PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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)
AUTHORS	Galvão, Daniel; Taaffe, Dennis; Hayne, Dickon; Lopez, Pedro; Lyons-Wall, P; Tang, Colin; Chambers, Suzanne; Devine, Amanda; Spry, Nigel; Jeffery, Emily; Kudiarasu, Christine; Joseph, David; Newton, Robert

VERSION 1 – REVIEW

REVIEWER	Yahia, Najat Central Michigan University College of Education and Human Services, Human Environmental Studies
REVIEW RETURNED	03-Jan-2022

GENERAL COMMENTS	Thank you for this interesting study. Well presented.

REVIEWER	Modgil, Vaibhav Manchester University NHS Foundation Trust, Manchester Andrology Centre
REVIEW RETURNED	16-Mar-2022

GENERAL COMMENTS	An important area, particularly in places like Western Australia where access to healthcare interventions isn't always equitable. If this can work there it may set an important precedence in other parts of the world.

REVIEWER	Costi, Stefania University of Modena and Reggio Emilia
REVIEW RETURNED	16-Mar-2022

GENERAL COMMENTS	I have read your work with great interest and I believe that the publication of this protocol is useful for readers. The study aims to verify the non-inferiority of a telemonitored exercise modality, which could help more individuals to follow the recommendations of exercise and nutrition useful for their health. I am attaching the manuscript pdf with some requests for minor revision. They are requests for greater clarification of few points and for consideration of recent research in this field. - The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Thank you for this interesting study. Well presented.

Response: Thank you for your positive comments.

Reviewer #2

An important area, particularly in places like Western Australia where access to healthcare interventions isn't always equitable. If this can work there it may set an important precedence in other parts of the world.

Response: Thank you for your positive comments.

Reviewer #3

Page 6, lines 26-27: You may consider adding this recent systematic review PMID: 33119791

Response: Thank you for the suggestion. The reference was added to the sentence in question and reads as:

"*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*."

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.

Page 7, lines 49-50: What does "previously treated" mean? could they have already finished the treatment? how long? How long ago could ADT treatment have been started?

Response: Thank you for the comment. We considered previously treated patients those who had completed androgen deprivation therapy (ADT) and are no longer on ADT for an unspecified period of time. Regarding the time between ADT start and enrolment in the study, there is no specified time limit. For example, patients could be at the onset of ADT or have been on ADT for the past two years. Increases in fat mass are a consequence of prior and current ADT and, as a result, patients with varying durations of ADT have been included in the trial. In addition, to account for variations in ADT duration, we have specified that randomisation will be balanced regarding stratification for time on ADT (< 6 months, ≥ 6 months, and previous ADT). As a result, we have amended the sentence in question to read as:

"*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.*"

Page 9, lines 26-28: Where will they be held? in presence? at a distance? how?

Response: All measurements will be undertaken in person at the Exercise Medicine Research Institute at Edith Cowan University in Perth, Australia. The sentence in question was amended and reads as:

"***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)."

Page 11, lines 42-50: I'm not sure this tool is validated to measure treatment adherence, if so please add a reference, otherwise explain better what you mean by adherence in this sentence, and also explain how you will measure treatment adherence in this trial, particularly for the self-managed component

Response: Thank you for the comment. The adapted Working Alliance Inventory for General Practice tool is not validated to measure treatment adherence. This tool will be used to identify and explain the mechanism or process that underlies the delivery of exercise and nutrition programs in this group of patients. To clarify this, we have amended the sentence in question to read as:

"*[…] 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).*"

Adherence to the exercise component will be defined as the number of sessions attended divided by the total number of sessions scheduled in both study groups (i.e., TENUT – Telehealth program; CENUT – Clinic-based program). 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. As a result, we have provided such information in the revised manuscript to reads as:

"***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."

Page 12, lines 10-11: how will AEs be monitored and categorized?

Response: The adverse events will be monitored as presented in the Safety and monitoring subheading. In addition, 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. We have revised the section to read as follows:

"***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)."

Page 12, lines 51-60: It would be helpful (for generalizability) to know what is requested by the participant? what type of device? technology? skills?

Response: Thank you for the comment. We have provided specific details to the section below.

"*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).*"

Regarding the skills set required, we undertook a focus group in participants from a previous study in a similar group of potential participants (Wilson et al. Med Sci Sports Exerc 2021, PMID: 33009195) and the skills required were generally equivalent to using a smartphone and related apps.

Page 15, lines 17-18: This is true. However, if I understand correctly, your trial will select a sample of individuals who will spontaneously accept to participate in this intervention and, consequently, can be considered individuals who are already contemplating the opportunity to change their lifestyle. But we recently showed that men with prostate cancer are insufficiently active and, even when exposed to behavioral risk factors, they are not willing to change their lifestyle. 35194723 So, perhaps you could discuss a little about how, if your hypothesis is verified, clinicians can use the results of this study to propose alternative pathways and lead overweight individuals with PCa to exercise and follow a healthy diet.

Response: Thank you for the suggestion. Yes, this is in agreement with a previous study of our team (Galvao et al. Psychooncology 2015, PMID: 26087455) measuring physical activity levels in a population-based cohort of 463 prostate cancer survivors, where only 57 men (12.3%) reported sufficient exercise levels (150 min of moderate intensity or 75 min of strenuous exercise per week and twice weekly resistance exercise). Additionally, we have also addressed this issue in a recent editorial in Prostate Cancer Prostatic Dis (Galvao & Chambers, Prostate Cancer Prostatic Dis 2021, PMID: 34145428), where we comment about the study of Sattar et al. (Prostate Cancer Prostatic Dis 2021, PMID: 34108646). In this study (Sattar et al. Prostate Cancer Prostatic Dis 2021, PMID: 34108646), treatment-related side-effects such as fatigue, and lack of time were the most common barriers for men with prostate cancer to participate in exercise programs. As a result, the utilisation of a telehealth exercise and nutrition program, if proved as effective as clinic-based programs, could overcome common barriers to supervised exercise. We have provided such details in the revised manuscript which reads as:

"*Moreover, changes in physical activity behaviour can be challenging in this group (48, 49), with common barriers being treatment-related symptoms and lack of time (50). 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.*"