BMJ Open

Weight loss for overweight and obese prostate cancer patients: a randomised trial of a clinic-based versus telehealth delivered exercise and nutrition intervention (The TelEX trial)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058899
Article Type:	Protocol
Date Submitted by the Author:	01-Nov-2021
Complete List of Authors:	Galvão, Daniel; Edith Cowan University, Exercise Medicine Research Institute Taaffe, Dennis; Edith Cowan University, Exercise Medicine Research Institute Hayne, Dickon; The University of Western Australia, School of Surgery Lopez, Pedro; Edith Cowan University, Exercise Medicine Research Institute Lyons-Wall, P; Edith Cowan University, Exercise Medicine Research Institute Tang, Colin; Sir Charles Gairdner Hospital, Department of Radiation Oncology Chambers, Suzanne; University of Technology Sydney Faculty of Health Devine, Amanda; Edith Cowan University, School of Medical and Health Sciences Spry, Nigel; Edith Cowan University, Exercise Medicine Research Institute Jeffery, Emily; Edith Cowan University, Exercise Medicine Research Institute; Curtin University Kudiarasu, Christine; Edith Cowan University, Exercise Medicine Research Institute Joseph, David; Sir Charles Gairdner Hospital, Department of Radiation Oncology Newton, Robert; Edith Cowan University, Exercise Medicine Research Institute
Keywords:	Prostate disease < UROLOGY, Adult oncology < ONCOLOGY, Nutritional support < ONCOLOGY

Weight loss for overweight and obese prostate cancer patients: a randomised trial of a clinic-based versus telehealth delivered exercise and nutrition intervention (The TelEX trial)

Daniel A. Galvão[1,2], Dennis R. Taaffe[1,2], Dickon Hayne[3,4], Pedro Lopez[1,2], Philippa Lyons-Wall[1,2], Colin Tang[1,5], Suzanne K. Chambers[1,6], Amanda Devine[2,7], Nigel Spry[2], Emily Jeffery[1,8], Christine Kudiarasu[1,2], David Joseph[1,5], Robert U. Newton[1,2]

[1]Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, Australia; [2]School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia; [3]Medical School, Surgery, University of Western Australia, Perth, Western Australia, Australia; [4]Urology Department, Fiona Stanley Hospital, Murdoch, Western Australia, Australia; [5]Department of Radiation Oncology, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [6]Faculty of Health Sciences, Australian Catholic University, Brisbane, QLD, Australia; [7]Institute for Nutrition Research, Edith Cowan University, Joondalup, WA, Australia; [8]School of Public Health, Curtin University, Perth, Western Australia, Australia.

Address for correspondence and reprint requests to:

Professor Daniel A. Galvão, PhD, FACSM

Exercise Medicine Research Institute

Edith Cowan University, 270 Joondalup Drive Joondalup

Western Australia 6027, Australia

Ph: 61-8-6304 3420

E-mail: d.galvao@ecu.edu.au

ABSTRACT

Introduction: Obese men with prostate cancer have an increased risk for biochemical recurrence, metastatic disease, and mortality. For those undergoing androgen deprivation therapy (ADT), substantial increases in fat mass are observed in the first year of treatment. Recently, we showed that a targeted supervised clinic-based exercise and nutrition intervention can result in a substantial reduction in fat mass with muscle mass preserved in ADT-treated patients. However, the intervention needs to be accessible to all patients and not just those who can access a supervised clinic-based program. The purpose of this study is to evaluate the efficacy of telehealth delivered compared to supervised clinic-based delivered exercise and nutrition intervention in overweight/obese prostate cancer patients.

Methods and analysis: A single-blinded, two-arm parallel group non-inferiority randomised trial will be undertaken with 104 overweight/obese men with prostate cancer (body fat percentage ≥ 25%) randomly allocated in a ratio of 1:1 to a telehealth delivered, virtual supervised, exercise and nutrition program or a clinic-based, face-to-face supervised exercise and nutrition program. Exercise will consist of supervised resistance and aerobic exercise performed three times per week plus additional self-directed aerobic exercise performed 4 days per week for the first 6 months. Thereafter, for months 7 to 12, the programs will be self-managed. The primary endpoint will be fat mass. Secondary endpoints include lean mass and abdominal aortic calcification, anthropometric measures and blood pressure assessment, objective measures of physical function and physical activity levels, patient-reported outcomes, and blood markers. Measurements will be undertaken at baseline and 6 months (postintervention), and at 12 months follow-up. Data will be analysed using an intention-to-treat and per protocol approaches.

Ethics and dissemination: Ethics has been obtained (ID: 2021-02157-GALVAO). Outcomes from the study will be published in peer-reviewed academic journals and presented in scientific, consumer and clinical meetings.

Trial registration number: ACTRN12621001312831

ARTICLE SUMMARY

Strengths and limitations of this study

- The TelEX trial is a novel non-inferiority randomised trial comparing a 6-month telehealth versus clinic-based supervised exercise and nutrition program in overweight/obese men with prostate cancer on treatment or previously treated with androgen deprivation therapy, with subsequent follow-up to monitor exercise and nutrition sustaining effects following self-managed programs.
- The study proposed here will determine if a telehealth exercise and nutrition program is comparable to a supervised clinic-based exercise and nutrition program for reducing fat mass in obese men with prostate cancer. Expanding such benefits to alternative exercise settings will help improve exercise delivery to those living in under-served areas during or following treatment.
- Although the current study is limited to Western Australia, the findings will be applicable across state and international borders.

INTRODUCTION

Prostate cancer is one of the most prevalent cancers worldwide accounting for ~1.4 million new cancer cases and more than 300,000 deaths in 2020 (1). Among the treatments available, androgen deprivation therapy (ADT) has been extensively used in the management of localised and advanced disease to delay cancer progression and improve survival (2). However, several adverse effects including increases in fat mass and reductions in muscle mass are common especially during the first year of ADT (3), increasing or aggravating obesity and metabolic syndrome (4). In turn, obesity increases the risk for complications during radical prostatectomy and radiation therapy (5, 6), as well as the risk for biochemical recurrence, metastatic disease and mortality (7-9).

We (10-17) and others (18-22) have shown that exercise can counteract several treatment-related toxicities such as reducing or mitigating fatigue, improving muscle mass and strength, bone mass, and physical function during or following ADT. However, the effects of exercise alone on fat mass are modest with reductions of ~0.7 kg observed in a recent meta-analysis of overweight men with prostate cancer (17) compared to the substantial gains of ~2.3 kg that can be experienced during the first year of treatment (3). As a result, exercise undertaken in trials to date has been largely insufficient to counteract the treatment-related gains in fat mass, which may be especially problematic for men already overweight or obese.

Recently, we presented new evidence that in obese ADT-treated prostate cancer patients, a targeted and supervised clinic-based 12-week exercise program allied with protein supplementation and energy restriction resulted in a substantial reduction of ~2.8 kg in fat mass while preserving muscle mass (23). However, it is necessary to expand such programs to alternative exercise settings where overweight/obese patients living in under-served areas, such as those in regional and rural settings, or those without the financial capacity to access such programs. Recently, telehealth has emerged as a viable method to deliver health-related

services such as exercise and nutrition interventions (24), and if effective in this group of prostate cancer patients, could be available at a lower cost and reach larger numbers of patients irrespective of their geographical location. Therefore, we propose to undertake a 6-month non-inferiority randomised trial to evaluate the efficacy of a telehealth delivered compared to a supervised clinic-based delivered exercise and nutrition intervention in overweight and obese prostate cancer patients. We will compare our previous reported supervised clinic-based exercise and nutrition weight loss program (27) to a program modified for delivery via telehealth in overweight/obese men with prostate cancer, with subsequent follow-up over 6 months to monitor sustainability. The primary outcome will be fat mass with secondary outcomes including lean mass and objective and patient-reported outcomes.

METHODS AND ANALYSIS

This is a single-blinded, two-arm parallel group non-inferiority randomised trial designed to examine the efficacy of implementing a Telehealth delivered, virtual supervised, Exercise and Nutrition (TENUT) program compared to a clinic-based, face-to-face supervised Exercise and Nutrition (CENUT) program on fat mass in overweight/obese men with prostate cancer (Figure 1). The protocol has been approved (ID: 2021-02157-GALVAO) by the Edith Cowan University Human Research Ethics Committee.

Patients and methods

One-hundred and four overweight/obese men (52 participants per arm) undergoing treatment or previously treated for prostate cancer involving ADT will be identified and recruited through attending physicians (general practitioner / radiation oncologist / urologist), specialist nurses, advertisements in local newspapers and presentations at cancer support groups and related events in Western Australia. Inclusion criteria are: 1) body fat percentage ≥25%,(25) and 2) ability to walk 400-m. Exclusion criteria are: 1) acute illness or any

musculoskeletal, cardiovascular or neurological disorder that could inhibit exercise performance or put participants at risk from exercising, and 2) inability to read and understand English. Eligible patients will undertake baseline measurements prior to randomisation. All patients must provide written informed consent prior to participation in addition to a physician clearance form. The study coordinator will obtain the consent and clearance forms from patients and physicians. Patients with metastases will be required to present their last bone imaging scan to establish location and extent of bone lesions with the exercise prescription modified according to Galvão et al.(26) and to the Exercise and Sports Science Australia exercise and cancer position statement (27). All data relevant to the study will be kept on password-encrypted computers accessible only by study investigators situated in the Exercise Medicine Research Institute (Perth, WA, Australia).

Patient and public involvement

We conducted a health consumer workshop reaching out to 14 men with prostate cancer that had completed our most recent exercise and nutrition intervention study (23). The men were overweight or obese and completed the 3-month diet and exercise program in our exercise clinics. We sought their input on the program they had just completed and how they would view a telehealth intervention. This input was used to inform this project and ensure that it engages participants in a respectful, ethical, and impactful way. We also worked closely with the Prostate Cancer Foundation of Australia (PCFA), their support groups and state offices. As the project evolves, PCFA will assist in the dissemination of findings to cancer support groups and the general public, while study participants will receive their individual results as well as overall study findings.

Randomisation

Patients will be randomly allocated by a computer random assignment program to the two study arms: 1) TENUT and 2) CENUT in a ratio of 1:1, subject to maintaining approximate balance regarding stratification for time on ADT (< 6 months, ≥ 6 months, and previous ADT). An investigator with no patient contact will be responsible for randomisation. The allocation sequence will be concealed from exercise physiologists involved in assigning participants to groups or conducting the study measures. In addition, participants will be requested to not reveal their group allocation to any members of the research team. The exercise will be provided by exercise physiologists not in the research team or performing the tests.

Measurements

All measurement study endpoints will take place at baseline, 6 months (end of intervention) and 12 months (6 months post intervention) and are presented in Figure 2. All assessment tools/procedures have established validity and reliability and are used widely in clinical research including by our team (10-15).

Study endpoints

Primary study endpoint

Fat mass

Regional and whole-body fat mass will be derived from a whole-body dual-energy X-ray absorptiometry (DXA; Horizon A, Hologic, Waltham, MA) scan. Trunk adiposity, visceral fat and adipose indices will be assessed using standard procedures (13, 14, 28).

Secondary study endpoints

Lean mass and abdominal aortic calcification

Regional and whole-body lean mass will be assessed by DXA. In addition, lateral spine images will be collected for abdominal aortic calcification assessment as a surrogate of cardiovascular disease (29).

Anthropometric measures and blood pressure assessment

Central adiposity will be assessed by waist circumference (WC) and hip circumference (HC) (30). WC will be measured at the level of the narrowest point between the lower costal (rib) border and the iliac crest. HC will be measured at the level of the greatest posterior protuberance of the buttocks which usually corresponds anteriorly to the level of the symphysis pubis. Body mass index (kg/m^2) will also be used to assess weight (kg) relative to height (m) squared. A validated oscillometric device (HEM-705CP, Omron Corporation, Japan) will be used to record brachial systolic and diastolic blood pressure at the dominant arm in triplicate.

Objective measures of physical function and physical activity levels

A battery of standard tests will be used to assess physical function: 1) one-repetition maximum (1RM) test for chest press and leg press strength, 2) submaximal cycle ergometer test for estimation of maximal oxygen uptake (VO_2max), 3) 400-m walk test for aerobic capacity and walking endurance, 4) repeated chair rise for lower body function, 5) 6-m usual and fast walk for gait speed, and 6) 6-m backwards tandem walk for dynamic balance (11-15, 31). Self-reported physical activity will be assessed by the leisure score index from the Godin Leisure-Time Exercise Questionnaire modified to include a question on resistance training (32).

Nutritional intervention adherence and monitoring

Adherence to dietary recommendations will be assessed using an adapted customised adherence questionnaire (23, 33, 34) designed to provide an estimated frequency of consumption and number of serves of food of interest based on the nutrition advice given. Food items of interest include fruit and vegetables, nuts, high protein foods, dairy, grains and cereals, beverages and alcoholic drinks, discretionary and take-away items. Patients will be asked 25 yes/no questions where a score of 1 is given if the patient met a predetermined desired outcome, or a 0 if they didn't. A higher total score indicates greater compliance with a maximum score

of 25. For nutrition monitoring, patients will complete a 3-day weighed food record (3d-WR) over 3 consecutive days (1 weekend day and 2 weekdays) at baseline, 6 and 12 months. This will provide an estimate of total energy intake ($kJ.d^{-1}$) and macro- and micronutrients consumed. The 3d-WR data will be analysed using FoodWorks (FoodWorks 10 Professional, Xyris Software Pty Ltd, QLD, Australia).

Patient-reported outcomes

Health-related quality of life will be assessed using the Medical Outcomes Short Form 36 (SF-36v2) (35), while cancer-related quality of life will be measured using the EORTC QLQ-C30 (36) and the EORTC-PR25 for disease-specific health-related quality of life (37). Fatigue will be assessed using the Functional assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire. The Brief Symptom Inventory-18 (BSI-18) will be used to assess psychological distress across the domains of anxiety, depression and somatisation, and global distress severity (38). These validated instruments are an integrated system to assess quality of life and psychological distress in cancer patients and has been extensively employed in clinical trials of exercise medicine (10-13, 39). In addition, the Masculinity in Chronic Disease Index will be used to assess the extent to which men identify with six masculine values: strength; sexual importance/priority; family responsibilities; emotional self-reliance; optimistic capacity and action approach (40, 41), while an adapted Working Alliance Inventory for General Practice tool will be used to assess the mediations between exercise and nutrition delivery and adherence as well as benefits derived from these programs in men with prostate cancer (42, 43).

Blood markers

Testosterone, prostate specific antigen (PSA), lipid profile, insulin, glucose, glycated haemoglobin (HbA_{1c}), C-reactive protein, adiponectin, leptin, insulin-like-growth factor-1 (IGF1), IGF-binding protein-3 (IGFBP3), interleukin 6 (IL6) and tumour necrosis factor (TNF-

α) will be measured commercially by an accredited Australian National Association of Testing Authorities (NATA) laboratory (Pathwest Diagnostics, Perth, Western Australia) (11, 13, 23).

Safety and monitoring

Patients will be monitored for any adverse events during training and testing by the Accredited Exercise Physiologists (AEP) with study clinicians overseeing aspects of patient management where required.

Exercise interventions

Telehealth and Face-To-Face delivered exercise and nutrition programs

The interventions will consist of 300 min per week of moderate to vigorous exercise per week for 6 months comprising a supervised resistance and aerobic exercise program performed three times per week for 60 min per session delivered face-to-face in an exercise clinic or via telehealth by AEP, plus 30 min of moderate/vigorous physical activity self-managed 4 days per week. For both TENUT and CENUT, resistance training will comprise 2-4 sets for 6-8 exercises targeting the major upper and lower body muscle groups performed using equipment such as exercise machines, dumbbells and elastic bands at an intensity of 6-12 repetition maximum (RM; i.e. the maximal weight that can be lifted 6 to 12 times which is equivalent to ~60-85% of 1RM). The supervised aerobic exercise component will involve 15 to 20 minutes of moderate to vigorous intensity cardiovascular exercise using a variety of modes such as walking, jogging or cycling. This approach has been extensively used by our team (11, 13, 14, 23), providing optimal stimulus while maximising safety, compliance and retention in clinic-based exercise programs. The self-directed aerobic component will comprise these modes for 30 minutes 4 days per week. For the telehealth intervention we will implement the latest digital platforms that we developed during COVID-19 restrictions in 2020 and related technological advancements in wearable sensors, online monitoring, cloud-based platforms, and video chat. Participants will receive their exercise program via their smart device or

computer, communicate with the AEP and fellow participants by video chat, and be monitored in real-time through the internet.

For the nutrition intervention, all participants will receive a total of 5 face-to-face or online consultations over the first 6 months of intervention (baseline, 2, 12, 18, 24 weeks) with an Accredited Practising Dietitian (APD) aiming to: 1) achieve an energy deficit of 2100-4200 kJ/day (500-1000 kcal/day); 2) reducing discretionary items including alcoholic drinks and foods containing refined sugars; and 3) maintain protein intake. In addition, participants will consume 40 g of a whey protein supplement 3 times per week immediately after the resistance exercise sessions.

At the end of the first 6-month period, participants from CENUT will receive a booklet with detailed information about a home exercise prescription, while the telehealth program will be maintained without supervision for participants from TENUT. Instructions on performing the home-based exercises and achieving dietary recommendations will be provided by the AEP and APD.

Calculation of sample size and statistical analysis

From our previous research in obese prostate cancer patients we reported that the standard deviation for change in fat mass equates to 2.6 kg (mean change of -2.8 kg) following 3 months of combined resistance and aerobic exercise with protein supplementation and caloric restriction (23). A priori, 43 patients per group will be required to achieve 80% power at an α level of .025 (one-tailed) and demonstrate a non-inferiority limit below 1.4 kg of fat mass between the TENUT and CENUT groups. Therefore, to adequately ensure that we have a sufficient number of participants at the end of the study (accounting for a drop-out rate of 20%), 52 participants will be randomised to each group.

Normality of the data will be assessed using the Kolmogorov-Smirnov test. Baseline characteristics will be analysed using Student's t tests or the Mann-Whitney U-test for

continuous measures, as appropriate, and Chi-square for categorical variables. For the study outcomes, data will be analysed using intention-to-treat and per protocol approaches. Testing for longitudinal changes will be performed using linear mixed models (LMM). Non-inferiority of the intervention for the primary outcome will be implied if the lower limit of a 1-sided 95% confidence interval of the difference between groups between baseline and 6 months is within the pre-stated limit of 1.4 kg for fat mass change.

Ethics and dissemination

Outcomes from the study will be published in peer-reviewed academic journals and presented in scientific, consumer and clinical meetings. The study investigators and trial coordinator will have access to the data.

DISCUSSION

Men with prostate cancer undergoing ADT experience increased fat and reduced muscle mass placing them at increased risk of morbidity and mortality from cardiovascular and metabolic diseases (3, 8, 44, 45). Targeted exercise medicine interventions for men with prostate cancer can improve quality of life, reduce treatment-related side-effects, and improve both physical and psychological health (10-17). More recently, we have shown that in obese men with prostate cancer, a targeted supervised clinic-based exercise and nutrition intervention resulted in a substantial reduction in fat mass (~3 kg) while muscle mass was preserved (23). This is a new finding, however, availability of these clinic-based services and patient support is limited and the vast majority of patients cannot access due to issues of distance, transport, inconvenience and financial capacity. The result is an unacceptable disparity between patients that have access to such supportive care and those that do not, resulting in suboptimal quality of life and ultimately survival for those men that cannot access current best practice care.

These issues are particularly pertinent to patients in Western Australia due to our geography (comprises about a third of the country with only one major metropolitan area) resulting in the majority of men with prostate cancer having limited or no capacity to access exercise and nutrition programs face-to-face with health professionals. Access to the latest exercise medicine and nutrition services has been unfortunately further impacted by the COVID-19 pandemic due to personal isolation, physical distancing and changes to public transport and procedures within cancer care clinics (46). Telehealth exercise and nutrition interventions have the potential to overcome most if not all these issues providing high-quality, effective and safe supportive care at a time and in a place of the patient's choosing. Translation of the outcomes of this research can be immediate. The underlying knowledge required to take this program out into the community will be a result of the research project.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021.

2. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. Jama. 2008;299(3):289-95.

3. Galvao DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008;102(1):44-7.

4. Bhindi B, Locke J, Alibhai SMH, Kulkarni GS, Margel DS, Hamilton RJ, et al. Dissecting the association between metabolic syndrome and prostate cancer risk: analysis of a large clinical cohort. Eur Urol. 2015;67(1):64-70.

5. Di Bella CM, Howard LE, Oyekunle T, De Hoedt AM, Salama JK, Song H, et al. Abdominal and pelvic adipose tissue distribution and risk of prostate cancer recurrence after radiation therapy. Prostate. 2020;80(14):1244-52.

6. Uchida T, Higure T, Kawakami M, Nakano M, Nakajima N, Kim H, et al. What factors affect the operative time of robot-assisted laparoscopic radical prostatectomy? Surg Endosc. 2020; Online ahead of print.

7. Bonn SE, Wiklund F, Sjolander A, Szulkin R, Stattin P, Holmberg E, et al. Body mass index and weight change in men with prostate cancer: progression and mortality. Cancer Causes Control. 2014;25(8):933-43.

8. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2011;4(4):486-501.

9. Troeschel AN, Hartman TJ, Jacobs EJ, Stevens VL, Gansler T, Flanders WD, et al. Postdiagnosis body mass index, weight change, and mortality from prostate cancer, cardiovascular disease, and all causes among survivors of nonmetastatic prostate cancer. J Clin Oncol. 2020;38(18):2018-27.

10. Galvão DA, Newton RU, Chambers SK, Spry N, Joseph D, Gardiner RA, et al. Psychological distress in men with prostate cancer undertaking androgen deprivation therapy: modifying effects of exercise from a year-long randomized controlled trial. Prostate Cancer Prostatic Dis. 2021.

11. Galvao DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. Eur Urol. 2014;65(5):856-64.

12. Galvao DA, Taaffe DR, Spry N, Cormie P, Joseph D, Chambers SK, et al. Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases. Med Sci Sports Exerc. 2018;50(3):393-9.

13. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol. 2010;28(2):340-7.

14. Newton RU, Galvao DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Exercise mode specificity for preserving spine and hip bone mineral density in prostate cancer patients. Med Sci Sports Exerc. 2019;51(4):607-14.

15. Taaffe DR, Galvao DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Immediate versus delayed exercise in men initiating androgen deprivation: effects on bone density and soft tissue composition. BJU Int. 2019;123(2):261-9.

16. Lopez P, Taaffe DR, Newton RU, Buffart LM, Galvao DA. What is the minimal dose for resistance exercise effectiveness in prostate cancer patients? Systematic review and meta-analysis on patient-reported outcomes. Prostate Cancer Prostatic Dis. 2020.

17. Lopez P, Taaffe DR, Newton RU, Galvao DA. Resistance exercise dosage in men with prostate cancer: Systematic review, meta-analysis, and meta-regression. Med Sci Sports Exerc. 2021;53(3):459-69.

18. Bourke L, Gilbert S, Hooper R, Steed LA, Joshi M, Catto JW, et al. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. Eur Urol. 2014;65(5):865-72.

19. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol. 2003;21(9):1653-9.

20. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol. 2009;27(3):344-51.

21. Ndjavera W, Orange ST, O'Doherty AF, Leicht AS, Rochester M, Mills R, et al. Exercise-induced attenuation of treatment side-effects in patients with newly diagnosed prostate cancer beginning androgen-deprivation therapy: a randomised controlled trial. BJU Int. 2020;125(1):28-37.

22. Winters-Stone KM, Dobek JC, Bennett JA, Maddalozzo GF, Ryan CW, Beer TM. Skeletal response to resistance and impact training in prostate cancer survivors. Med Sci Sports Exerc. 2014;46(8):1482-8.

23. Wilson RL, Newton RU, Taaffe DR, Hart NH, Lyons-Wall P, GalvÃo DA. Weight loss for obese prostate cancer patients on androgen deprivation therapy. Med Sci Sports Exerc. 2021;53(3):470-8.

24. Collins IM, Burbury K, Underhill CR. Teletrials: implementation of a new paradigm for clinical trials. Med J Aust. 2020;213(6):263-5.e1.

25. Kennedy AP, Shea JL, Sun G. Comparison of the classification of obesity by BMI vs. dual-energy X-ray absorptiometry in the Newfoundland population. Obesity (Silver Spring). 2009;17(11):2094-9.

26. Galvao DA, Taaffe DR, Spry N, Cormie P, Joseph D, Chambers SK, et al. Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases. Med Sci Sport Exer. 2018;50(3):393-9.

27. Hayes SC, Newton RU, Spence RR, Galvão DA. The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. J Sci Med Sport. 2019;22(11):1175-99.

28. Messina C, Albano D, Gitto S, Tofanelli L, Bazzocchi A, Ulivieri FM, et al. Body composition with dual energy X-ray absorptiometry: from basics to new tools. Quant Imaging Med Surg. 2020;10(8):1687-98.

29. Lewis JR, Schousboe JT, Lim WH, Wong G, Wilson KE, Zhu K, et al. Long-Term Atherosclerotic Vascular Disease Risk and Prognosis in Elderly Women With Abdominal Aortic Calcification on Lateral Spine Images Captured During Bone Density Testing: A Prospective Study. J Bone Miner Res. 2018;33(6):1001-10.

30. Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. J Clin Endocrinol Metab. 1983;57(2):304-10.

31. Mijwel S, Cardinale D, Ekblom-Bak E, Sundberg CJ, Wengström Y, Rundqvist H. Validation of 2 Submaximal Cardiorespiratory Fitness Tests in Patients With Breast Cancer Undergoing Chemotherapy. Rehabil Oncol. 2016;34(4):137-43.

32. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci. 1985;10(3):141-6.

33. Martínez-González MA, García-Arellano A, Toledo E, Salas-Salvadó J, Buil-Cosiales P, Corella D, et al. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. PLoS One. 2012;7(8):e43134.

34. Erdrich S, Bishop KS, Karunasinghe N, Han DY, Ferguson LR. A pilot study to investigate if New Zealand men with prostate cancer benefit from a Mediterranean-style diet. PeerJ. 2015;3:e1080.

35. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

36. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

37. Chu D, Popovic M, Chow E, Cella D, Beaumont JL, Lam H, et al. Development, characteristics and validity of the EORTC QLQ-PR25 and the FACT-P for assessment of quality of life in prostate cancer patients. J Comp Eff Res. 2014;3(5):523-31.

38. Derogatis LR. BSI 18, Brief Symptom Inventory 18: Administration, scoring and procedures manual: NCS Pearson, Incorporated; 2001.

39. Galvao DA, Taaffe DR, Chambers SK, Fairman CM, Spry N, Joseph D, et al. Exercise intervention and sexual function in advanced prostate cancer: a randomised controlled trial. BMJ Support Palliat Care. 2020.

40. Chambers SK, Hyde MK, Oliffe JL, Zajdlewicz L, Lowe A, Wootten AC, et al. Measuring masculinity in the context of chronic disease. Psychology of Men & Masculinity. 2016;17(3):228-42.

41. Hyde MK, Zajdlewicz L, Wootten AC, Nelson CJ, Lowe A, Dunn J, et al. Medical Help-Seeking for Sexual Concerns in Prostate Cancer Survivors. Sex Med. 2016;4(1):e7-e17.

42. Sturgiss EA, Rieger E, Haesler E, Ridd MJ, Douglas K, Galvin SL. Adaption and validation of the Working Alliance Inventory for General Practice: qualitative review and cross-sectional surveys. Fam Pract. 2019;36(4):516-22.

43. Tracey TJ, Kokotovic AM. Factor structure of the working alliance inventory. Psychological Assessment: A journal of consulting and clinical psychology. 1989;1(3):207.

44. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24(27):4448-56.

45. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab. 2006;91(4):1305-8.

46. Lopez P, Taaffe DR, Newton RU, Spry N, Shannon T, Frydenberg M, et al. Can Exercise Adaptations Be Maintained in Men with Prostate Cancer Following Supervised Programmes? Implications to the COVID-19 Landscape of Urology and Clinical Exercise. Eur Urol Open Sci. 2020;21:47-50.

AUTHORS' CONTRIBUTIONS: DAG, DRT, DH, PL, PLW, CT, SKC, NS, CK and RUN collaboratively developed the concept and protocol, including intervention, outcomes of interests, and planned data analysis procedures. AD, EJ, DJ further contributed to the study protocol. DAG, DRT, DH, PL, PLW, CT, SKC, NS, CK and RUN contributed to writing, reviewing, editing and final approval of the manuscript. AD, EJ, DJ further contributed to editing and final approval of the manuscript.

FUNDING STATEMENT: This work was supported by Cancer Council Western Australia Prostate Cancer Research Initiative grant (2021-2023 Prostate Cancer Research Initiative). DAG and RUN are funded by a NHMRC CRE in Prostate Cancer Survivorship. PL is supported by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence (CRE) in Prostate Cancer Survivorship Scholarship.

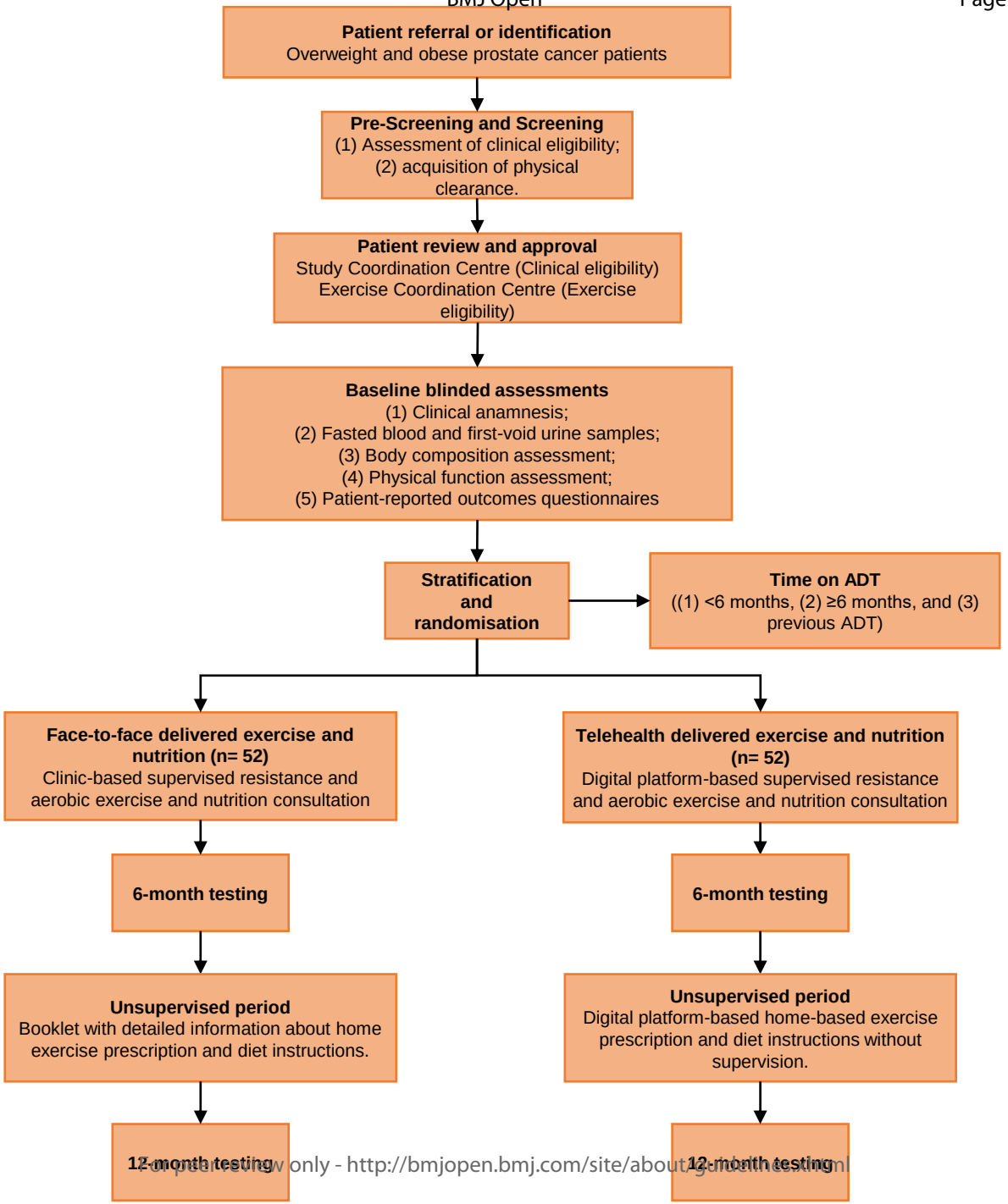
COMPETING INTERESTS STATEMENT: None declared.

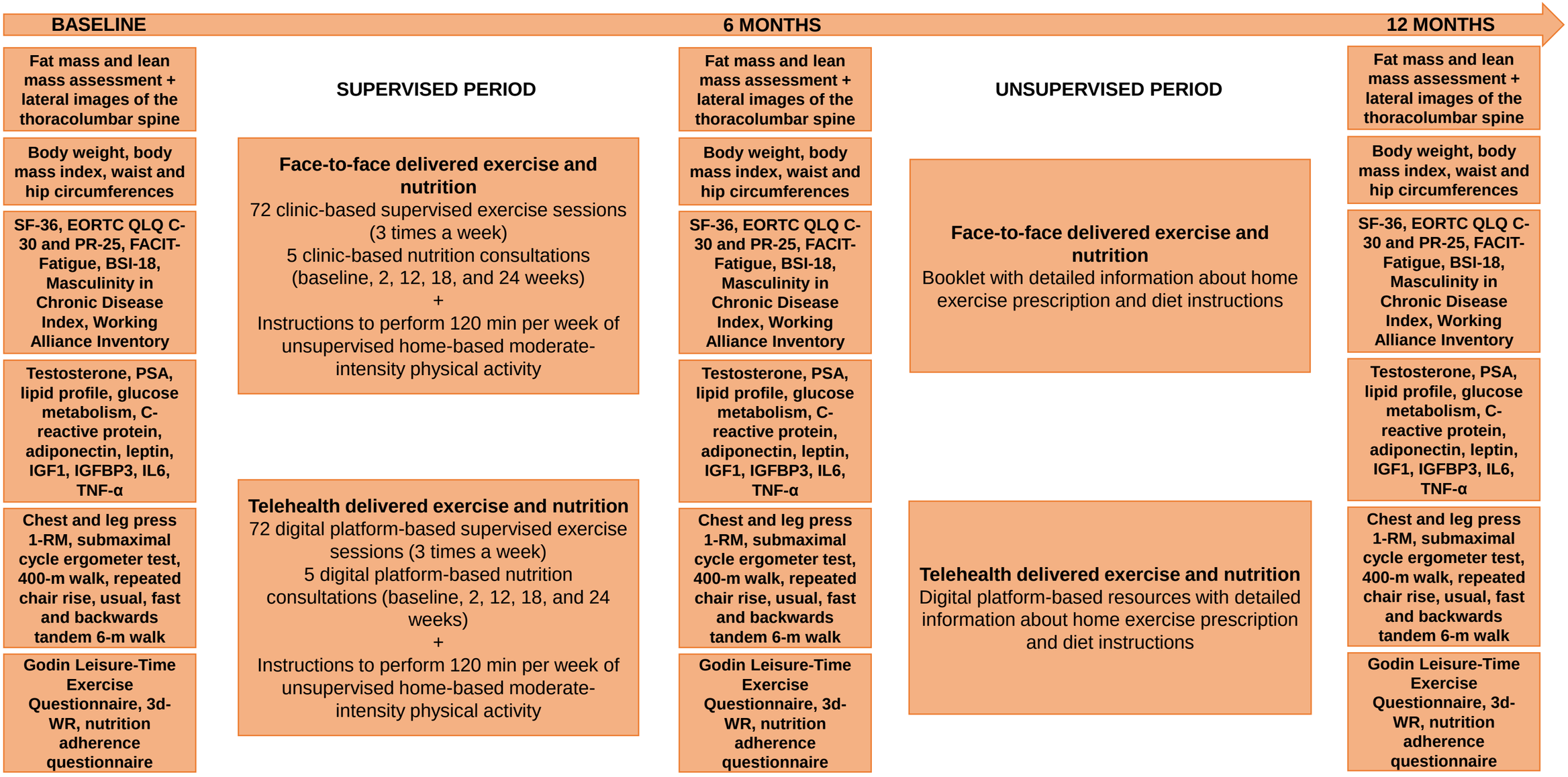
ETHICS APPROVAL: Edith Cowan University Human Ethics Committee (ID: 2021-02157-GALVAO)

FIGURE LEGENDS

Figure 1. CONSORT diagram depicting the of participants throughout the trial.

Figure 2. Study design, exercise and nutrition interventions and timeline assessments.




BASELINE
6 MONTHS
12 MONTHS
Fat mass and lean mass assessment + lateral images of the thoracolumbar spine
Body weight, body mass index, waist and hip circumferences
SF-36, EORTC QLQ C-30 and PR-25, FACIT-Fatigue, BSI-18, Masculinity in Chronic Disease Index, Working Alliance Inventory
Testosterone, PSA, lipid profile, glucose metabolism, C-reactive protein, adiponectin, leptin, IGF1, IGFBP3, IL6, TNF-α
Chest and leg press 1-RM, submaximal cycle ergometer test, 400-m walk, repeated chair rise, usual, fast and backwards tandem 6-m walk
Godin Leisure-Time Exercise Questionnaire, 3d-WR, nutrition adherence questionnaire
SUPERVISED PERIOD
Face-to-face delivered exercise and nutrition
72 clinic-based supervised exercise sessions (3 times a week)
5 clinic-based nutrition consultations (baseline, 2, 12, 18, and 24 weeks)
+
Instructions to perform 120 min per week of unsupervised home-based moderate-intensity physical activity
Telehealth delivered exercise and nutrition
72 digital platform-based supervised exercise sessions (3 times a week)
5 digital platform-based nutrition consultations (baseline, 2, 12, 18, and 24 weeks)
+
Instructions to perform 120 min per week of unsupervised home-based moderate-intensity physical activity
UNSUPERVISED PERIOD
Face-to-face delivered exercise and nutrition
Booklet with detailed information about home exercise prescription and diet instructions
Telehealth delivered exercise and nutrition
Digital platform-based resources with detailed information about home exercise prescription and diet instructions

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 and 3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 22
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	N/A

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	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
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)	9 and Figure 2

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	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7 and 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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 (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
	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	9-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
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	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14
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	N/A
	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	N/A
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	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	7-8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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	7-8
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	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4 and 14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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.

BMJ Open

Weight loss for overweight and obese prostate cancer patients: a study protocol of a randomised trial comparing clinic-based versus telehealth delivered exercise and nutrition intervention (The TelEX trial)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058899.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Mar-2022
Complete List of Authors:	Galvão, Daniel; Edith Cowan University, Exercise Medicine Research Institute Taaffe, Dennis; Edith Cowan University, Exercise Medicine Research Institute Hayne, Dickon; The University of Western Australia, School of Surgery Lopez, Pedro; Edith Cowan University, Exercise Medicine Research Institute Lyons-Wall, P; Edith Cowan University, Exercise Medicine Research Institute Tang, Colin; Sir Charles Gairdner Hospital, Department of Radiation Oncology Chambers, Suzanne; University of Technology Sydney Faculty of Health Devine, Amanda; Edith Cowan University, School of Medical and Health Sciences Spry, Nigel; Edith Cowan University, Exercise Medicine Research Institute Jeffery, Emily; Edith Cowan University, Exercise Medicine Research Institute; Curtin University Kudiarasu, Christine; Edith Cowan University, Exercise Medicine Research Institute Joseph, David; Sir Charles Gairdner Hospital, Department of Radiation Oncology Newton, Robert; Edith Cowan University, Exercise Medicine Research Institute
Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology
Keywords:	Prostate disease < UROLOGY, Adult oncology < ONCOLOGY, Nutritional support < ONCOLOGY

Weight loss for overweight and obese prostate cancer patients: a study protocol of a randomised trial comparing clinic-based versus telehealth delivered exercise and nutrition intervention (The TelEX trial)

Daniel A. Galvão[1,2], Dennis R. Taaffe[1,2], Dickon Hayne[3,4], Pedro Lopez[1,2], Philippa Lyons-Wall[1,2], Colin Tang[1,5], Suzanne K. Chambers[1,6], Amanda Devine[2,7], Nigel Spry[2], Emily Jeffery[1,8], Christine Kudiarasu[1,2], David Joseph[1,5], Robert U. Newton[1,2]

[1]Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, Australia; [2]School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia; [3]Medical School, Surgery, University of Western Australia, Perth, Western Australia, Australia; [4]Urology Department, Fiona Stanley Hospital, Murdoch, Western Australia, Australia; [5]Department of Radiation Oncology, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [6]Faculty of Health Sciences, Australian Catholic University, Brisbane, QLD, Australia; [7]Institute for Nutrition Research, Edith Cowan University, Joondalup, WA, Australia; [8]School of Public Health, Curtin University, Perth, Western Australia, Australia.

Address for correspondence and reprint requests to:

Professor Daniel A. Galvão, PhD, FACSM

Exercise Medicine Research Institute

Edith Cowan University, 270 Joondalup Drive Joondalup

Western Australia 6027, Australia

Ph: 61-8-6304 3420

E-mail: d.galvao@ecu.edu.au

ABSTRACT

Introduction: Obese men with prostate cancer have an increased risk for biochemical recurrence, metastatic disease, and mortality. For those undergoing androgen deprivation therapy (ADT), substantial increases in fat mass are observed in the first year of treatment. Recently, we showed that a targeted supervised clinic-based exercise and nutrition intervention can result in a substantial reduction in fat mass with muscle mass preserved in ADT-treated patients. However, the intervention needs to be accessible to all patients and not just those who can access a supervised clinic-based program. The purpose of this study is to evaluate the efficacy of telehealth delivered compared to supervised clinic-based delivered exercise and nutrition intervention in overweight/obese prostate cancer patients.

Methods and analysis: A single-blinded, two-arm parallel group non-inferiority randomised trial will be undertaken with 104 overweight/obese men with prostate cancer (body fat percentage ≥25%) randomly allocated in a ratio of 1:1 to a telehealth delivered, virtual supervised, exercise and nutrition program or a clinic-based, face-to-face supervised exercise and nutrition program. Exercise will consist of supervised resistance and aerobic exercise performed thrice weekly plus additional self-directed aerobic exercise performed 4 days per week for the first 6 months. Thereafter, for months 7-12, the programs will be self-managed. The primary endpoint will be fat mass. Secondary endpoints include lean mass and abdominal aortic calcification, anthropometric measures and blood pressure assessment, objective measures of physical function and physical activity levels, patient-reported outcomes, and blood markers. Measurements will be undertaken at baseline, 6 months (postintervention), and at 12 months follow-up. Data will be analysed using an intention-to-treat and per protocol approaches.

Ethics and dissemination: Ethics has been obtained in the Edith Cowan University Human Research Ethics Committee (ID: 2021-02157-GALVAO). Outcomes from the study will be published in academic journals and presented in scientific and consumer meetings.

Trial registration number: ACTRN12621001312831

Key words: Prostate cancer; Obesity; Exercise; Nutrition; Fat mass; Lean mass

ARTICLE SUMMARY

Strengths and limitations of this study

- Direct comparison between telehealth and clinic-based supervised exercise and nutrition program in obese/overweight men with prostate cancer.
- Year-long trial comprising 6 months direct intervention followed by 6 months self-management.
- Comprehensive assessment of objective and patient-reported outcomes including dual-energy X-ray absorptiometry for the primary outcome.
- The study is limited to patients previously treated or currently undergoing androgen deprivation therapy.

INTRODUCTION

Prostate cancer is one of the most prevalent cancers worldwide accounting for ~1.4 million new cancer cases and more than 300,000 deaths in 2020 (1). Among the treatments available, androgen deprivation therapy (ADT) has been extensively used in the management of localised and advanced disease to delay cancer progression and improve survival (2). However, several adverse effects including increases in fat mass and reductions in muscle mass are common especially during the first year of ADT (3), increasing or aggravating obesity and metabolic syndrome (4). In turn, obesity increases the risk for complications during radical prostatectomy and radiation therapy (5, 6), as well as the risk for biochemical recurrence, metastatic disease and mortality (7-9).

We (10-17) and others (18-23) have shown that exercise can counteract several treatment-related toxicities such as reducing or mitigating fatigue, improving muscle mass and strength, bone mass, and physical function during or following ADT. However, the effects of exercise alone on fat mass are modest with reductions of ~0.7 kg observed in a recent meta-analysis of overweight men with prostate cancer (17) compared to the substantial gains of ~2.3 kg that can be experienced during the first year of treatment (3). As a result, exercise undertaken in trials to date has been largely insufficient to counteract the treatment-related gains in fat mass, which may be especially problematic for men already overweight or obese.

Recently, we presented new evidence that in obese ADT-treated prostate cancer patients, a targeted and supervised clinic-based 12-week exercise program allied with protein supplementation and energy restriction resulted in a substantial reduction of ~2.8 kg in fat mass while preserving muscle mass (24). However, it is necessary to expand such programs to alternative exercise settings where overweight/obese patients living in under-served areas, such as those in regional and rural settings, or those without the financial capacity to access such programs. Recently, telehealth has emerged as a viable method to deliver health-related

services such as exercise and nutrition interventions (25), and if effective in this group of prostate cancer patients, could be available at a lower cost and reach larger numbers of patients irrespective of their geographical location. Therefore, we propose to undertake a 6-month non-inferiority randomised trial to evaluate the efficacy of a telehealth delivered compared to a supervised clinic-based delivered exercise and nutrition intervention in overweight and obese prostate cancer patients. We will compare our previous reported supervised clinic-based exercise and nutrition weight loss program (24) to a program modified for delivery via telehealth in overweight/obese men with prostate cancer, with subsequent follow-up over 6 months to monitor sustainability. The primary outcome will be fat mass with secondary outcomes including lean mass and objective and patient-reported outcomes.

METHODS AND ANALYSIS

This is a single-blinded, two-arm parallel group non-inferiority randomised trial designed to examine the efficacy of implementing a Telehealth delivered, virtual supervised, Exercise and Nutrition (TENUT) program compared to a clinic-based, face-to-face supervised Exercise and Nutrition (CENUT) program on fat mass in overweight/obese men with prostate cancer (Figure 1). The protocol has been approved (ID: 2021-02157-GALVAO) by the Edith Cowan University Human Research Ethics Committee. This trial expects to enrol participants to baseline testing between December 2021 to December 2023.

Patients and methods

One-hundred and four overweight/obese men (52 participants per arm) undergoing treatment or previously treated (i.e., those who had completed treatment and are no longer on treatment) for prostate cancer involving ADT will be identified and recruited through attending physicians (general practitioner / radiation oncologist / urologist), specialist nurses, advertisements in local newspapers and presentations at cancer support groups and related

events in Western Australia. Inclusion criteria are: 1) body fat percentage ≥25%,(26) and 2) ability to walk 400-m. Exclusion criteria are: 1) acute illness or any musculoskeletal, cardiovascular or neurological disorder that could inhibit exercise performance or put participants at risk from exercising, and 2) inability to read and understand English. Eligible patients will undertake baseline measurements prior to randomisation. All patients must provide written informed consent prior to participation in addition to a physician clearance form. The study coordinator will obtain the consent and clearance forms from patients and physicians. Patients with metastases will be required to present their last bone imaging scan to establish location and extent of bone lesions with the exercise prescription modified according to Galvão et al.(27) and to the Exercise and Sports Science Australia exercise and cancer position statement (28). All data relevant to the study will be kept on password-encrypted computers accessible only by study investigators situated in the Exercise Medicine Research Institute (Perth, WA, Australia).

Patient and public involvement

We conducted a health consumer workshop reaching out to 14 men with prostate cancer that had completed our most recent exercise and nutrition intervention study (24). The men were overweight or obese and completed the 3-month diet and exercise program in our exercise clinics. We sought their input on the program they had just completed and how they would view a telehealth intervention. This input was used to inform this project and ensure that it engages participants in a respectful, ethical, and impactful way. We also worked closely with the Prostate Cancer Foundation of Australia (PCFA), their support groups and state offices. As the project evolves, PCFA will assist in the dissemination of findings to cancer support groups and the general public, while study participants will receive their individual results as well as overall study findings.

Randomisation

Patients will be randomly allocated by a computer random assignment program to the two study arms: 1) TENUT and 2) CENUT in a ratio of 1:1, subject to maintaining approximate balance regarding stratification for time on ADT (< 6 months, ≥ 6 months, and previous ADT). An investigator with no patient contact will be responsible for randomisation. The allocation sequence will be concealed from exercise physiologists involved in assigning participants to groups or conducting the study measures. In addition, participants will be requested to not reveal their group allocation to any members of the research team. The exercise will be provided by exercise physiologists not in the research team or performing the tests.

Measurements

All measurement study endpoints will take place at baseline, 6 months (end of intervention) and 12 months (6 months post intervention) and will be undertaken in person at the Exercise Medicine Research Institute at Edith Cowan University in Perth, Australia (Figure 2). All assessment tools/procedures have established validity and reliability and are used widely in clinical research including by our team (10-15).

Study endpoints

Primary study endpoint

Fat mass

Regional and whole-body fat mass will be derived from a whole-body dual-energy X-ray absorptiometry (DXA; Horizon A, Hologic, Waltham, MA) scan. Trunk adiposity, visceral fat and adipose indices will be assessed using standard procedures (13, 14, 29).

Secondary study endpoints

Lean mass and abdominal aortic calcification

Regional and whole-body lean mass will be assessed by DXA. In addition, lateral spine images will be collected for abdominal aortic calcification assessment as a surrogate of cardiovascular disease (30).

Anthropometric measures and blood pressure assessment

Central adiposity will be assessed by waist circumference (WC) and hip circumference (HC) (31). WC will be measured at the level of the narrowest point between the lower costal (rib) border and the iliac crest. HC will be measured at the level of the greatest posterior protuberance of the buttocks which usually corresponds anteriorly to the level of the symphysis pubis. Body mass index (kg/m^2) will also be used to assess weight (kg) relative to height (m) squared. A validated oscillometric device (HEM-705CP, Omron Corporation, Japan) will be used to record brachial systolic and diastolic blood pressure at the dominant arm in triplicate.

Objective measures of physical function and physical activity levels

A battery of standard tests will be used to assess physical function: 1) one-repetition maximum (1RM) test for chest press and leg press strength, 2) submaximal cycle ergometer test for estimation of maximal oxygen uptake (VO_2max), 3) 400-m walk test for aerobic capacity and walking endurance, 4) repeated chair rise for lower body function, 5) 6-m usual and fast walk for gait speed, and 6) 6-m backwards tandem walk for dynamic balance (11-15, 32). Self-reported physical activity will be assessed by the leisure score index from the Godin Leisure-Time Exercise Questionnaire modified to include a question on resistance training (33).

Intervention adherence and monitoring

Adherence to the direct supervised exercise component will be defined as the number of sessions attended divided by the total number of sessions scheduled in both TENUT (i.e., telehealth program) and CENUT (clinic-based program) groups. For the self-managed phase of the study, patients in the TENUT will continue with the digital platform for recording, while the CENUT group will receive a self-managed exercise log with instructions to be completed.

Adherence to dietary recommendations will be assessed using an adapted customised adherence questionnaire (24, 34, 35) designed to provide an estimated frequency of consumption and number of serves of food of interest based on the nutrition advice given. Food items of interest include fruit and vegetables, nuts, high protein foods, dairy, grains and cereals, beverages and alcoholic drinks, discretionary and take-away items. Patients will be asked 25 yes/no questions where a score of 1 is given if the patient met a predetermined desired outcome, or a 0 if they didn't. A higher total score indicates greater compliance with a maximum score of 25. For nutrition monitoring, patients will complete a 3-day weighed food record (3d-WR) over 3 consecutive days (1 weekend day and 2 weekdays) at baseline, 6 and 12 months. This will provide an estimate of total energy intake ($kJ.d^{-1}$) and macro- and micronutrients consumed. The 3d-WR data will be analysed using FoodWorks (FoodWorks 10 Professional, Xyris Software Pty Ltd, QLD, Australia).

Patient-reported outcomes

Health-related quality of life will be assessed using the Medical Outcomes Short Form 36 (SF-36v2) (36), while cancer-related quality of life will be measured using the EORTC QLQ-C30 (37) and the EORTC-PR25 for disease-specific health-related quality of life (38). Fatigue will be assessed using the Functional assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire. The Brief Symptom Inventory-18 (BSI-18) will be used to assess psychological distress across the domains of anxiety, depression and somatisation, and

global distress severity (39). These validated instruments are an integrated system to assess quality of life and psychological distress in cancer patients and has been extensively employed in clinical trials of exercise medicine (10-13, 40). In addition, the Masculinity in Chronic Disease Index will be used to assess the extent to which men identify with six masculine values: strength; sexual importance/priority; family responsibilities; emotional self-reliance; optimistic capacity and action approach (41, 42), while an adapted Working Alliance Inventory for General Practice tool will be used to identify and explain the mechanism or process that underlies the delivery of exercise and nutrition as well as benefits derived from these programs in men with prostate cancer (43, 44).

Blood markers

Testosterone, prostate specific antigen (PSA), lipid profile, insulin, glucose, glycated haemoglobin (HbA_{1c}), C-reactive protein, adiponectin, leptin, insulin-like-growth factor-1 (IGF1), IGF-binding protein-3 (IGFBP3), interleukin 6 (IL6) and tumour necrosis factor (TNF-α) will be measured commercially by an accredited Australian National Association of Testing Authorities (NATA) laboratory (Pathwest Diagnostics, Perth, Western Australia) (11, 13, 24).

Safety and monitoring

Patients will be monitored for any adverse events during training and testing by Accredited Exercise Physiologists (AEPs) with study clinicians overseeing aspects of patient management where required. During the self-management phase of the study, participants will record any adverse events which will be monitored by AEPs via monthly phone calls. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, V.5.0) will be used for grading the severity of adverse events during the study (45).

Exercise interventions

Telehealth and Face-To-Face delivered exercise and nutrition programs

The interventions will consist of 300 min per week of moderate to vigorous exercise per week for 6 months comprising a supervised resistance and aerobic exercise program performed three times per week for 60 min per session delivered face-to-face in an exercise clinic or via telehealth by AEP, plus 30 min of moderate/vigorous physical activity self-managed 4 days per week. For both TENUT and CENUT, resistance training will comprise 2-4 sets for 6-8 exercises targeting the major upper and lower body muscle groups performed using equipment such as exercise machines, dumbbells and elastic bands at an intensity of 6-12 repetition maximum (RM; i.e. the maximal weight that can be lifted 6 to 12 times which is equivalent to ~60-85% of 1RM). The supervised aerobic exercise component will involve 15 to 20 minutes of moderate to vigorous intensity cardiovascular exercise using a variety of modes such as walking, jogging or cycling. This approach has been extensively used by our team (11, 13, 14, 24), providing optimal stimulus while maximising safety, compliance and retention in clinic-based exercise programs. The self-directed aerobic component will comprise these modes for 30 minutes 4 days per week. For the telehealth intervention we will implement the latest digital platforms that we developed during COVID-19 restrictions in 2020 and related technological advancements in wearable sensors (Fitbit Charge 5 ®, Fitbit Inc, USA), online monitoring and video chat (Microsoft Teams, Microsoft, Redmond, WA, USA), cloud-based platforms (MyWellness TechnoGym Cloud platform, TechnoGym Australia Pty, Australia). Participants will receive their exercise program via their smart device or computer, communicate with the AEP and fellow participants by video chat, and be monitored in real-time through the internet.

For the nutrition intervention, all participants will receive a total of 5 face-to-face or online consultations over the first 6 months of intervention (baseline, 2, 12, 18, 24 weeks) with an Accredited Practising Dietitian (APD) aiming to: 1) achieve an energy deficit of 2100-4200 kJ/day (500-1000 kcal/day); 2) reducing discretionary items including alcoholic drinks and

foods containing refined sugars; and 3) maintain protein intake. In addition, participants will consume 40 g of a whey protein supplement 3 times per week immediately after the resistance exercise sessions.

At the end of the first 6-month period, participants from CENUT will receive a booklet with detailed information about a home exercise prescription, while the telehealth program will be maintained without supervision for participants from TENUT. Instructions on performing the home-based exercises and achieving dietary recommendations will be provided by the AEP and APD.

Calculation of sample size and statistical analysis

From our previous research in obese prostate cancer patients we reported that the standard deviation for change in fat mass equates to 2.6 kg (mean change of -2.8 kg) following 3 months of combined resistance and aerobic exercise with protein supplementation and caloric restriction (24). A priori, 43 patients per group will be required to achieve 80% power at an α level of .025 (one-tailed) and demonstrate a non-inferiority limit below 1.4 kg of fat mass between the TENUT and CENUT groups. Therefore, to adequately ensure that we have a sufficient number of participants at the end of the study (accounting for a drop-out rate of 20%), 52 participants will be randomised to each group.

Normality of the data will be assessed using the Kolmogorov-Smirnov test. Baseline characteristics will be analysed using Student's t tests or the Mann-Whitney U-test for continuous measures, as appropriate, and Chi-square for categorical variables. For the study outcomes, data will be analysed using intention-to-treat and per protocol approaches. Testing for longitudinal changes will be performed using linear mixed models (LMM). Non-inferiority of the intervention for the primary outcome will be implied if the lower limit of a 1-sided 95%

confidence interval of the difference between groups between baseline and 6 months is within the pre-stated limit of 1.4 kg for fat mass change.

Ethics and dissemination

Outcomes from the study will be published in peer-reviewed academic journals and presented in scientific, consumer and clinical meetings. The study investigators and trial coordinator will have access to the data.

DISCUSSION

Men with prostate cancer undergoing ADT experience increased fat and reduced muscle mass placing them at increased risk of morbidity and mortality from cardiovascular and metabolic diseases (3, 8, 46, 47). Targeted exercise medicine interventions for men with prostate cancer can improve quality of life, reduce treatment-related side-effects, and improve both physical and psychological health (10-17). More recently, we have shown that in obese men with prostate cancer, a targeted supervised clinic-based exercise and nutrition intervention resulted in a substantial reduction in fat mass (~3 kg) while muscle mass was preserved (24). This is a new finding, however, availability of these clinic-based services and patient support is limited and the vast majority of patients cannot access due to issues of distance, transport, inconvenience and financial capacity. The result is an unacceptable disparity between patients that have access to such supportive care and those that do not, resulting in suboptimal quality of life and ultimately survival for those men that cannot access current best practice care.

These issues are particularly pertinent to patients in Western Australia due to our geography (comprises about a third of the country with only one major metropolitan area) resulting in the majority of men with prostate cancer having limited or no capacity to access

exercise and nutrition programs face-to-face with health professionals. Access to the latest exercise medicine and nutrition services has been unfortunately further impacted by the COVID-19 pandemic due to personal isolation, physical distancing and changes to public transport and procedures within cancer care clinics (48). Moreover, changes in physical activity behaviour can be challenging in this group (49, 50), with common barriers being treatment-related symptoms and lack of time (51). Therefore, telehealth exercise and nutrition interventions have the potential to overcome a number of these issues providing high-quality, effective and safe supportive care at a time and in a place of the patient's choosing. Translation of the outcomes of this research can be immediate. The underlying knowledge required to take this program out into the community will be a result of the research project.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021.

2. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. Jama. 2008;299(3):289-95.

3. Galvao DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008;102(1):44-7.

4. Bhindi B, Locke J, Alibhai SMH, Kulkarni GS, Margel DS, Hamilton RJ, et al. Dissecting the association between metabolic syndrome and prostate cancer risk: analysis of a large clinical cohort. Eur Urol. 2015;67(1):64-70.

5. Di Bella CM, Howard LE, Oyekunle T, De Hoedt AM, Salama JK, Song H, et al. Abdominal and pelvic adipose tissue distribution and risk of prostate cancer recurrence after radiation therapy. Prostate. 2020;80(14):1244-52.

6. Uchida T, Higure T, Kawakami M, Nakano M, Nakajima N, Kim H, et al. What factors affect the operative time of robot-assisted laparoscopic radical prostatectomy? Surg Endosc. 2020; Online ahead of print.

7. Bonn SE, Wiklund F, Sjolander A, Szulkin R, Stattin P, Holmberg E, et al. Body mass index and weight change in men with prostate cancer: progression and mortality. Cancer Causes Control. 2014;25(8):933-43.

8. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2011;4(4):486-501.

9. Troeschel AN, Hartman TJ, Jacobs EJ, Stevens VL, Gansler T, Flanders WD, et al. Postdiagnosis body mass index, weight change, and mortality from prostate cancer, cardiovascular disease, and all causes among survivors of nonmetastatic prostate cancer. J Clin Oncol. 2020;38(18):2018-27.

10. Galvao DA, Newton RU, Chambers SK, Spry N, Joseph D, Gardiner RA, et al. Psychological distress in men with prostate cancer undertaking androgen deprivation therapy: modifying effects of exercise from a year-long randomized controlled trial. Prostate Cancer Prostatic Dis. 2021.

11. Galvao DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. Eur Urol. 2014;65(5):856-64.

12. Galvao DA, Taaffe DR, Spry N, Cormie P, Joseph D, Chambers SK, et al. Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases. Med Sci Sports Exerc. 2018;50(3):393-9.

13. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol. 2010;28(2):340-7.

14. Newton RU, Galvao DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Exercise Mode Specificity for Preserving Spine and Hip Bone Mineral Density in Prostate Cancer Patients. Med Sci Sports Exerc. 2019;51(4):607-14.

15. Taaffe DR, Galvao DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Immediate versus delayed exercise in men initiating androgen deprivation: effects on bone density and soft tissue composition. BJU Int. 2019;123(2):261-9.

16. Lopez P, Taaffe DR, Newton RU, Buffart LM, Galvao DA. What is the minimal dose for resistance exercise effectiveness in prostate cancer patients? Systematic review and meta-analysis on patient-reported outcomes. Prostate Cancer Prostatic Dis. 2020.

17. Lopez P, Taaffe DR, Newton RU, Galvao DA. Resistance exercise dosage in men with prostate cancer: Systematic review, meta-analysis, and meta-regression. Med Sci Sports Exerc. 2021;53(3):459-69.

18. Bourke L, Gilbert S, Hooper R, Steed LA, Joshi M, Catto JW, et al. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. Eur Urol. 2014;65(5):865-72.

19. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol. 2003;21(9):1653-9.

20. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol. 2009;27(3):344-51.

21. Ndjavera W, Orange ST, O'Doherty AF, Leicht AS, Rochester M, Mills R, et al. Exercise-induced attenuation of treatment side-effects in patients with newly diagnosed prostate cancer beginning androgen-deprivation therapy: a randomised controlled trial. BJU Int. 2020;125(1):28-37.

22. Winters-Stone KM, Dobek JC, Bennett JA, Maddalozzo GF, Ryan CW, Beer TM. Skeletal response to resistance and impact training in prostate cancer survivors. Med Sci Sports Exerc. 2014;46(8):1482-8.

23. Bressi B, Cagliari M, Contesini M, Mazzini E, Bergamaschi FAM, Moscato A, et al. Physical exercise for bone health in men with prostate cancer receiving androgen deprivation therapy: a systematic review. Support Care Cancer. 2021;29(4):1811-24.

24. Wilson RL, Newton RU, Taaffe DR, Hart NH, Lyons-Wall P, Galvao DA. Weight loss for obese prostate cancer patients on androgen deprivation therapy. Med Sci Sports Exerc. 2021;53(3):470-8.

25. Collins IM, Burbury K, Underhill CR. Teletrials: implementation of a new paradigm for clinical trials. Med J Aust. 2020;213(6):263-5.e1.

26. Kennedy AP, Shea JL, Sun G. Comparison of the classification of obesity by BMI vs. dual-energy X-ray absorptiometry in the Newfoundland population. Obesity (Silver Spring). 2009;17(11):2094-9.

27. Galvao DA, Taaffe DR, Spry N, Cormie P, Joseph D, Chambers SK, et al. Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases. Med Sci Sport Exer. 2018;50(3):393-9.

28. Hayes SC, Newton RU, Spence RR, Galvão DA. The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. J Sci Med Sport. 2019;22(11):1175-99.

29. Messina C, Albano D, Gitto S, Tofanelli L, Bazzocchi A, Ulivieri FM, et al. Body composition with dual energy X-ray absorptiometry: from basics to new tools. Quant Imaging Med Surg. 2020;10(8):1687-98.

30. Lewis JR, Schousboe JT, Lim WH, Wong G, Wilson KE, Zhu K, et al. Long-Term Atherosclerotic Vascular Disease Risk and Prognosis in Elderly Women With Abdominal Aortic Calcification on Lateral Spine Images Captured During Bone Density Testing: A Prospective Study. J Bone Miner Res. 2018;33(6):1001-10.

31. Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. J Clin Endocrinol Metab. 1983;57(2):304-10.

32. Mijwel S, Cardinale D, Ekblom-Bak E, Sundberg CJ, Wengström Y, Rundqvist H. Validation of 2 Submaximal Cardiorespiratory Fitness Tests in Patients With Breast Cancer Undergoing Chemotherapy. Rehabil Oncol. 2016;34(4):137-43.

33. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci. 1985;10(3):141-6.

34. Martínez-González MA, García-Arellano A, Toledo E, Salas-Salvadó J, Buil-Cosiales P, Corella D, et al. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. PLoS One. 2012;7(8):e43134.

35. Erdrich S, Bishop KS, Karunasinghe N, Han DY, Ferguson LR. A pilot study to investigate if New Zealand men with prostate cancer benefit from a Mediterranean-style diet. PeerJ. 2015;3:e1080.

36. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

37. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

38. Chu D, Popovic M, Chow E, Cella D, Beaumont JL, Lam H, et al. Development, characteristics and validity of the EORTC QLQ-PR25 and the FACT-P for assessment of quality of life in prostate cancer patients. J Comp Eff Res. 2014;3(5):523-31.

39. Derogatis LR. BSI 18, Brief Symptom Inventory 18: Administration, scoring and procedures manual: NCS Pearson, Incorporated; 2001.

40. Galvao DA, Taaffe DR, Chambers SK, Fairman CM, Spry N, Joseph D, et al. Exercise intervention and sexual function in advanced prostate cancer: a randomised controlled trial. BMJ Support Palliat Care. 2020.

41. Chambers SK, Hyde MK, Oliffe JL, Zajdlewicz L, Lowe A, Wootten AC, et al. Measuring masculinity in the context of chronic disease. Psychology of Men & Masculinity. 2016;17(3):228-42.

42. Hyde MK, Zajdlewicz L, Wootten AC, Nelson CJ, Lowe A, Dunn J, et al. Medical Help-Seeking for Sexual Concerns in Prostate Cancer Survivors. Sex Med. 2016;4(1):e7-e17.

43. Sturgiss EA, Rieger E, Haesler E, Ridd MJ, Douglas K, Galvin SL. Adaption and validation of the Working Alliance Inventory for General Practice: qualitative review and cross-sectional surveys. Fam Pract. 2019;36(4):516-22.

44. Tracey TJ, Kokotovic AM. Factor structure of the working alliance inventory. Psychological Assessment: A journal of consulting and clinical psychology. 1989;1(3):207.

45. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) 2017 https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

46. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24(27):4448-56.

47. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab. 2006;91(4):1305-8.

48. Lopez P, Taaffe DR, Newton RU, Spry N, Shannon T, Frydenberg M, et al. Can Exercise Adaptations Be Maintained in Men with Prostate Cancer Following Supervised Programmes? Implications to the COVID-19 Landscape of Urology and Clinical Exercise. Eur Urol Open Sci. 2020;21:47-50.

49. Bressi B, Iotti C, Cagliari M, Fugazzaro S, Cavuto S, Bergamaschi FAM, et al. Physical exercise habits, lifestyle behaviors, and motivation to change among men with prostate cancer: a cross-sectional study. Support Care Cancer. 2022.

50. Galvão DA, Newton RU, Gardiner RA, Girgis A, Lepore SJ, Stiller A, et al. Compliance to exercise-oncology guidelines in prostate cancer survivors and associations with psychological distress, unmet supportive care needs, and quality of life. Psychooncology. 2015;24(10):1241-9.

51. Galvão DA, Chambers SK. Exercise medicine in men with prostate cancer: breaking barriers to increase participation. Prostate Cancer Prostatic Dis. 2021;24(4):942-3.

AUTHORS' CONTRIBUTIONS: DAG, DRT, DH, PL, PLW, CT, SKC, NS, CK and RUN collaboratively developed the concept and protocol, including intervention, outcomes of interests, and planned data analysis procedures. AD, EJ, DJ further contributed to the study protocol. DAG, DRT, DH, PL, PLW, CT, SKC, NS, CK and RUN contributed to writing, reviewing, editing and final approval of the manuscript. AD, EJ, DJ further contributed to editing and final approval of the manuscript.

FUNDING STATEMENT: This work was supported by Cancer Council Western Australia Prostate Cancer Research Initiative grant (2021-2023 Prostate Cancer Research Initiative). DAG and RUN are funded by a NHMRC CRE in Prostate Cancer Survivorship. PL is supported by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence (CRE) in Prostate Cancer Survivorship Scholarship.

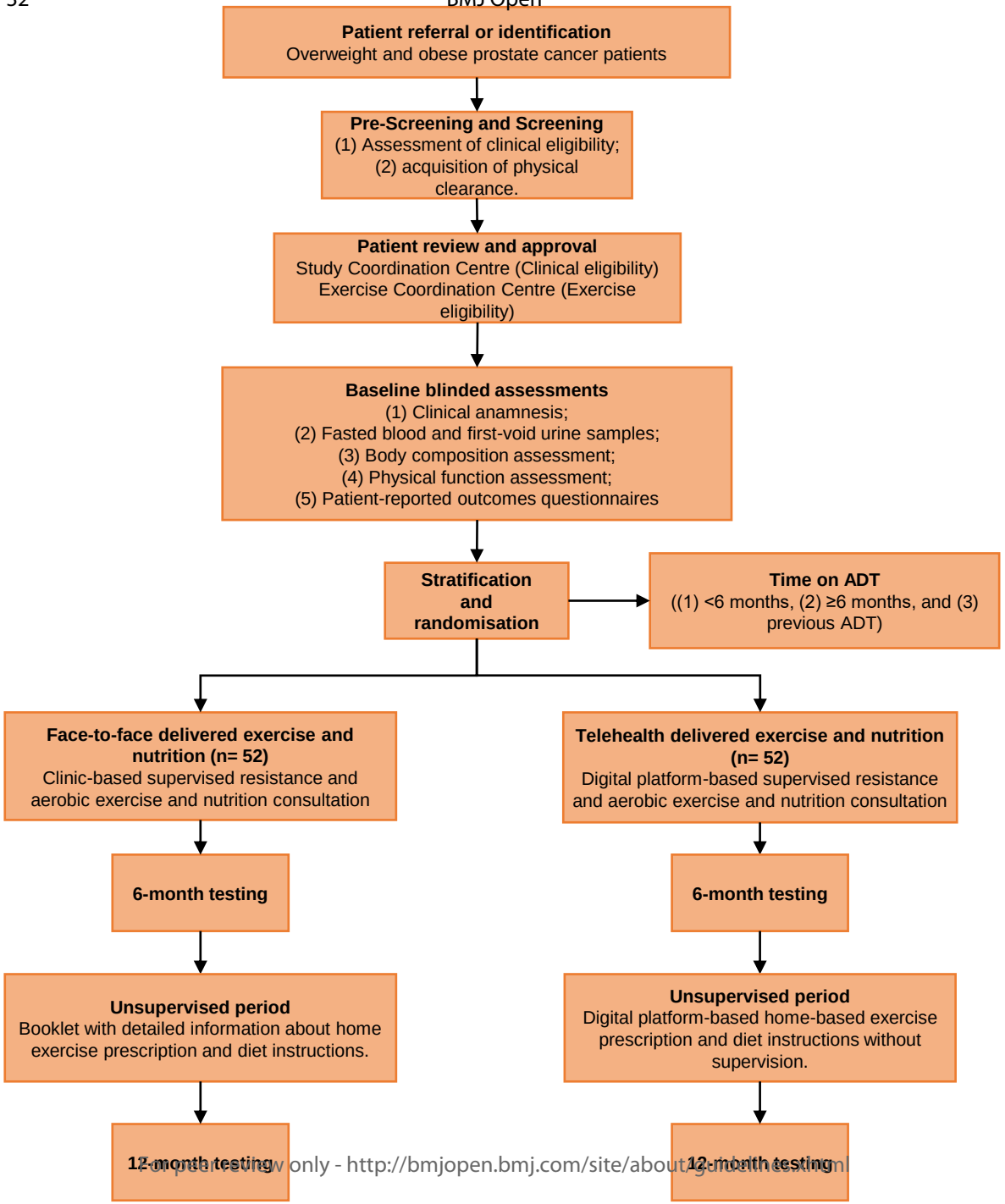
COMPETING INTERESTS STATEMENT: None declared.

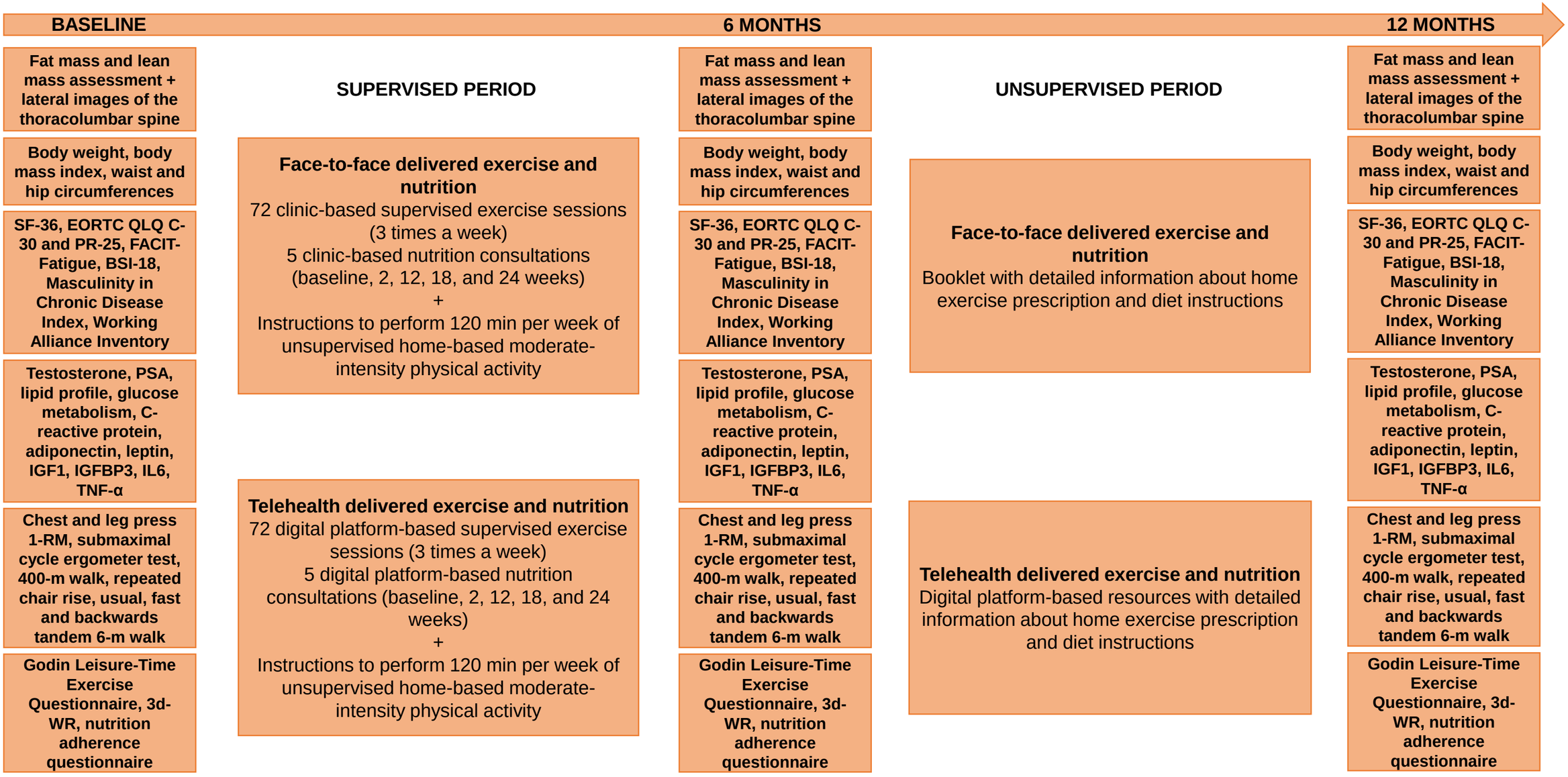
ETHICS APPROVAL: Edith Cowan University Human Ethics Committee (ID: 2021-02157-GALVAO)

FIGURE LEGENDS

Figure 1. CONSORT diagram depicting the of participants throughout the trial.

Figure 2. Study design, exercise and nutrition interventions and timeline assessments.




BASELINE
6 MONTHS
12 MONTHS
Fat mass and lean mass assessment + lateral images of the thoracolumbar spine
Body weight, body mass index, waist and hip circumferences
SF-36, EORTC QLQ C-30 and PR-25, FACIT-Fatigue, BSI-18, Masculinity in Chronic Disease Index, Working Alliance Inventory
Testosterone, PSA, lipid profile, glucose metabolism, C-reactive protein, adiponectin, leptin, IGF1, IGFBP3, IL6, TNF-α
Chest and leg press 1-RM, submaximal cycle ergometer test, 400-m walk, repeated chair rise, usual, fast and backwards tandem 6-m walk
Godin Leisure-Time Exercise Questionnaire, 3d-WR, nutrition adherence questionnaire
SUPERVISED PERIOD
Face-to-face delivered exercise and nutrition
72 clinic-based supervised exercise sessions (3 times a week)
5 clinic-based nutrition consultations (baseline, 2, 12, 18, and 24 weeks)
+
Instructions to perform 120 min per week of unsupervised home-based moderate-intensity physical activity
Telehealth delivered exercise and nutrition
72 digital platform-based supervised exercise sessions (3 times a week)
5 digital platform-based nutrition consultations (baseline, 2, 12, 18, and 24 weeks)
+
Instructions to perform 120 min per week of unsupervised home-based moderate-intensity physical activity
UNSUPERVISED PERIOD
Face-to-face delivered exercise and nutrition
Booklet with detailed information about home exercise prescription and diet instructions
Telehealth delivered exercise and nutrition
Digital platform-based resources with detailed information about home exercise prescription and diet instructions

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 and 3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 22
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	N/A

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	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
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)	9 and Figure 2

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	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7 and 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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 (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
	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	9-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
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	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14
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	N/A
	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	N/A
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	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	7-8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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	7-8
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	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4 and 14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
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	N/A

*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.