Study Proposal

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

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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 range of treatments, androgen deprivation therapy (ADT) has been extensively used in the management of localised and advanced disease aiming to delay cancer progression and improve survival (2), with patients achieving a 5-year survival rate approaching 100% when diagnosed at an early stage. However, several adverse effects including increases in fat mass and reductions in muscle mass are common during the first year of ADT (3), increasing or aggravating obesity and metabolic syndrome (4) and complications during radical prostatectomy or radiation therapy procedures in men with prostate cancer (5, 6), as well as the risk for biochemical recurrence, metastatic disease and mortality (7-9).

For more than a decade, exercise has been endorsed as a therapy by many professional organisations such as the *American College of Sports Medicine* (10, 11) and *Exercise and Sports Science Australia* (12, 13) given its significant benefits to prostate cancer patients. We (14-21) and others (22-26) have shown the benefits of exercise medicine as a countermeasure to 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 overweight men with prostate cancer (21) compared to the substantial gains of ~2.3 kg experienced during the first year of treatment (3). As a result, exercise undertaken in trials to date has been insufficient to counteract the treatment-related gains in fat mass, which may be especially problematic for men already overweight or obese.

Another important outcome for men with prostate cancer is preservation of muscle mass during or following ADT (27-30). Significant associations have been demonstrated between

sarcopenia and shorter survival, suggesting that muscle mass is an important prognostic factor in this group of patients (27-29). Nevertheless, studies to date have generally focused on aerobic exercise and/or energy restriction to effectively reduce body weight and fat mass, while not addressing the importance of muscle mass in men with prostate cancer (31-34). In a previous study from our team, one month of a very low-kilojoule diet combined with aerobic exercise resulted in a very impressive reduction in body weight and fat mass (~7 and ~5 kg, respectively) but unfortunately was accompanied by a significant reduction of -2.4 kg in muscle mass in overweight/obese men preparing for radical prostatectomy (34). This clearly indicates that although effective in reducing body weight and fat mass, a weight-loss strategy without anabolic stimulus such a resistance training may be putting patients at increased risk of mortality (27-29), infections and surgical complications due to the drastic reductions in muscle mass (35, 36).

Recently, we presented initial 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 (37). These are promising new findings (37); however, it is still necessary to expand such benefits to alternative exercise settings where overweight/obese patients living in under-served areas, or those without financial ability to pay may be able to receive the benefits derived from this program during or following treatment. Recently, telehealth has emerged as a viable method to deliver health-related services such as exercise and nutrition therapy (38), and if effective in this group of prostate cancer patients, can be available at a low cost to patients, regardless of their financial position or geographical location.

Therefore, the purpose of this study is to evaluate the efficacy of telehealth delivered to a supervised clinic-based delivered exercise and nutrition intervention in overweight and obese prostate cancer patients, we propose to undertake a 6-month non-inferiority randomised trial.

We will compare our successful supervised clinic-based exercise and nutrition weight loss program (27) to the program modified for delivery via telehealth in 104 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. Participants will be randomly assigned to TENUT or CENUT and will complete a 6-month supervised exercise and nutritional intervention either by telehealth or face-to-face, respectively, followed by 6 months self-managed maintenance (Figure 1). The protocol is being submitted to 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%, 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 consent form. The study coordinator will obtain the consent forms from patients and physicians. Patients with metastases will require additional clearance from their physician and bone imaging within the last 4 weeks to establish location and extent of bone lesions with the exercise prescription modified according to the Exercise and Sports Science Australia exercise and cancer position statement (12). 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 diet intervention study (37). The men were overweight or obese and completed the three-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 feedback 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 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). A research methods consultant with no patient contact will be responsible for randomisation. The study allocation will be concealed,

and exercise physiologists and other researchers conducting the study measures blinded to a given participant's group allocation. 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 (14-19).

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 (15-19).

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 (39). Abdominal aortic calcification scores range from 0 to 24 and will be derived from digitally enhanced lateral single-energy images of the thoracolumbar spine. A single experienced investigator will read all images using an established technique (40-42). Severity of abdominal aortic calcification

will be categorized as previously reported (40): low (score 0 or 1), moderate (score 2–5), and high (score ≥6).

Anthropometric measures and blood pressure assessment

Central adiposity will be assessed by waist circumference (WC) and hip circumference (HC) (43). 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). 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.

Patient-reported outcomes

Health-related quality of life will be assessed using the Medical Outcomes Short Form 36 (SF-36v2) (44), while cancer-related quality of life will be measured using the EORTC QLQ-C30 (45) and the EORTC-PR25 for disease-specific health-related quality of life (46). 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 (47). 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 (14-17, 48). In addition, The Masculinity in Chronic Disease Index will be used to assess will 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 (49, 50), while an adapted Working Alliance Inventory for General Practice tool will be used to assess the mediations between exercise and

nutrition delivery and benefits derived from these programs in men with prostate cancer (51, 52).

Blood markers

30 ml of blood samples – 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) (15, 17, 37). Additional blood markers (i.e. cytokines, myokines) may be required for future analysis to be performed at Edith Cowan University.

Other measurements: objective measure of physical function and physical activity levels, and nutritional intervention adherence and monitoring

A battery of standard tests will be used to assess physical function: 1) one-repetition maximum (1RM) test for chest press and leg press, 2) submaximal cycle ergometer test for maximal oxygen uptake (VO_{2max}) estimation, 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 (15-19, 53). 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 (54).

Nutritional adherence will be assessed using an adapted customised adherence questionnaire (37, 55, 56) 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 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) and macro- and micronutrients consumed. The 3d-WR data will be analysed using FoodWorks (FoodWorks 10 Professional, Xyris Software Pty Ltd, QLD, Australia).

Safety and monitoring

Patients will be monitored for any adverse events during training and testing by the exercise physiologists with study clinicians overseeing all aspects of patient management where required.

Exercise interventions

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

The interventions will consist of a similar resistance and aerobic exercise program performed over 3 sessions per week for 6 months delivered face-to-face in an exercise clinic or via telehealth by Accredited Exercise Physiologists (AEP). Both TENUT and CENUT groups will undertake resistance training comprising 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) using 1-4 sets per exercise for 6 exercises targeting the major upper and lower body muscle groups performed using different equipment such as exercise machines, dumbbells, Gymsticks™ and elastic bands. The 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 and will be self-directed and undertaken daily. This approach has been extensively used by our team (15, 17, 18, 37), providing optimal stimulus while maximising safety,

compliance and retention in clinic-based exercise programs. In addition, participants will also be instructed to perform the general recommendations of 30 min of moderate/vigorous physical activity in the remaining 4 days of the week (a total of 120 minutes per week of moderate physical activity) to achieve at least 300 min of moderate to vigorous physical activity per week. This volume of physical activity has been considered optimal to produce significant fat loss whether combined with caloric restriction or not (57). 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 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, as well as the consumption of a 40 g whey protein supplement 3 times per week immediately after the resistance exercise sessions. Safety and monitoring will be assessed by recording the incidence and severity of any adverse events.

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 diet 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 have 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 (37). 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 six 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 greatly increased risk of morbidity and mortality from cardiovascular and metabolic diseases (3, 8, 58, 59). Targeted exercise medicine interventions

are highly beneficial for men with prostate cancer improving quality of life, reducing treatment side-effects, improving both physical and psychological health (14-21). More recently, we have shown that in obese men with prostate cancer, a targeted supervised clinic-based exercise and nutrition intervention resulted in a large reduction in fat mass (~3 kg) with muscle mass preserved (37). This is a new finding, however, availability of these services and patient support is very 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 inherent demographics and geography resulting in most men with prostate cancer having little or no capacity to access exercise and nutrition programs face-to-face with health professionals. Even within metropolitan Perth there is a dearth of exercise clinics making it costly and inconvenient for men to attend face-to-face exercise sessions. 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 (60). 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 in the community will already be a result of the research project. Our team already has extensive experience in translating our exercise and nutrition programs as demonstrated by the LifeNow program we developed in collaboration with Cancer Council WA. Telehealth

implementation is the logical next step however this is palpably more urgent due to the immediate and long-term effects of the COVID-19 pandemic.

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Figure Legends

Figure 1: Study Design.

Figure 2: Time points for Study Assessments.

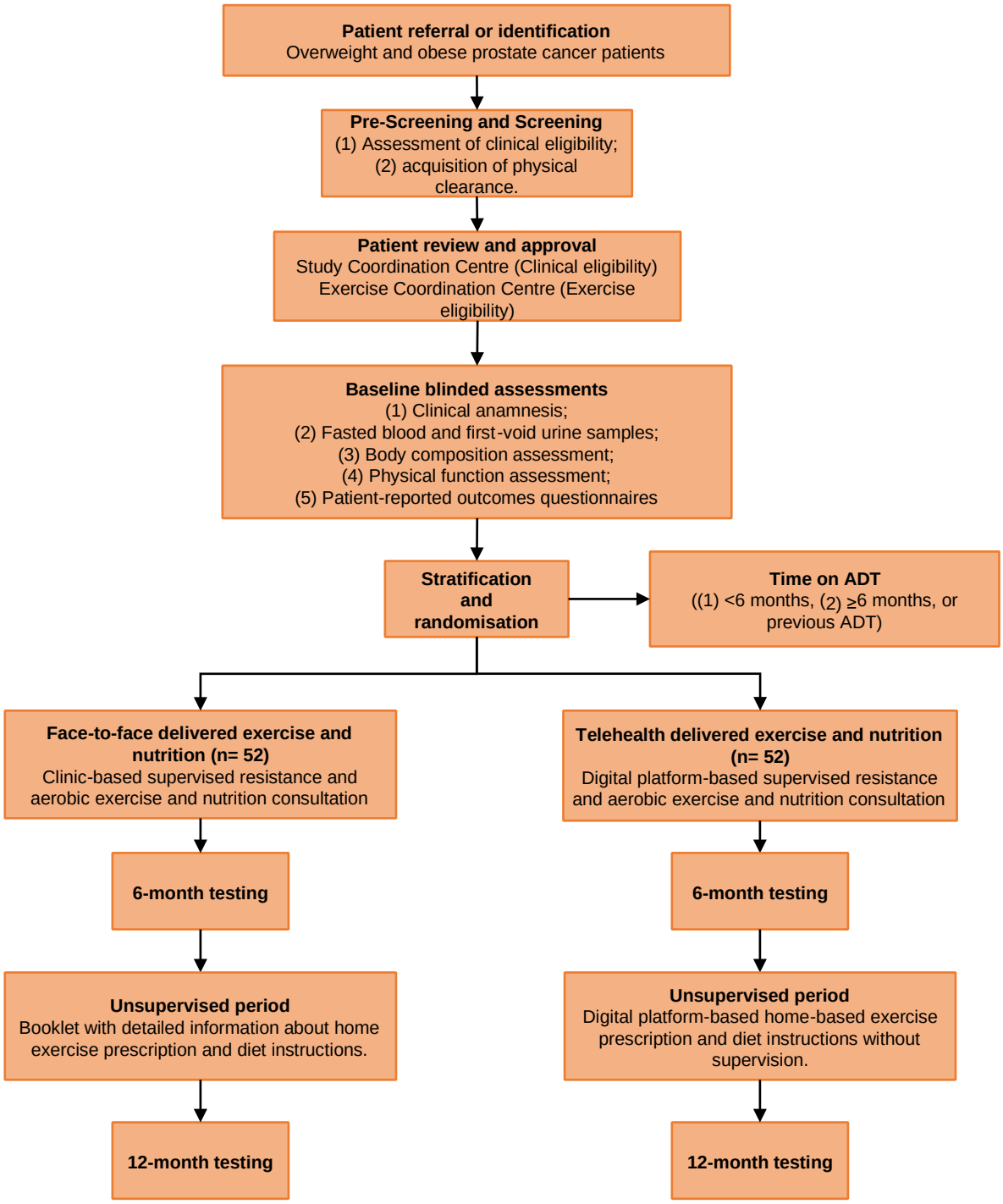
Patient referral or identification
Overweight and obese prostate cancer patients
Pre-Screening and Screening
(1) Assessment of clinical eligibility;
(2) acquisition of physical clearance.
Patient review and approval
Study Coordination Centre (Clinical eligibility)
Exercise Coordination Centre (Exercise eligibility)
Baseline blinded assessments
(1) Clinical anamnesis;
(2) Fasted blood and first-void urine samples;
(3) Body composition assessment;
(4) Physical function assessment;
(5) Patient-reported outcomes questionnaires
Stratification and randomisation
Time on ADT
((1) <6 months, (2) ≥6 months, or previous ADT)
Face-to-face delivered exercise and nutrition (n= 52)
Clinic-based supervised resistance and aerobic exercise and nutrition consultation
Telehealth delivered exercise and nutrition (n= 52)
Digital platform-based supervised resistance and aerobic exercise and nutrition consultation
6-month testing
6-month testing
Unsupervised period
Booklet with detailed information about home exercise prescription and diet instructions.
Unsupervised period
Digital platform-based home-based exercise prescription and diet instructions without supervision.
12-month testing
12-month testing

Figure 1

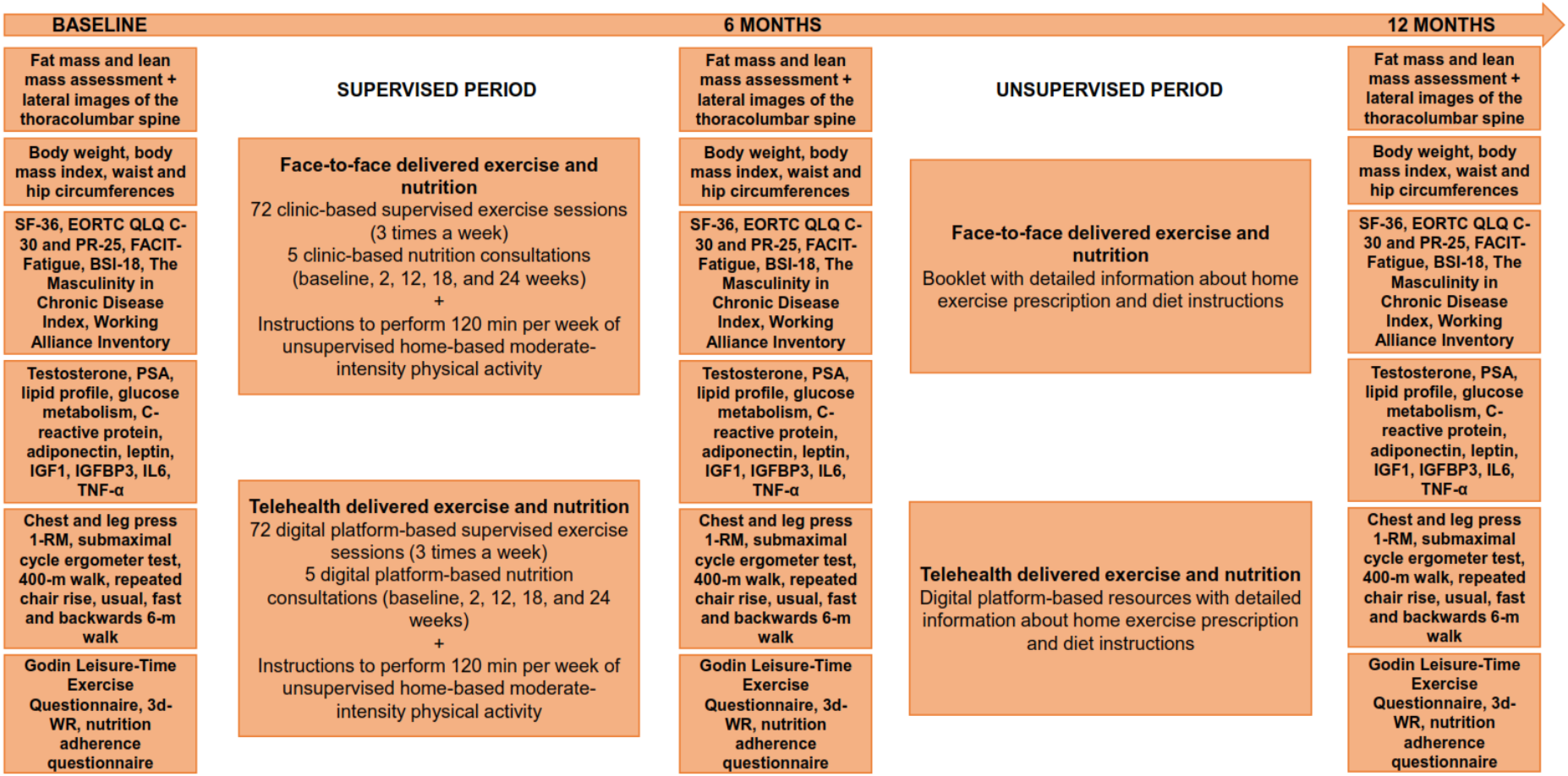
BASELINE
6 MONTHS
12 MONTHS
Fat mass and lean mass assessment + lateral images of the thoracolumbar spine
Body weight, body mass index, waist and hip circumferences
SF-36, EORTC QLQ C-30 and PR-25, FACIT-Fatigue, BSI-18, The Masculinity in Chronic Disease Index, Working Alliance Inventory
Testosterone, 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 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
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, The 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 6-m walk
Godin Leisure-Time Exercise Questionnaire, 3d-WR, nutrition adherence questionnaire
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
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, The 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 6-m walk
Godin Leisure-Time Exercise Questionnaire, 3d-WR, nutrition adherence questionnaire

Figure 2