[14] Although these interventions were feasible for most participants in the RCT, those study protocols did not systematically record the adherence rate or adverse events associated with the experimented physical exercise interventions (Cagliari M et al. Feasibility and Safety of Physical Exercise to Preserve Bone Health in Men with Prostate Cancer Undergoing Androgen Deprivation Therapy: a Systematic Review. Unpublished material).[12,13] However, these data are fundamental to fostering individual compliance with the recommended dose of exercise.[12] In fact, despite the well-known benefits of physical exercise for cancer survivors,[15,16] this population is frequently unactive[17] and reports several common barriers to exercise, such as the location or distance to facilities.[18—20] Furthermore, hospital-based supervised physical exercise interventions can be challenging to implement because they requires the use of complex hospital resources.[18,21,22] This modality does not promote long-term adherence to physical exercise or changes towards a healthier lifestyle, which are considered contemporary health priorities for physical therapy practice.[23,24]

It is suggested that an intensive lifestyle programme that includes dietary supplements, moderate aerobic exercise, stress management, and support group participation may affect the progression of prostate cancer at the early stage.[25] Furthermore, a healthier lifestyle seems to be associated with a better health-related quality of life.[26]

In this regard, we are investigating the lifestyle of patients recently diagnosed of prostate cancer, their perceived barriers and facilitators to physical exercise, and motivation to change towards healthier lifestyle (Bressi et al. Physical exercise and lifestyle behaviours among men with prostate cancer: a cross sectional study. Unpublished Material). Therefore, based on previous research and our current descriptive study, we developed a structured experimental physical exercise intervention that combines supervised and unsupervised exercise with a step-down approach. This physical exercise intervention is implemented in a community sports facility and is currently being tested in a small group of patients with prostate cancer receiving ADT and RT for feasibility and safety. Secondary outcomes include muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up. This study protocol describes the experimental physical exercise intervention in detail, with related outcomes, to allow for reproducibility and adaptation to other contexts.

METHODS AND ANALYSIS

Patients and study design

This single group feasibility pilot study was approved by the Comitato Etico dell'Area Vasta Emilia Nord (June 23, 2020, Number 520/2020/SPER/IRCCSRE) and was registered with ClinicalTrials.gov (Identifier NCT04500080). This study protocol adheres to the recommendation for clinical trials (SPIRIT) guidelines (additional file 1), and the study registration data set is shown in Table 1.[27] Eligible patients are adult men (≥18 years) with a histological diagnosis of prostate cancer who are currently treated with ADT and RT and are able to communicate in the Italian language. Participants with musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate exercise will be excluded. All patients referred to RT which are also candidate to receive ADT will be assessed for eligibility. If confirmed, written informed consent will be obtained from all participants, who will be invited to participate in a 20-week structured, supervised and unsupervised, multicomponent physical exercise programme. Patients will be assessed at baseline (T0), at the end of the intervention (T1), and at follow-up, which will occur 12 months from recruitment (T2).

So, the experimental physical exercise intervention will start concomitantly with RT, which lasts about two months. As regard to ADT, its duration can vary from six to thirty-six months, and it can begin up to three months before patient's enrolment in this study and RT commencement.

Recruitment strategies

Between September 2020 and September 2021, eligible patients treated by the Radiotherapy Unit of Santa Maria Nuova Hospital of Reggio Emilia (Italy) will be given brief, written information about the study by their attending physician (radiotherapist or oncologist). Upon written consent, patients willing to receive more information will be referred to the Physical Medicine and Rehabilitation Unit and will receive a phone call by a research staff member (physiotherapist), who describes the study aim and modalities to them in detail. Patients who confirm their interest in participating will receive written information and consent forms to participate in the study to be filled out and signed. They will also make the first appointment to provide written consent and to perform the baseline assessment. The patient recruitment process is shown in Figure 1, and the example of the patient consent form is provided on additional file 2.

Baseline assessment

In the baseline assessment, demographic, anthropometric, clinical data, and physical function data will be collected. Clinical data include the date of diagnosis, tumour stage, time since receiving ADT and RT, and the presence of comorbidities assessed through the Charlson Comorbidity Index (CCI).[28] Physical function will be measured using a six-minute walk test (6MWT)[29] to calculate the intensity of aerobic exercise.

Experimental physical exercise intervention

The multicomponent experimental physical exercise intervention will last 20 weeks and consists of supervised and unsupervised exercise sessions held three times per week. Following a step-down approach, during the first eight weeks, all physical exercise sessions will be supervised by a physiotherapist, while during the following four weeks, only one weekly session will be supervised, whereas the other two will be unsupervised; finally, during the last eight weeks of experimental physical exercise, all sessions will be unsupervised. Supervised sessions will be conducted in small groups or individually at the Municipal Athletics Field in Reggio Emilia according to scheduled appointments, whereas the unsupervised sessions can be completed by participants in times, modalities and places of their convenience, providing for them the possibility to access the Municipal Athletics Field.

The multicomponent physical exercise intervention meets the dictates for exercise components, posology (frequency, sets, repetitions, intensity) and progression recommended for healthy adults.[30] Its components are aerobic, resistance, core muscle stabilization, and neuromotor exercises associated with cognitive tasks. In addition, exercise intervention will include impact-loading exercise to provide an effective bone osteogenic stimulus. This type of exercise has been considered an effective strategy to prevent loss of bone mineral density (BMD) in elderly patients[31,32] and has been applied in patients with prostate cancer receiving ADT in previous studies.[14] Altogether, the components of this intervention should preserve muscle strength and improve fatigue, balance, and cognitive function,[30] and eventually, it should prevent accidental falls and fractures.

The intervention is tailored to individual general health, functional capacity and, as far as possible, preferences.

Supervised physical exercise sessions

Supervised sessions last one hour and 15 minutes and include a period of warm up and cool-down and a combination of the following physical exercise components:

• Aerobic exercise consists of 20-30 minutes of aerobic activity at moderate-high intensity, from 60 to 80% of maximum heart rate (% HRmax), previously determined through the 6MWT,[29] which is conducted according to the current guidelines.[33] To obtain the greatest effects on bone health, the proposed aerobic exercise activities are walking or jogging, depending on individual capacity and habitual or previous experiences of physical activity. The perceived effort will be monitored by the Borg's Rate of Perceived Exertion scale (RPE) to maintain it between fairly light to hard, which corresponds to RPE scores 11 to 15.[34] To ensure that participants reach the target HR, we will use HR monitors.

• Progressive resistance exercise consists of strength activity of the major lower and upper extremity muscle groups, using body weight as a load and free weights (resistance bands, dumbbells, anklets with weight, medicine ball). During each session, the goal is to perform four to eight exercises targeting different muscle groups by performing two to four sets of 8-15 repetitions for each exercise. The perceived effort will be measured by the individual using the Borg RPE scale[35] (score between 11 and 15). The progression of intensity will be provided, starting the exercises with body weight and gradually increasing the load using free weights.[36] Adjustments to load will be made when participants can complete the highest number of specified repetitions (≥ 15 repetitions, see also Table 2). Thus, the number of exercises, dose progression (sets, repetitions) and related difficulties (e.g., squat depth and/or duration, double task exercises) will be changed during the weeks based on the patient's compliance and performance (see also Table 2). For isometric exercises, dose will be incrementally increased by adding free weights, further limb exercise or asking for double task exercise, and/or increasing the duration of exercise from 20 to 60 seconds.

• Core muscle stabilization exercise consists of postural and trunk stability exercises (e.g., strengthening of transverse abdominis and pelvic floor muscles). Participants will perform two core exercises per session in two-four sets of 8-15 repetitions. Sets, repetitions, additional free weights, additional upper body and/or lower body movements and time of exercise from 20 to 60 seconds will be used to increase the intensity of exercises.

• Neuromotor exercise consists of balance and functional (coordination) exercises associated with cognitive tasks (e.g., counting, adding, subtracting, saying day of weeks) and includes fit ball exercises (e.g., knee and contralateral upper limb extension sitting on fit ball), standing balance activities (e.g., stand on one leg) and dynamic functional tasks (e.g., stop walking balanced on one foot, walking backward). Participants will be asked to complete two to four static and dynamic exercises per session. Static exercises are performed in two-four sets of 20-60 seconds, while dynamic exercises are performed in two-four sets of 8-15 repetitions. To provide progression, exercises are modified by introducing difficulties

(e.g., closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task).

• Impact-loading exercise consists of jumping, leaping, jumping rope, hopping on one leg, going up and down steps, etc., in other words, exercises that provide impact with the ground using the body weight as a load. Two to four exercises per session will be performed. Training intensity is increased by adding repetitions, additional free weights, introducing multidirectional movement, and raising the exercise speed. To provide a large number of stimuli, several tools will be used.

Also, for core muscle stabilization, neuromotor, and impact-loading exercises, adjustments to load will be made when participants can complete the highest number of repetitions (≥15 repetitions) at the target exertion (RPE score between 11 and 15).

A detailed description of exercises, posology, tools, and progressivity is available in Table 2. Altogether, progressive resistance, core muscle stabilization, neuromotor, and impact-loading exercises are performed for 30-40 minutes each session.

Unsupervised physical exercise sessions

Unsupervised sessions also consist in all exercise components. In addition to walking or jogging, aerobic exercise can also be performed using bikes, stationary bikes, or other aerobic activities based on individual availability and preferences. Regarding the progressive resistance, core muscle stabilization, neuromotor, and impact-loading exercise components, exercises that trade on body weight or with resistance bands that will be provided to patients are taught and suggested to overcome the possible unavailability of appropriate tools. Each activity and exercise will be explained to participants and practised by them during the supervised sessions. Furthermore, written educational material with instructions and pictures of the exercises will be provided to maximize accuracy of the unsupervised execution. The physiotherapist provides individualised indications regarding the activities to be performed during unsupervised sessions but also supports participants in progressively increasing the exercise workload when the individual perceives an improvement in their functional capacity.

Outcome measures

Primary outcome

Feasibility will be measured through recruitment, adherence, and dropout rates.

The recruitment rate is the proportion of eligible individuals referred to the Physical Medicine and Rehabilitation Unit by their treating physician included in the study.

Protocol adherence is the proportion of exercise sessions that are attempted and completed by each participant. The percentage of patients who withdraw from the study and their reason for withdrawal will also be registered.

Safety is measured through the recording of any adverse events related and not related to exercise and its grading for seriousness,[37] causality and health consequences by the researcher during the study.

Feasibility and safety are monitored by the physiotherapist through direct inquiry during the first 12 weeks of the programme when supervised sessions are implemented and through a weekly phone call during the last eight weeks of unsupervised sessions.

Secondary outcomes

Secondary outcome measures include changes in muscle strength, fatigue, cognitive function, balance, quality of life, symptoms of anxiety and depression, number of accidental falls and associated fractures, and participant satisfaction.

Muscle strength

The strength of the major lower and upper extremity muscle groups will be measured with the 10-RM test (extensor muscle group). The 10-RM test assesses the maximum weight that can be lifted for ten repetitions while maintaining the correct technique. Prior to attempting this test, participants will complete five minutes of aerobic warm-up and 1-2 sets of 15-20 repetitions with a light load. Then, the load will be progressively increased while the number of repetitions will decrease accordingly until only ten repetitions can be completed. A recovery period of two minutes will be provided between each set.[38,39]

Fatigue

Fatigue will be measured using the Fatigue Severity Scale (FSS), a 9-item questionnaire on how fatigue interferes with activities and that rates its severity. The item is scored on a 7-point Likert scale with 1 = strongly disagree and 7 = strongly agree. The minimum score = 9, and the maximum score = 63. A higher score indicates greater fatigue severity.[40]

Cognitive function

Cognitive function will be measured using the Mini Mental State Examination (MMSE), a brief cognitive test designed to assess the overall cognitive status of patients. The MMSE tests five areas of mental status (orientation; registration; attention and calculation; recall; language) and is scored on a scale of 30, with adequate cognition for most adults indicated by scores from 24 to 30.[41]

Balance

Balance will be measured using the Tinetti Performance Oriented Mobility Assessment (POMA). The Tinetti POMA scale is a clinical test used to measure balance and gait abilities. The balance section (POMA-B) consists of 9 items, while the gait section (POMA-G) consists of 8 items. Each item can receive an ordinal score from 0 to 2, where "0" indicates the highest level of impairment and "2" indicates individual independence. The maximum possible total score for POMA-T is 28, for POMA-B is 16, and for POMA-G is 12. A POMA-T cut-off score < 19 indicates a high risk of falling.[42,43]

Quality of life

Quality of life will be measured using the Short Form-12 questionnaire (SF-12), which consists of twelve items measuring different physical and mental health parameters. Higher scores indicate better physical and mental health.[44]

Anxiety and depression level

Anxiety and depression level will be measured using the Hospital Anxiety and Depression Scale (HADS), a fourteen-item scale equally distributed across anxiety and depression states. The total score ranges from 0-21, with higher scores indicating greater levels of mood disturbances. In patients with cancer, a cut-off score of > 9 for the HADS-A and > 7 for the HADS-D indicates clinically relevant anxiety and depression levels, respectively.[45]

Accidental falls and fractures

During the intervention, accidental falls and fractures were recorded directly by the physiotherapist who supervised the sessions and performed the weekly phone call and thereafter at the 12-month follow-up.

Participant satisfaction

Patient satisfaction will be assessed through a simple structured interview. At the end of the intervention, each participant will be invited to answer the following four open-ended questions that investigate its acceptability:

• How do you assess the overall experience you have had by participating in this study?

• Which activities did you like the most?

• Which activities did you like least?

• What can to be improved in your opinion, or what would you have liked to have been offered?

A summary of the outcome measures and their assessments at follow-up is shown in Table 3.

Sample size calculation

No formal sample size requirement is needed for this single-group, pilot, feasibility study. At the Santa Maria Nuova Hospital of Reggio Emilia, nearly 30 patients/year undergo ADT and RT, and we aim to recruit 25 patients during the 12-month recruitment period.

Data analysis

All statistical analyses will be performed by the local Clinical Trials and Statistics Unit of the AUSL-IRCCS of Reggio Emilia. The SAS System or R software will be used according to their availability at the time of data analyses. Descriptive statistics will be reported for feasibility and safety outcomes. For each percentage, the exact two-sided confidence interval will be calculated according to the Clopper-Pearson approach, ensuring a confidence level of at least 95%. In fact, since it is an exact technique, the confidence level typically does not coincide with 95%, the discrepancy for small samples being more noticeable. Adverse events will be described and grouped into homogeneous classes. The data regarding patient satisfaction will be analysed to identify patterns of response and grouped into categories emerging from the data.

Descriptive statistics for secondary outcomes will be reported to inform potential future studies in terms of clinical health outcome measures. For all variables, percentiles, minimum, maximum, mean, and SD will be calculated. For the mean, a 95% two-sided confidence interval will be calculated assuming a t distribution. The changing over time of the secondary outcomes will be studied by the analysis of variance for repeated measures.

Concerning the number of accidental falls and fractures, as counts, the confidence interval for the mean will be calculated according to the Poisson distribution. No missing data imputation techniques have been planned, therefore only the available data will be analyzed. However, missing data will be appropriately described in their distributional aspects of relevance.

Data management and archiving

The dataset will be stored on a password-protected computer and managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia to protect patient privacy and data.

Patient and public involvement

Patients will participate in the study design so that the time and spaces necessary for the home-based intervention can be adapted according to their availability and discretion. Participants may suggest changes related to the frequency and intensity of the sessions and inform the study team about which type of exercises they prefer.

ETHICS AND DISSEMINATION

This study was approved by the Area Vasta Nord Local Ethics Committee of Azienda USL-IRCCS of Reggio Emilia (June 23, 2020, Number 520/2020/SPER/IRCCSRE), which will also review potential modifications, if any. All patients will provide consent prior to participation. Results will be disseminated through scientific peer-reviewed journals and conference presentations. The expected impact for this study is the development of a useful and acceptable physical exercise programme integrated into the daily routine of patients with prostate cancer receiving ADT and RT.

These results will inform which type of physical exercise is required to improve adherence to the recommended exercise guidelines for cancer survivors and will help researchers plan feasible physical exercise interventions whose efficacy on bone health is to be verified through well-designed RCTs.

Author contributions BB, CI, MC, SC, SF and SCo contributed to study conceptualization and design and provided input into the development of the protocol. BB, MC and SCo drafted the manuscript, and all authors revised it critically and approved the final version for publication.

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46.

Table 1 Study registration data set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04500080
Date of registration in primary registry	August 5, 2020
Secondary identifying numbers	520/2020/SPER/IRCCSRE
Source of monetary or material support	Manodori Foundation
Primary sponsor	Azienda USL-IRCCS di Reggio Emilia
Secondary sponsor	NA
Contact for public queries	BB [barbara.bressi@ausl.re.it], SC [stefania.costi@unimore.it]
Contact for scientific queries	SC [stefania.costi@unimore.it], BB [barbara.bressi@ausl.re.it]
Public title	Feasibility and Safety of Physical Exercise in Men With Prostate Cancer (PCa_Ex)
Scientific title	"The Feasibility and Safety of Physical Exercise Programme in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol"
Countries of recruitment	Italy
Health conditions or problems studied	Prostate cancer, androgen deprivation therapy and radiotherapy
Intervention	Physical exercise intervention
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: man Accepts healthy volunteers: no
	Inclusion criteria: Adult male patient (≥ 18 years) Histologically documented diagnosis of PCa Undergoing ADT and RT during the study period Willing and able to give written informed consent Able to read and understand Italian Language Exclusion criteria: Any musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate physical exercise

Study type	Interventional Allocation: single group assignment Primary purpose: supportive care
Date of first enrolment	April 2021
Target sample size	25 patients
Recruitment status	Recruiting
Primary outcomes	Feasibility: recruitment, adherence, and drop-out rates Safety: any adverse events related and not related to the intervention
Key secondary outcomes	Muscle strength, fatigue, cognitive function, balance, quality of life, anxiety and depression level, and number of falls and fractures. Patient's satisfaction: patient feedback via interview with open-ended question

Table 2 Description of exercise programme and dose progression

Weeks		**1-4**	**5-8**	**9-12**	**13-16**	**17-20**
Component	**Dose**					
Aerobic exercise	Intensity (% HRmax)	60-80%	60-80%	60-80%	60-80%	60-80%
	Duration	15-20 min	20 min	20 min	25 min	30 min
Progressive resistance exercise	Sets	2	2	3	3	4
	Repetitions	8-12	12-15	8-12	12-15	8-12
	Difficulties	Additional free weights, range of motion, number and time* of exercise, additional upper body and/or lower body movements				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), step				
Core muscle stabilization exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, additional upper body and/or lower body movements and time* of exercise				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), fit ball				
Neuromotor exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Time* of exercise, closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), fit ball, balance board				
Impact-loading exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, introducing multi-directional movement, and raising the exercise speed				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), hurdles/hoops/training cone markers, rope, steps				

Abbreviations: % HRmax, percent maximum heart rate.

*varies from 20 to 60 seconds and regards isometric exercise and static balance exercise

Table 3 Data collected

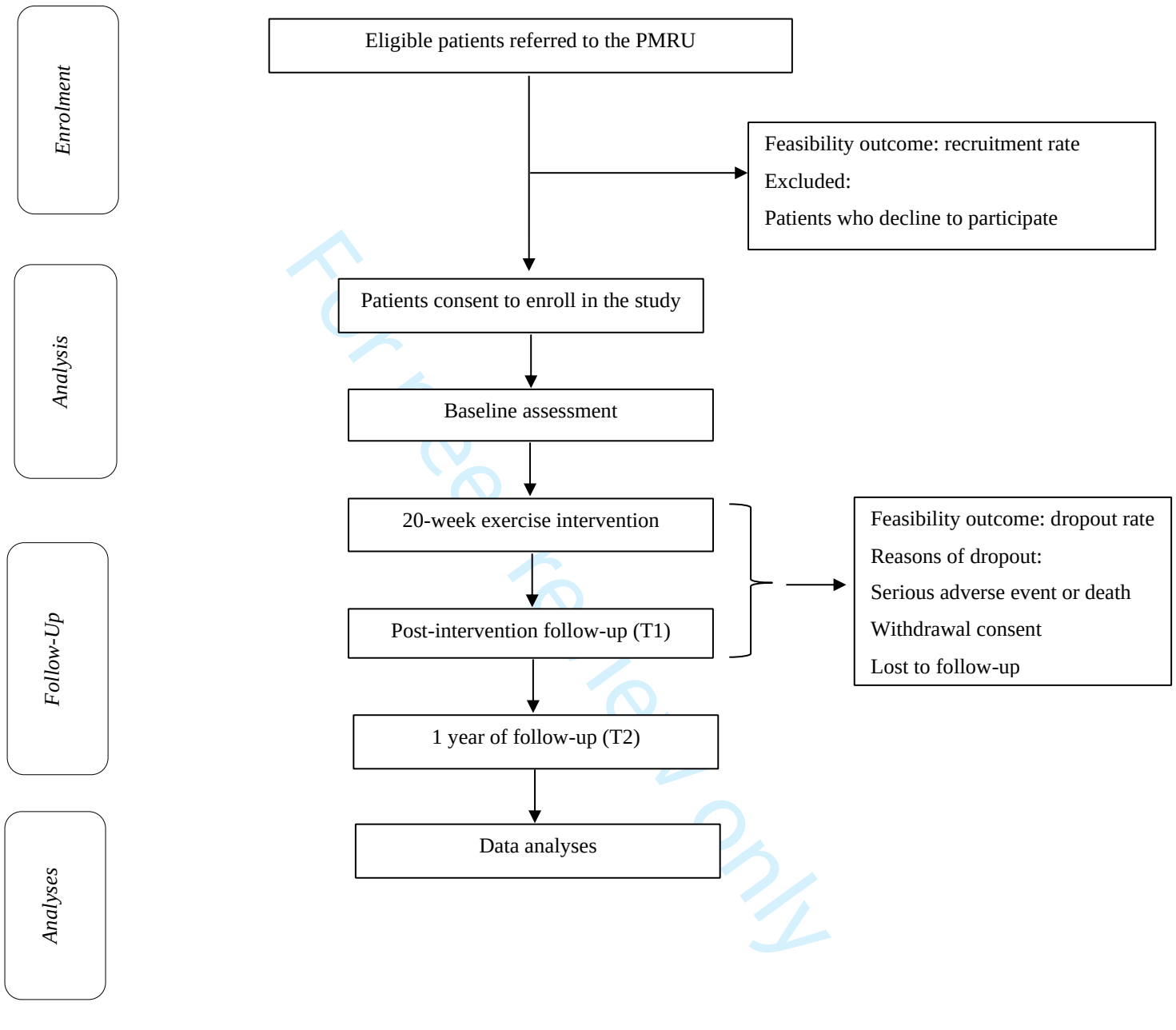
Variables	**Data collection method**	**Data collection points**		
		Baseline	T1 (20 weeks*)	T2 (1 year*)
Primary outcome measures				
Feasibility	Recruitment rate	x		
	Adherence rate		x	
	Drop-out rate		x	
Safety	Number and type of AEs related and not related to intervention		x	
Secondary outcome measures				
Muscle strength	Ten repetitions maximum (10-RM) Test	x	x	
Fatigue	Fatigue Severity Scale (FSS)	x	x	
Cognitive function	Mini mental State examination (MMSE)	x	x	
Balance	Tinetti Performance Oriented Mobility Assessment (POMA)	x	x	
Quality of life	Short form-12 questionnaire (SF-12)	x	x	
Anxiety and depression level	Hospital Anxiety and Depression Scale (HADS)	x	x	
Numbers of fall and fractures	Recorded directly by the physiotherapist during the supervised sessions and with weekly phone call during unsupervised session	x	x	x
Participant satisfaction	Patient satisfaction		x	
Additional measures	Anthropometry (height, weight, BMI)	x	x	
	Demographic data	x		
	Clinical data	x		
	Functional capacity (6MWT)	x		

Abbreviations: AEs, adverse events; BMI, body mass index; 6MWT, six minutes walking test.
*from baseline.

Figure legend

Fig 1 Schematic study flow diagram

Fig 1 Schematic study flow diagram[27]



Abbreviations: PMRU= Physical Medicine and Rehabilitation Unit

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 3
	2b	All items from the World Health Organization Trial Registration Data Set	3, Table 1
Protocol version	3	Date and version identifier	3, Table 1
Funding	4	Sources and types of financial, material, and other support	Title page
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	Title page, Table 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	Title page, Table 1
	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)	NA
Introduction			
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	2, 3
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4, 5, Table 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	4, 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
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)	3, Fig. 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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	3, 4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., 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	3, 6-8
	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	5-8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8, 9
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	8, 9
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	NA
Methods: Monitoring			
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	NA
	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	NA
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	6, 7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 9
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Title page
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	Title page
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	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1, 9
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 2
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

*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" license.

Additional file 2 Example of patient consent form

Consent form

Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy

I, the undersigned (name and surname)_____

born in_____ on_____ declare that I have received from Physiotherapist…… on …… exhaustive explanations regarding the participation in the study, as reported in the information sheet attached, a copy of which was given me on ……

Following what I have learned, I declare that:

- I have been informed about the purposes, procedures, duration of this study, the possible advantages and disadvantages and I agree to participate in this study promoted by the Azienda USL-IRCCS of Reggio Emilia.
- I was provided with a summary of the information relating to the characteristics of the study, I was able to discuss these explanations, to ask all the questions I considered necessary, and I received satisfactory answers.
- I am aware that I am free to refuse to participate in the study and that I can withdraw my consent at any time during the duration of the study.
- I understand that my participation in the study is completely voluntary.
- I have been informed and agree that my data will be available not only to the responsible party of the study and their delegates, but also to the national and international health authorities, to the Ethics Committee, should they be requested; I have also been informed that my data may be presented at national and international scientific conferences or published for scientific reasons in national and international medical journals, but in any case my identity will be protected by confidentiality (i.e. the data will always be used in ANONYMOUS and AGGREGATE modality)
- I was also informed of my right to have free access to the documentation relating to the trial and to the evaluation expressed by the Ethics Committee.
- I agree □ I not agree □ that my GP is informed.
- I have been given a copy of this consent to withhold.

By signing this form, I agree to participate in the above study.

Name and surname of patient ……

Date ……

Signature of patient……

Name and surname of Physiotherapist ……

Date……

Signature of Physiotherapist…….

Date of approval and version number

BMJ Open

Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048854.R3
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TITLE PAGE

Title: Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

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Declarations

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Patient consent for publication: not required.

Availability of data and material: Data collected in the current study are stored on a password-protected computer and managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia to protect patient privacy. Data are available from the corresponding author upon reasonable request.

Author contributions: BB, CI, MC, SC, SF and SCo contributed to study conceptualization and design and provided input into the development of the protocol. BB, MC and SCo drafted the manuscript, and all authors revised it critically and approved the final version for publication.

Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol

ABSTRACT

Introduction Androgen deprivation therapy (ADT) and radiotherapy (RT) increase survival in selected patients with prostate cancer. Nevertheless, the side effects of these therapies are associated with an increased risk of accidental falls and fractures and a decreased quality of life. Preliminary evidence suggests that physical exercise can be a valid strategy to reduce the side effects of ADT and RT in men with prostate cancer. Despite this knowledge, most patients with prostate cancer are insufficiently active, and there is a lack of data on the safety and adherence to the recommended dose of physical exercise. This study protocol is designed to examine the feasibility and safety of a multicomponent experimental physical exercise intervention targeting psychophysical and cognitive functions and the quality of life in this population.

Methods and analysis This is a pilot feasibility study. Twenty-five men currently treated with ADT and RT for prostate cancer will be invited to participate in a 20-week, multicomponent physical exercise intervention, including supervised and unsupervised exercise sessions and meeting the current recommendation for exercise in cancer. The primary outcomes are physical exercise feasibility (recruitment, adherence, and drop-out rates) and safety (adverse events related and unrelated to the intervention). The secondary outcomes are muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life, and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up.

Ethics and dissemination The study has received ethics approval from The Area Vasta Nord Local Ethics Committee (Province of Reggio Emilia, June 23, 2020, Number 520/2020/SPER/IRCCSRE). Recruitment began in September 2020 and will be completed in September 2021. The results will be disseminated through scientific journals and conference presentations.

Trial registration ClinicalTrial.gov (NCT04500080)

Keywords Prostatic neoplasms, Accidental falls, Bone fractures, Exercise, Androgen deprivation therapy, Radiotherapy.

Strengths and limitations of this study

- This pilot study thoroughly assesses the feasibility and safety of a multicomponent experimental physical exercise intervention for individuals with prostate cancer receiving ADT and RT.
- Preliminary data regarding the efficacy of structured, supervised, and unsupervised aerobic, resistance, neuromotor, and impact-loading exercise on the bone health of this population will be provided.

- Both the ecological setting, a community sport facility, and the step-down approach, from supervised to unsupervised physical exercise intervention, should foster the adoption of exercise as daily habits, promoting healthy behaviour.
- The single-group design does not allow for assessment of the efficacy of the multicomponent experimental physical exercise intervention on the bone health outcomes of interest.
- The proposed intervention does not target all the factors associated with lifestyle, such as eating, smoking, and alcohol drinking habits, which together with physical exercise, are modifiable behaviours that play a role in cancer prevention.

INTRODUCTION

Prostate cancer affects approximately 3.7 million people worldwide, ranking first among the most prevalent cancers in the male population.[1] Curative treatment of locally advanced prostate cancer usually entails radiotherapy (RT) frequently associated with androgen deprivation therapy (ADT).[2] This type of multimodal treatment is unfortunately associated with a large number of side effects.[3,4] Previous studies have demonstrated a significant increase in cancer-related fatigue in patients receiving RT, which not only decreases physical well-being but also affects daily activities, cognitive function, and quality of life.[5—7] Furthermore, it is well known that the cardiovascular, metabolic, cognitive, and musculoskeletal adverse effects of ADT lead to an increased number of accidental falls and fractures in this population.[8] Furthermore, since prostate cancer incidence increases with age,[1] older patients are normally already at a greater risk of frailty due to the presence of other comorbidities that can dramatically affect physical function.[9] Exercise interventions can prevent a large number of these complications, improving the health and quality of life of individuals with prostate cancer.[10,11] These exercise programmes should include moderate-high intensity activities that must be performed regularly to maintain exercise-related benefits.[12,13] A recent systematic review of randomized controlled trials (RCTs) showed that to counteract the negative effects of ADT on bone, multicomponent physical exercise interventions involving aerobic, resistance and impact-loading exercise have been performed.[14] Although these interventions were feasible for most participants in the RCT, those study protocols did not systematically record the adherence rate or adverse events associated with the experimented physical exercise interventions.[12,13,15] However, these data are fundamental to fostering individual compliance with the recommended dose of exercise.[12] In fact, despite the well-known benefits of physical exercise for cancer survivors,[12,16] this population is frequently unactive[17] and reports several common barriers to exercise, such as the location or distance to facilities.[18—20] Furthermore, hospital-based supervised physical exercise interventions can be challenging to implement because they requires the use of complex hospital resources.[18,21,22] This modality does

not promote long-term adherence to physical exercise or changes towards a healthier lifestyle, which are considered contemporary health priorities for physical therapy practice.[23,24]

It is suggested that an intensive lifestyle programme that includes dietary supplements, moderate aerobic exercise, stress management, and support group participation may affect the progression of prostate cancer at the early stage.[25] Furthermore, a healthier lifestyle seems to be associated with a better health-related quality of life.[26]

In this regard, we investigated the lifestyle of patients recently diagnosed of prostate cancer, their perceived barriers and facilitators to physical exercise, and motivation to change towards healthier lifestyle.[27] Therefore, based on previous research and our descriptive study, we developed a structured experimental physical exercise intervention that combines supervised and unsupervised exercise with a step-down approach. This physical exercise intervention is implemented in a community sports facility and is currently being tested in a small group of patients with prostate cancer receiving ADT and RT for feasibility and safety. Secondary outcomes include muscle strength, balance, fatigue, symptoms of anxiety and depression, cognitive function, quality of life and patient satisfaction. We will also record the number of accidental falls and fractures occurring during the intervention and at one year of follow-up. This study protocol describes the experimental physical exercise intervention in detail, with related outcomes, to allow for reproducibility and adaptation to other contexts.

METHODS AND ANALYSIS

Patients and study design

This single group feasibility pilot study was approved by the Comitato Etico dell'Area Vasta Emilia Nord (June 23, 2020, Number 520/2020/SPER/IRCCSRE) and was registered with ClinicalTrials.gov (Identifier NCT04500080). This study protocol adheres to the recommendation for clinical trials (SPIRIT) guidelines (additional file 1), and the study registration data set is shown in Table 1.[28] Eligible patients are adult men (≥18 years) with a histological diagnosis of prostate cancer who are currently treated with ADT and RT and are able to communicate in the Italian language. Participants with musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate exercise will be excluded. All patients referred to RT which are also candidate to receive ADT will be assessed for eligibility. If confirmed, written informed consent will be obtained from all participants, who will be invited to participate in a 20-week structured, supervised and unsupervised, multicomponent physical exercise programme. Patients will be assessed at baseline (T0), at the end of the intervention (T1), and at follow-up, which will occur 12 months from recruitment (T2).

So, the experimental physical exercise intervention will start concomitantly with RT, which lasts about two months. As regard to ADT, its duration can vary from six to thirty-six months, and it can begin up to three months before patient's enrolment in this study and RT commencement.

Table 1 Study registration data set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04500080
Date of registration in primary registry	August 5, 2020
Secondary identifying numbers	520/2020/SPER/IRCCSRE
Source of monetary or material support	Manodori Foundation
Primary sponsor	Azienda USL-IRCCS di Reggio Emilia
Secondary sponsor	NA
Contact for public queries	BB [barbara.bressi@ausl.re.it], SC [stefania.costi@unimore.it]
Contact for scientific queries	SC [stefania.costi@unimore.it], BB [barbara.bressi@ausl.re.it]
Public title	Feasibility and Safety of Physical Exercise in Men With Prostate Cancer (PCa_Ex)
Scientific title	"The Feasibility and Safety of Physical Exercise Programme in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy: a Study Protocol"
Countries of recruitment	Italy
Health conditions or problems studied	Prostate cancer, androgen deprivation therapy and radiotherapy
Intervention	Physical exercise intervention
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: man Accepts healthy volunteers: no
	Inclusion criteria: Adult male patient (≥ 18 years) Histologically documented diagnosis of PCa Undergoing ADT and RT during the study period Willing and able to give written informed consent Able to read and understand Italian Language Exclusion criteria: Any musculoskeletal, cardiovascular, psychiatric, or neurological disorders that contraindicate physical exercise
Study type	Interventional

	Allocation: single group assignment Primary purpose: supportive care
Date of first enrolment	April 2021
Target sample size	25 patients
Recruitment status	Recruiting
Primary outcomes	Feasibility: recruitment, adherence, and drop-out rates Safety: any adverse events related and not related to the intervention
Key secondary outcomes	Muscle strength, fatigue, cognitive function, balance, quality of life, anxiety and depression level, and number of falls and fractures. Patient's satisfaction: patient feedback via interview with open-ended question

Recruitment strategies

Between September 2020 and September 2021, eligible patients treated by the Radiotherapy Unit of Santa Maria Nuova Hospital of Reggio Emilia (Italy) will be given brief, written information about the study by their attending physician (radiotherapist or oncologist). Upon written consent, patients willing to receive more information will be referred to the Physical Medicine and Rehabilitation Unit and will receive a phone call by a research staff member (physiotherapist), who describes the study aim and modalities to them in detail. Patients who confirm their interest in participating will receive written information and consent forms to participate in the study to be filled out and signed. They will also make the first appointment to provide written consent and to perform the baseline assessment. The patient recruitment process is shown in Figure 1, and the example of the patient consent form is provided on additional file 2.

Baseline assessment

In the baseline assessment, demographic, anthropometric, clinical data, and physical function data will be collected. Clinical data include the date of diagnosis, tumour stage, time since receiving ADT and RT, and the presence of comorbidities assessed through the Charlson Comorbidity Index (CCI).[29] Physical function will be measured using a six-minute walk test (6MWT)[30] to calculate the intensity of aerobic exercise.

Experimental physical exercise intervention

The multicomponent experimental physical exercise intervention will last 20 weeks and consists of supervised and unsupervised exercise sessions held three times per week. Following a step-down approach, during the first eight weeks, all physical exercise sessions will be supervised by a physiotherapist, while during the following four weeks, only one weekly session will be supervised, whereas the other two will be unsupervised; finally, during the last eight weeks of experimental physical exercise, all sessions will be unsupervised. Supervised sessions will be conducted in small groups

or individually at the Municipal Athletics Field in Reggio Emilia according to scheduled appointments, whereas the unsupervised sessions can be completed by participants in times, modalities and places of their convenience, providing for them the possibility to access the Municipal Athletics Field.

The multicomponent physical exercise intervention meets the dictates for exercise components, posology (frequency, sets, repetitions, intensity) and progression recommended for healthy adults.[31] Its components are aerobic, resistance, core muscle stabilization, and neuromotor exercises associated with cognitive tasks. In addition, exercise intervention will include impact-loading exercise to provide an effective bone osteogenic stimulus. This type of exercise has been considered an effective strategy to prevent loss of bone mineral density (BMD) in elderly patients[32,33] and has been applied in patients with prostate cancer receiving ADT in previous studies.[14] Altogether, the components of this intervention should preserve muscle strength and improve fatigue, balance, and cognitive function,[32] and eventually, it should prevent accidental falls and fractures.

The intervention is tailored to individual general health, functional capacity and, as far as possible, preferences.

Supervised physical exercise sessions

Supervised sessions last one hour and 15 minutes and include a period of warm up and cool-down and a combination of the following physical exercise components:

• Aerobic exercise consists of 20-30 minutes of aerobic activity at moderate-high intensity, from 60 to 80% of maximum heart rate (% HRmax), previously determined through the 6MWT,[30] which is conducted according to the current guidelines.[34] To obtain the greatest effects on bone health, the proposed aerobic exercise activities are walking or jogging, depending on individual capacity and habitual or previous experiences of physical activity. The perceived effort will be monitored by the Borg's Rate of Perceived Exertion scale (RPE) to maintain it between fairly light to hard, which corresponds to RPE scores 11 to 15.[35] To ensure that participants reach the target HR, we will use HR monitors.

• Progressive resistance exercise consists of strength activity of the major lower and upper extremity muscle groups, using body weight as a load and free weights (resistance bands, dumbbells, anklets with weight, medicine ball). During each session, the goal is to perform four to eight exercises targeting different muscle groups by performing two to four sets of 8-15 repetitions for each exercise. The perceived effort will be measured by the individual using the Borg RPE scale[36] (score between 11 and 15). The progression of intensity will be provided, starting the exercises with body weight and gradually increasing the load using free weights.[37] Adjustments to load will be made when participants can complete the highest number of specified repetitions (≥ 15 repetitions, see also Table 2). Thus, the number of exercises, dose progression (sets, repetitions) and related difficulties (e.g., squat depth and/or duration, double task exercises) will be changed during the weeks based on the patient's compliance and performance (see also Table 2). For isometric exercises,

dose will be incrementally increased by adding free weights, further limb exercise or asking for double task exercise, and/or increasing the duration of exercise from 20 to 60 seconds.

• Core muscle stabilization exercise consists of postural and trunk stability exercises (e.g., strengthening of transverse abdominis and pelvic floor muscles). Participants will perform two core exercises per session in two-four sets of 8-15 repetitions. Sets, repetitions, additional free weights, additional upper body and/or lower body movements and time of exercise from 20 to 60 seconds will be used to increase the intensity of exercises.

• Neuromotor exercise consists of balance and functional (coordination) exercises associated with cognitive tasks (e.g., counting, adding, subtracting, saying day of weeks) and includes fit ball exercises (e.g., knee and contralateral upper limb extension sitting on fit ball), standing balance activities (e.g., stand on one leg) and dynamic functional tasks (e.g., stop walking balanced on one foot, walking backward). Participants will be asked to complete two to four static and dynamic exercises per session. Static exercises are performed in two-four sets of 20-60 seconds, while dynamic exercises are performed in two-four sets of 8-15 repetitions. To provide progression, exercises are modified by introducing difficulties (e.g., closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task).

• Impact-loading exercise consists of jumping, leaping, jumping rope, hopping on one leg, going up and down steps, etc., in other words, exercises that provide impact with the ground using the body weight as a load. Two to four exercises per session will be performed. Training intensity is increased by adding repetitions, additional free weights, introducing multidirectional movement, and raising the exercise speed. To provide a large number of stimuli, several tools will be used.

Also, for core muscle stabilization, neuromotor, and impact-loading exercises, adjustments to load will be made when participants can complete the highest number of repetitions (≥15 repetitions) at the target exertion (RPE score between 11 and 15).

A detailed description of exercises, posology, tools, and progressivity is available in Table 2. Altogether, progressive resistance, core muscle stabilization, neuromotor, and impact-loading exercises are performed for 30-40 minutes each session.

Table 2 Description of exercise programme and dose progression

Weeks		**1-4**	**5-8**	**9-12**	**13-16**	**17-20**
Component	**Dose**					
Aerobic exercise	Intensity (% HRmax)	60-80%	60-80%	60-80%	60-80%	60-80%
	Duration	15-20 min	20 min	20 min	25 min	30 min
Progressive resistance exercise	Sets	2	2	3	3	4
	Repetitions	8-12	12-15	8-12	12-15	8-12
	Difficulties	Additional free weights, range of motion, number and time* of exercise, additional upper body and/or lower body movements				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), step				
Core muscle stabilization exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, additional upper body and/or lower body movements and time* of exercise				
	Materials	Free weights (resistance bands, dumbbells, anklets with weight, medicine balls), fit ball				
Neuromotor exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Time* of exercise, closing eyes, reducing base of support, introducing unstable support, adding free weights, or adding a second cognitive or manual task				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), fit ball, balance board				
Impact-loading exercise	Sets	2	2	3	3	4
	Repetitions	8-10	10-12	10-12	12-15	12-15
	Difficulties	Additional free weights, introducing multi-directional movement, and raising the exercise speed				
	Materials	Free weights (dumbbells, anklets with weight, medicine balls), hurdles/hoops/training cone markers, rope, steps				

Abbreviations: % HRmax, percent maximum heart rate.

*varies from 20 to 60 seconds and regards isometric exercise and static balance exercise

Unsupervised physical exercise sessions

Unsupervised sessions also consist in all exercise components. In addition to walking or jogging, aerobic exercise can also be performed using bikes, stationary bikes, or other aerobic activities based on individual availability and preferences. Regarding the progressive resistance, core muscle stabilization, neuromotor, and impact-loading exercise components, exercises that trade on body weight or with resistance bands that will be provided to patients are taught and suggested to overcome the possible unavailability of appropriate tools. Each activity and exercise will be explained to participants and practised by them during the supervised sessions. Furthermore, written educational material with instructions and pictures of the exercises will be provided to maximize accuracy of the unsupervised execution. The physiotherapist provides individualised indications regarding the activities to be performed during unsupervised sessions but also supports participants in progressively increasing the exercise workload when the individual perceives an improvement in their functional capacity.

Outcome measures

Primary outcome

Feasibility will be measured through recruitment, adherence, and dropout rates.

The recruitment rate is the proportion of eligible individuals referred to the Physical Medicine and Rehabilitation Unit by their treating physician included in the study.

Protocol adherence is the proportion of exercise sessions that are attempted and completed by each participant. The percentage of patients who withdraw from the study and their reason for withdrawal will also be registered.

Safety is measured through the recording of any adverse events related and not related to exercise and its grading for seriousness,[38] causality and health consequences by the researcher during the study.

Feasibility and safety are monitored by the physiotherapist through direct inquiry during the first 12 weeks of the programme when supervised sessions are implemented and through a weekly phone call during the last eight weeks of unsupervised sessions.

Secondary outcomes

Secondary outcome measures include changes in muscle strength, fatigue, cognitive function, balance, quality of life, symptoms of anxiety and depression, number of accidental falls and associated fractures, and participant satisfaction.

Muscle strength

The strength of the major lower and upper extremity muscle groups will be measured with the 10-RM test (extensor muscle group). The 10-RM test assesses the maximum weight that can be lifted for ten repetitions while maintaining the correct technique. Prior to attempting this test, participants will complete five minutes of aerobic warm-up and 1-2 sets of 15-20 repetitions with a light load. Then, the load will be progressively increased while the number of repetitions will

decrease accordingly until only ten repetitions can be completed. A recovery period of two minutes will be provided between each set.[39,40]

Fatigue

Fatigue will be measured using the Fatigue Severity Scale (FSS), a 9-item questionnaire on how fatigue interferes with activities and that rates its severity. The item is scored on a 7-point Likert scale with 1 = strongly disagree and 7 = strongly agree. The minimum score = 9, and the maximum score = 63. A higher score indicates greater fatigue severity.[41]

Cognitive function

Cognitive function will be measured using the Mini Mental State Examination (MMSE), a brief cognitive test designed to assess the overall cognitive status of patients. The MMSE tests five areas of mental status (orientation; registration; attention and calculation; recall; language) and is scored on a scale of 30, with adequate cognition for most adults indicated by scores from 24 to 30.[42]

Balance

Balance will be measured using the Tinetti Performance Oriented Mobility Assessment (POMA). The Tinetti POMA scale is a clinical test used to measure balance and gait abilities. The balance section (POMA-B) consists of 9 items, while the gait section (POMA-G) consists of 8 items. Each item can receive an ordinal score from 0 to 2, where "0" indicates the highest level of impairment and "2" indicates individual independence. The maximum possible total score for POMA-T is 28, for POMA-B is 16, and for POMA-G is 12. A POMA-T cut-off score < 19 indicates a high risk of falling.[43,44]

Quality of life

Quality of life will be measured using the Short Form-12 questionnaire (SF-12), which consists of twelve items measuring different physical and mental health parameters. Higher scores indicate better physical and mental health.[45]

Anxiety and depression level

Anxiety and depression level will be measured using the Hospital Anxiety and Depression Scale (HADS), a fourteen-item scale equally distributed across anxiety and depression states. The total score ranges from 0-21, with higher scores indicating greater levels of mood disturbances. In patients with cancer, a cut-off score of > 9 for the HADS-A and > 7 for the HADS-D indicates clinically relevant anxiety and depression levels, respectively.[46]

Accidental falls and fractures

During the intervention, accidental falls and fractures were recorded directly by the physiotherapist who supervised the sessions and performed the weekly phone call and thereafter at the 12-month follow-up.

Participant satisfaction

Patient satisfaction will be assessed through a simple structured interview. At the end of the intervention, each participant will be invited to answer the following four open-ended questions that investigate its acceptability:

• How do you assess the overall experience you have had by participating in this study?

• Which activities did you like the most?

• Which activities did you like least?

• What can to be improved in your opinion, or what would you have liked to have been offered?

A summary of the outcome measures and their assessments at follow-up is shown in Table 3.

Table 3 Data collected

Variables	**Data collection method**	**Data collection points**		
		Baseline	T1 (20 weeks*)	T2 (1 year*)
Primary outcome measures				
Feasibility	Recruitment rate Adherence rate Drop-out rate	x	 x x	
Safety	Number and type of AEs related and not related to intervention		x	
Secondary outcome measures				
Muscle strength	Ten repetitions maximum (10-RM) Test	x	x	
Fatigue	Fatigue Severity Scale (FSS)	x	x	
Cognitive function	Mini mental State examination (MMSE)	x	x	
Balance	Tinetti Performance Oriented Mobility Assessment (POMA)	x	x	
Quality of life	Short form-12 questionnaire (SF-12)	x	x	
Anxiety and depression level	Hospital Anxiety and Depression Scale (HADS)	x	x	
Numbers of fall and fractures	Recorded directly by the physiotherapist during the supervised sessions and with weekly phone call during unsupervised session	x	x	x
Participant satisfaction	Patient satisfaction		x	
Additional measures	Anthropometry (height, weight, BMI) Demographic data Clinical data Functional capacity (6MWT)	x x x x	x	

Abbreviations: AEs, adverse events; BMI, body mass index; 6MWT, six minutes walking test.
*from baseline.

Sample size calculation

No formal sample size requirement is needed for this single-group, pilot, feasibility study. At the Santa Maria Nuova Hospital of Reggio Emilia, nearly 30 patients/year undergo ADT and RT, and we aim to recruit 25 patients during the 12-month recruitment period.

Data analysis

All statistical analyses will be performed by the local Clinical Trials and Statistics Unit of the AUSL-IRCCS of Reggio Emilia. The SAS System or R software will be used according to their availability at the time of data analyses. Descriptive statistics will be reported for feasibility and safety outcomes. For each percentage, the exact two-sided confidence interval will be calculated according to the Clopper-Pearson approach, ensuring a confidence level of at least 95%. In fact, since it is an exact technique, the confidence level typically does not coincide with 95%, the discrepancy for small samples being more noticeable. Adverse events will be described and grouped into homogeneous classes. The data regarding patient satisfaction will be analysed to identify patterns of response and grouped into categories emerging from the data. Descriptive statistics for secondary outcomes will be reported to inform potential future studies in terms of clinical health outcome measures. For all variables, percentiles, minimum, maximum, mean, and SD will be calculated. For the mean, a 95% two-sided confidence interval will be calculated assuming a t distribution. The changing over time of the secondary outcomes will be studied by the analysis of variance for repeated measures.

Concerning the number of accidental falls and fractures, as counts, the confidence interval for the mean will be calculated according to the Poisson distribution. No missing data imputation techniques have been planned, therefore only the available data will be analyzed. However, missing data will be appropriately described in their distributional aspects of relevance.

Data management and archiving

The dataset will be stored on a password-protected computer and managed by the Information and Technologies Service (STIT) of the Azienda USL-IRCCS of Reggio Emilia to protect patient privacy and data.

Patient and public involvement

Patients will participate in the study design so that the time and spaces necessary for the home-based intervention can be adapted according to their availability and discretion. Participants may suggest changes related to the frequency and intensity of the sessions and inform the study team about which type of exercises they prefer.

ETHICS AND DISSEMINATION

This study was approved by the Area Vasta Nord Local Ethics Committee of Azienda USL-IRCCS of Reggio Emilia (June 23, 2020, Number 520/2020/SPER/IRCCSRE), which will also review potential modifications, if any. All patients will provide consent prior to participation. Results will be disseminated through scientific peer-reviewed journals and

conference presentations. The expected impact for this study is the development of a useful and acceptable physical exercise programme integrated into the daily routine of patients with prostate cancer receiving ADT and RT.

These results will inform which type of physical exercise is required to improve adherence to the recommended exercise guidelines for cancer survivors and will help researchers plan feasible physical exercise interventions whose efficacy on bone health is to be verified through well-designed RCTs.

Author contributions BB, CI, MC, SC, SF and SCo contributed to study conceptualization and design and provided input into the development of the protocol. BB, MC and SCo drafted the manuscript, and all authors revised it critically and approved the final version for publication.

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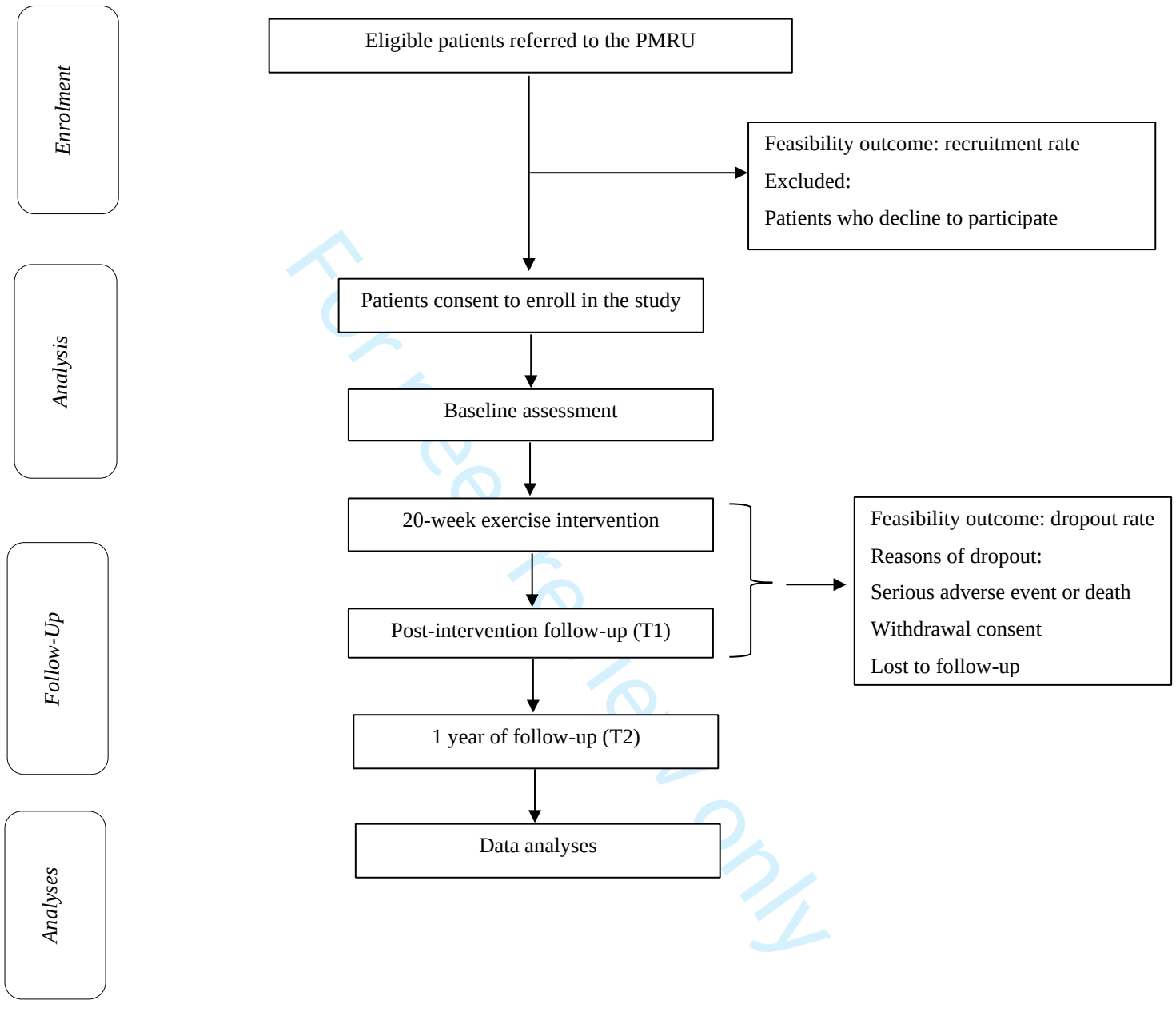
Figure legend

Fig 1 Schematic study flow diagram

Fig 1 Schematic study flow diagram[28]



Abbreviations: PMRU= Physical Medicine and Rehabilitation Unit

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 3
	2b	All items from the World Health Organization Trial Registration Data Set	3, Table 1
Protocol version	3	Date and version identifier	3, Table 1
Funding	4	Sources and types of financial, material, and other support	Title page
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	Title page, Table 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	Title page, Table 1
	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)	NA
Introduction			
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	2, 3
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4, 5, Table 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	4, 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
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)	3, Fig. 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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target size	3, 4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., 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	3, 6-8
	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	5-8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8, 9
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	8, 9
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	NA
Methods: Monitoring			
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	NA
	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	NA
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	6, 7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 9
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Title page
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	Title page
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	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1, 9
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 2
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

*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" license.

Additional file 2 Example of patient consent form

Consent form

Feasibility and Safety of Physical Exercise in Men with Prostate Cancer Receiving Androgen Deprivation Therapy and Radiotherapy

I, the undersigned (name and surname)_____

born in_____ on_____ declare that I have received from Physiotherapist…… on …… exhaustive explanations regarding the participation in the study, as reported in the information sheet attached, a copy of which was given me on ……

Following what I have learned, I declare that:

- I have been informed about the purposes, procedures, duration of this study, the possible advantages and disadvantages and I agree to participate in this study promoted by the Azienda USL-IRCCS of Reggio Emilia.
- I was provided with a summary of the information relating to the characteristics of the study, I was able to discuss these explanations, to ask all the questions I considered necessary, and I received satisfactory answers.
- I am aware that I am free to refuse to participate in the study and that I can withdraw my consent at any time during the duration of the study.
- I understand that my participation in the study is completely voluntary.
- I have been informed and agree that my data will be available not only to the responsible party of the study and their delegates, but also to the national and international health authorities, to the Ethics Committee, should they be requested; I have also been informed that my data may be presented at national and international scientific conferences or published for scientific reasons in national and international medical journals, but in any case my identity will be protected by confidentiality (i.e. the data will always be used in ANONYMOUS and AGGREGATE modality)
- I was also informed of my right to have free access to the documentation relating to the trial and to the evaluation expressed by the Ethics Committee.
- I agree □ I not agree □ that my GP is informed.
- I have been given a copy of this consent to withhold.

By signing this form, I agree to participate in the above study.

Name and surname of patient ……

Date ……

Signature of patient……

Name and surname of Physiotherapist ……

Date……

Signature of Physiotherapist…….

Date of approval and version number