PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Group-based exercise in daily clinical practice to improve the physical fitness in men with prostate cancer undergoing androgen deprivation therapy: study protocol
AUTHORS	Østergren, Peter; Ragle, Anne-Mette; Jakobsen, Henrik; Klausen, Tobias; Vinther, Anders; Sønksen, Jens

VERSION 1 - REVIEW

REVIEWER	Liam Bourke Sheffield Hallam University UK I receive funding from CRUK and the NIHR to conduct exercise and cancer research
REVIEW RETURNED	03-Mar-2016

GENERAL COMMENTS	Interesting study. Efficacy trial findings certainly do need to be explored in clinical delivery. ABSTRACT • 'Effect' cannot be ascertained with an observational study (certainly not one of this size without appropriate matching to the Bradford Hill criteria). Cause and effect can only be evaluated in RCTs. Please amend. INTRODUCTION • The phrase physical exercise is odd. The terms physical activity or exercise are more frequently used. You can pick either; they are the same from a physiology point of view. • Same issue with use of the word 'effect'. METHODS • As this is an observational study, can you not involve more than one site? Would help with generalization of results. • Are men on 2nd line ADT (Enzalutamide / Abiraterone) eligible? What about me on Docetaxal? • To facilitate reproducibility, I would suggest just to be clear, the authors quantify frequency, intensity, and duration for any aerobic exercise and reps, sets, load/intensity and total volume of resistance training to be performed. Makes things easier for the reader. Possibly the best way to do this would be to put it all in Table 1. • What behaviour change techniques will be used in this study? Refer the authors to Bourke et al 2013 Cochrane review for a full itemisation of the Michie et al taxonomy. • Aim number 1 is stated as " Examine the effect of exercise implemented in daily clinical practice on functional capacity, QoL and body composition in men with prostate cancer…" yet the primary endpoint is change in cycle test performance? These don't

	quite match up.

REVIEWER	Univ. Prof. Dr. Richard Crevenna, MBA, MSc Medical University of Vienna, Austria Department of PM&R
REVIEW RETURNED	07-Mar-2016

GENERAL COMMENTS	This study protocol of an ongoing study describes a group-based exercise-intervention in daily clinical practice to improve the functional capacity in men with prostate cancer on androgen deprivation therapy.

REVIEWER	Laurien Buffart VU University Medical Center
REVIEW RETURNED	23-Mar-2016

GENERAL COMMENTS	This is a clearly written paper describing the monitoring of an exercise program that is implemented in health care. Although I'm in favour of publishing protocols of clinical trials to inform other researchers, this paper does not present a clinical trial, it presents the systematic monitoring of health care. The inclusion is already over halfway (started in August 2014, and the inclusion is expected to be completed in October of this year). Therefore, to me, it seems more logical to wait until the results are available. The study that is presented and currently being conducted is a very interesting study, and worth reporting on the (un)successes of implementation. However several clarifications would be helpful. • Reporting (un)successes of implementation of programs in clinical practice is important. However, it is unclear whether the specific program that was implemented has been tested for its efficacy in a randomised controlled trial. This first step is essential to ensure evidence-based medicine. • Intervention program: Some relevant details regarding the exercise program are missing. It is important that all relevant exercise components, including frequency, intensity, type and time, are described in detail. It seems that the intensity of the resistance exercises are missing, was it based on a specific proportion of the 1 RM? And the intensity of the aerobic exercises are unclear, and how was the intensity monitored? In addition to the supervised exercise, also home based sessions are encouraged according to a given program. It would be helpful to further specify the program. • Endpoints: What is known about the sensitivity to detect changes of the GCT-TT? Also the 30s chair stand test that was chosen as primary outcome to assess lower body function, may have limited ability to detect the exercise-induced changes over time. It is therefore unclear why these outcomes were chosen, instead of gold standard outcomes for aerobic capacity and muscle strength. Body composition is assessed using BMI, WC and HC. However, because of the ADT, the men are at increased risk of losing muscle mass, and BMI may remain stable in muscle mass in decreased and fat mass is increased. How will they capture this loss due to ADT or maintenance of muscle mass as a result of resistance exercises? • Adherence was assessed according to session attendance. But it is also important to examine whether patients are able to comply to the prescribed exercises, for example the adequate intensity or whether changes were necessary.

	• Statistical analyses: it is mentioned that clinically relevant covariates will be included. Please specify which covariates are considered. It is mentioned that subgroup analysis are presented, but please provide the rationale for these subgroup analysis and in general, stratified analyses are only performed in case effect modification is present, and it should therefore be preceded by testing interactions.

REVIEWER	Jacob Uth The University Hospitals Centre for Health Research (UCSF), Rigshospitalet, University of Copenhagen, Denmark.
REVIEW RETURNED	29-Mar-2016

GENERAL COMMENTS	Abstract: P.2, L. 14: 'Undergoing' or 'receiving' ADT would be preferable to 'on ADT'. This is also the case later in the manuscript. Generally, I would recommend the authors to have the manuscript checked by an English language native speaker or other language expert. P.2, L.18: The abbreviation ECOG is not used subsequently in the abstract and should therefore be omitted. This is also the case for GCT-TT and 30s-CST. P2., L. 24: Usually only one primary outcome is reported. Consider whether the primary endpoint is chair stand- or cycling performance and correct accordingly in both the abstract and the main text (p. 7, L. 26.) Introduction: P. 4, L. 15-20: Consider to revise or omit the questions raised as they are different from the aims of the study and this may confuse the reader. P.4, L. 55: 'using machines' instead of 'on machines'. Methods: P.6, L.26: 'leg extension' or 'knee extension' instead of 'quadriceps curls'. P.9, L. 34: Please specify the covariates you intend to include in the analysis. Discussion: P10, L. 19-22: consider rephrasing.

VERSION 1 – AUTHOR RESPONSE

Answer to Peer-Reviewer #1:

We appreciate that the Reviewer finds this to be an “interesting study” and that “efficacy trial findings certainly do need to be explored in clinical delivery”.

ABSTRACT

• 'Effect' cannot be ascertained with an observational study (certainly not one of this size without appropriate matching to the Bradford Hill criteria). Cause and effect can only be evaluated in RCTs. Please amend.

We agree with the Peer-Reviewer that “cause and effect” cannot in general be evaluated in observational studies. “Effect” has been changed to “potential benefits” in the abstract; this also applies in the ‘introduction’ section.

INTRODUCTION

• The phrase physical exercise is odd. The terms physical activity or exercise are more frequently used. You can pick either; they are the same from a physiology point of view.

The term ‘exercise’ has been chosen.

• Same issue with use of the word 'effect'.

The wording has been changed (see previous answer).

METHODS
• As this is an observational study, can you not involve more than one site? Would help with generalization of results.

We agree with the Peer-Reviewer that having multiple centres involved would help with generalization of results. However, the exercise programme is completely funded by our institution (a public hospital) and has therefore not been implemented at other urological centres so far. For this reason we cannot report data from other sites.

• Are men on 2nd line ADT (Enzalutamide / Abiraterone) eligible? What about me on Docetaxal?

We appreciate the reviewer’s question. Mainly patients commencing or already undergoing androgen deprivation (ADT) therapy are referred to the programme by the treating physicians. However, patients undergoing treatment for castration resistant prostate cancer with Enzalutamide, Abiraterone or Docetaxel meeting inclusion criteria are also eligible. Patients starting early docetaxel in combination with ADT are likewise eligible for the program. This has been clarified in the method section. Data on treatment and cancer stage is available to the authors and will be presented as baseline data in a future publication.

• To facilitate reproducibility, I would suggest just to be clear, the authors quantify frequency, intensity, and duration for any aerobic exercise and reps, sets, load/intensity and total volume of resistance training to be performed. Makes things easier for the reader. Possibly the best way to do this would be to put it all in Table 1.

Table 1 has been revised to also include a description of the aerobic exercise and the intensity of the resistance training. The total resistance training volume – i.e. total weight lifted in each session is, however, not included. We feel this addition is less meaningful as the individualized approach results in very large variation in total training volume. The intensity described as repetition maximum (RM) as suggested by reviewer 3 was chosen to enable generalization to other patients.

• What behaviour change techniques will be used in this study? Refer the authors to Bourke et al 2013 Cochrane review for a full itemisation of the Michie et al taxonomy.

We thank the Peer-Reviewer for addressing this issue. Behaviour change techniques used in this programme have been specified in the ‘intervention’ section last paragraph.

• Aim number 1 is stated as "Examine the effect of exercise implemented in daily clinical practice on functional capacity, QoL and body composition in men with prostate cancer…" yet the primary endpoint is change in cycle test performance? These don’t quite match up.

We agree with the Peer-Reviewer that “functional capacity” is not covered by the cycle test. The term “physical fitness” is more appropriate as it incorporates both primary outcomes (cycle test and chair stand test). Wording has been changed throughout the manuscript including the title. We have also

clarified that the primary aim is investigating the benefits of exercise on “physical fitness” under the aims of the study.

Answer to Peer-Reviewer #2:
No questions asked.

Answer to Peer-Reviewer #3:

• This is a clearly written paper describing the monitoring of an exercise program that is implemented in health care. Although I’m in favour of publishing protocols of clinical trials to inform other researchers, this paper does not present a clinical trial, it presents the systematic monitoring of health care. The inclusion is already over halfway (started in August 2014, and the inclusion is expected to be completed in October of this year). Therefore, to me, it seems more logical to wait until the results are available. The study that is presented and currently being conducted is a very interesting study, and worth reporting on the (un)successes of implementation. However several clarifications would be helpful.

We are pleased that the reviewer finds the study “very interesting and worth reporting on”. The reviewer questions the need for publishing the protocol prior to having the results. We believe that in doing so we can heighten the quality of this observational study by reducing potential publication bias and by documentation of intended analyses. Even though recruitment started in August 2014 data collection will go on until April 2017. At time of submission less than half of the data was collected. For this reason it is our opinion, that publication of the protocol is still important and in line with the trend of publication transparency.

• Reporting (un)successes of implementation of programs in clinical practice is important. However, it is unclear whether the specific program that was implemented has been tested for its efficacy in a randomised controlled trial. This first step is essential to ensure evidence-based medicine.

We agree with the Peer-Reviewer that implementation of new treatments, i.e. exercise programmes should be evidence-based. The implemented programme has been designed based on the evidence from currently available randomized trials. We have clarified this in the ‘method’ section under ‘intervention’ 3rd paragraph with adding appropriate citations REF# 15-17, 19 and 21. In addition, implementation of exercise as a mitigating treatment for the adverse effects of ADT is currently recommended in the National Institute of Health and Care Excellence (NICE) guidelines of the United Kingdom as well as the guidelines of the European Association of Urology (EAU). We therefor believe, that implementation of this specific programme is evidence-based.

• Intervention program: Some relevant details regarding the exercise program are missing. It is important that all relevant exercise components, including frequency, intensity, type and time, are described in detail. It seems that the intensity of the resistance exercises are missing, was it based on a specific proportion of the 1 RM? And the intensity of the aerobic exercises are unclear, and how was the intensity monitored? In addition to the supervised exercise, also home based sessions are encouraged according to a given program. It would be helpful to further specify the program.

Table 1 has been revised to also include a description of the aerobic exercise and the intensity of the resistance training. Due to the pragmatic and low-tech approach of the study and the emphasis on the resistance training aerobic exercise intensity has not been monitored (i.e. heart rate) rather estimated based on the patient’s ability to talk during exercise. During stairclimbing, cycling intervals and treadmill training the patients are encouraged to aim for an intensity where speaking is not possible corresponding to 16-17 on the Borg RPE scale and approximately 80 % VO2-max.

• Endpoints: What is known about the sensitivity to detect changes of the GCT-TT? Also the 30s chair stand test that was chosen as primary outcome to assess lower body function, may have limited ability to detect the exercise-induced changes over time. It is therefore unclear why these outcomes were chosen, instead of gold standard outcomes for aerobic capacity and muscle strength.

Gold standard outcomes of aerobic capacity and muscle strength such as direct measurement of VO2-max and measurement of maximal isometric or isokinetic muscle strength in isokinetic dynamometers (Biodex, Cybex or similar) were not chosen as the present study is a pragmatic study of an intervention implemented in daily clinical practice. Consequently, the outcome measures chosen represent tests and measurements that could easily be used in daily clinical practice without access to expensive equipment and experts. Thus, both the exercise intervention and the test procedures can be implemented at other facilities at relatively low cost.

The responsiveness of the GCT-TT has very recently been investigated in patients undergoing 8 weeks of cardiac rehabilitation. The test was responsive to changes as patients reporting a substantial increase in self perceived physical fitness exhibited a bigger increase in power output compared to patients reporting moderate and low increases in physical fitness. Furthermore, the average improvement in the patients who did improve was above 25 W indicating that the test was sensitive to change. The manuscript has recently been accepted for publication (in press) and is now referenced in the section ‘Primary study endpoints’ as Ref#26.

The 30s-CST was chosen to assess lower body function/strength. It is our opinion, that a functional outcome measure can be considered to be more meaningful to patients than a measurement of knee extension strength in a laboratory setting. Previous exercise trials including other cancer patient cohorts showed improved 30s-CST test results to the same extend as muscle strength measured on an isokinetic dynamometer (already stated under ‘primary endpoints’ third paragraph). Further, the study by Wright et al. (Ref# 35) found that the 30s-CST was the most consistently responsive functional outcome measure in patients with osteoarthritis undergoing rehabilitation.

• Body composition is assessed using BMI, WC and HC. However, because of the ADT, the men are at increased risk of losing muscle mass, and BMI may remain stable in muscle mass in decreased and fat mass is increased. How will they capture this loss due to ADT or maintenance of muscle mass as a result of resistance exercises?

Changes in body composition (BMI, waist and hip circumference) are a secondary endpoint of this study. We agree with the Peer-Reviewer that changes in BMI do not reflect loss of muscle mass/ maintenance of muscle mass as a result of resistance exercise in men undergoing ADT. This has been clarified under the ‘Secondary endpoints’ section, 2nd paragraph. As this is a pragmatic study we chose BMI, waist and hip circumference over image modalities such as dual energy X-ray absorptiometry as they represent cheap and easily implemented measurements in daily clinical practice. One of the major concerns in men undergoing ADT is an increased risk of the metabolic syndrome, diabetes mellitus and cardiovascular disease. WC and waist-hip ratio are correlated to the volume of abdominal adipose tissue and with an increased risk of all three diseases. Further, increased waist circumference is one of the five key criteria of the metabolic syndrome. It is therefore our opinion that these endpoints are clinically relevant.

• Adherence was assessed according to session attendance. But it is also important to examine whether patients are able to comply to the prescribed exercises, for example the adequate intensity or whether changes were necessary.

The ability of participants to perform the exercises as prescribed, that is correct intensity and number of repetitions, will be reported as percentage of exercises during attended sessions completed as

prescribed. Data relies on self-reports filled out by each patient during each session. We have specified this in the manuscript under ‘secondary endpoints’ paragraph 4. The exercises of the programme are supervised so any technical difficulties in performing the exercises are resolved continuously.

• Statistical analyses: it is mentioned that clinically relevant covariates will be included. Please specify which covariates are considered. It is mentioned that subgroup analysis are presented, but please provide the rationale for these subgroup analysis and in general, stratified analyses are only performed in case effect modification is present, and it should therefore be preceded by testing interactions.

Clinically relevant covariates have been specified in the ‘Sample size and statistical analysis’ section 2nd paragraph. Subgroup analyses will only be performed in case of effect modification of the covariate in accordance with the Peer-Reviewer’s suggestion. This has been clarified in the manuscript (same paragraph).

Answer to Peer-Reviewer #4:

Abstract:
• P.2, L. 14: 'Undergoing' or 'receiving' ADT would be preferable to 'on ADT'. This is also the case later in the manuscript. Generally, I would recommend the authors to have the manuscript checked by an English language native speaker or other language expert.

Wording has been changed to comply with the Peer-Reviewer’s suggestion. The manuscript has prior to first submission undergone editing for English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at American Journal Experts (AJE).

• P.2, L.18: The abbreviation ECOG is not used subsequently in the abstract and should therefore be omitted. This is also the case for GCT-TT and 30s-CST.

The abbreviations GCT-TT and 30s-CST have been omitted. The abbreviation ECOG is in many circumstances more recognized by clinicians than “Eastern Cooperative Oncology Group”. It is therefore our opinion, that stating this abbreviation is helpful to the reader.

P2., L. 24: Usually only one primary outcome is reported. Consider whether the primary endpoint is chair stand- or cycling performance and correct accordingly in both the abstract and the main text (p. 7, L. 26.)

We agree with the Peer-Reviewer that it is a recommendation in randomized clinical trials only to include one primary endpoint. However, this is not a randomized clinical trial and the primary aim of this study is to investigate the benefits of this programme on physical fitness. It is therefore our opinion that both endpoints should be included as primary endpoints, as the chair-stand test (30s-CST) and the graded cycling test (GCT-TT) both measure physical fitness. Sample size calculations have been carried out for both endpoints and are depicted in the ‘Sample size and statistical analysis’ section.

Introduction:
• P. 4, L. 15-20: Consider to revise or omit the questions raised as they are different from the aims of the study and this may confuse the reader.

We have changed the wording and deleted question 2: “Can sufficient compliance rates above 80% be obtained?” according to the Peer-Reviewer’s suggestion so the aims and questions match.

• P.4, L. 55: 'using machines' instead of 'on machines'.

Wording has been changed according to the Peer-Reviewer’s suggestion.

Methods:
• P.6, L.26: 'leg extension' or 'knee extension' instead of 'quadriceps curls'.

Wording has been changed to ‘knee extension’ according to the Peer-Reviewer’s suggestion.

• P.9, L. 34: Please specify the covariates you intend to include in the analysis.

Please see the answer to the last question of Peer-Reviewer #3. Covariates have been specified.

Discussion:
• P10, L. 19-22: consider rephrasing.

Wording (P10, L.19-22) has been changed to: “Thus, time-related worsening can in itself hide a positive effect of the exercise intervention. However, this will only strengthen a potential significant positive result. Successful outcomes of this study will support the implementation of exercise programmes for men with prostate cancer receiving ADT in clinical practice.”

VERSION 2 – REVIEW

REVIEWER	Liam Bourke Sheffield Hallam University, UK Research funding through CRUK and the NIHR. Received honorarium from Sanofi for lecturing.
REVIEW RETURNED	16-May-2016

GENERAL COMMENTS	All amendments made are satisfactory.

REVIEWER	Laurien Buffart VU University Medical Center, the Netherlands
REVIEW RETURNED	25-May-2016

GENERAL COMMENTS	Authors have addressed all issues raised. Looking forward to reading the results from the study.