Author’s response to reviews

Title: Exercise for advanced prostate cancer: A multicomponent, feasibility trial protocol for men with metastatic castrate-resistant prostate cancer (EXACT)

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Author’s response to reviews:

Please find the response to specific reviewer and editor comments attached. Additionally, we have provide the material below, to satisfy the requirements of re-submission.

RE: PAFS-D-19-00028

Exercise for advanced prostate cancer: A multicomponent, feasibility, trial protocol for men with metastatic castrate-resistant prostate cancer (EXACT).

Dear Dr Husband,

Thank you for considering our manuscript, "Exercise for advanced prostate cancer: A multicomponent, feasibility, trial protocol for men with metastatic castrate-resistant prostate cancer (EXACT)", for publication in Pilot and Feasibility Studies.

We are pleased that our manuscript is of interest and hope that our revisions in response to the expert reviewer comments enable this revised manuscript to be published. We greatly appreciate
the time and effort spent by the expert reviewers on their constructive comments, and would like to take this opportunity to thank them for their valuable contributions made to the manuscript.

Please see attached our point-by-point responses to the each of the peer reviewer queries, which we hope will fully address their concerns. We have also attached our revised manuscript with any revisions or additions, marked in red.

We are happy to answer any other queries and hope this revised version of our manuscript is acceptable for publication in Pilot and Feasibility Studies.

Yours truly,
Malcolm Brown, Ph.D.
(On behalf of the authors)

REPLIES TO SPECIFIC COMMENTS OF REVIEWERS

The authors wish to thank the reviewers for their interest in our manuscript and their positive observations. We are delighted to hear the reviewers believe the manuscript is well constructed and has merit. To that end, we aim to provide satisfactory responses to all the points as raised by the reviewers. Please see the following responses for your approval.

REVIEWER 1

We thank reviewer 1 for their kind observations and for highlighting the strengths in our manuscript. Please find below our responses to each of the comments raised, for your approval. We hope our responses are satisfactory and provide further clarity.

Reviewer comment:
Pg 3, Lines 16-17: Replace 'in' with 'such as'.

Author response
We have amended this sentence, now reading as follows:
Numerous physical problems are presented (e.g. sexual dysfunction, urinary incontinence, reduced bone mineral density, increased fat mass and reduced muscle mass) while psychological issues such as anxiety and depression also arise.

Reviewer comment:
Pg 3, Lines 45-46: First instance of acronyms (IGF-1 and RONS) so should be defined.

Author response
Many thanks for drawing our attention to this oversight. We have amended this sentence in the revised manuscript as follows:

However, the potential mechanism(s) remains a topic of debate but may be founded in endocrine regulation (insulin-like growth factor (IGF)-1 or testosterone signalling), metabolism, reactive oxygen species and antioxidant signalling, epigenetics or cytokine signalling among potential others.

Reviewer comment:
Pg 3, Line 50: Comma between 'findings' and 'advanced'.

Author response
We have included a comma between the words ‘findings’ and ‘advanced’.

Reviewer comment:
Pg 4, Lines 4-5: Comma between 'increasing' and 'clinical'.

Author response
We have included a comma between the words ‘increasing’ and ‘clinical’.

Reviewer comment:
Pg 5, Line 56: In describing the inclusion criteria, it would be easier to read if it was also in a box like the exclusion criteria.
Author response

We thank the reviewer for their comment and although we agree and appreciate that presenting the inclusion criteria in a box format is appealing, making the information more concise, we believe that including a further box detracts from the flow of the manuscript. Further, we have prepared the current manuscript in line with the INTERVAL protocol paper (the parallel trial discussed within). Therefore we have not made any changes and hope that this decision is acceptable.

Reviewer comment:

Pg 6, Lines 38-59: It would be nice if you could make clearer the types of questions you will ask when determining if a participant is meeting the current physical activity guidelines. I have previously screened individuals based on this criteria and it can sometimes be tricky to determine as individuals can find it difficult to comprehend what this actually means (e.g. walking around the house versus going to circuits). Also, why are you using > 60 mins of high intensity exercise as a cut-off? Should this not be > 75 mins?

Author response

Many thanks for directing our attention to the typing error regarding high intensity exercise. We have now amended the sentence to state the most recent guidelines:

Participants meeting current physical activity guidelines (≥ 150 mins moderate intensity or ≥ 75 mins of high intensity exercise per week) at screening will be deemed suitably active and excluded.

We agree that gauging self-rated exercise levels is a complex process and we too have found it tricky to comprehend perceived exertion (exercise intensity). Therefore within our study, each patient firstly completes the International Physical Activity Questionnaire to determine baseline levels of activity. During its completion, a member of the research team will ask a range of follow up questions including:

- Is your walking speed casual or brisk?
- Do you typically walk uphill and for how long?
- How many steps would you typically take per minute (on average)?
- Is your breathing and heart rate elevated?
- Do you develop a sweat after approximately 10 minutes?
During exercise, could you talk or sing?

During your typical bouts of exercise, how would you categorise your perceived exertion using the Borg scale?

We have previously been presented with certain cases whereby individuals feel they complete more vigorous exercise, when in fact it is less than perceived. Typically, patients with metastatic prostate cancer and their current treatment regime, have heightened fatigue and tend to engage in little to no exercise. To complement the subjective assessment of activity/exercise, each patient wears an accelerometer to provide an objective measure and confirm their level of activity at baseline, as well as during follow up. We have modified the physical activity levels subsection to account for this consultation with the Exercise Physiologist and clarified the dual methods of capturing activity levels.

Reviewer comment:

Pg 7, Lines 1-44: Will the moderate-intensity exercise always be based on walking or can participants complete other activities instead (e.g. swimming or cycling)? I recognise that these options may not be appropriate for this patient population but it would be good if you can make this clearer. It would also be nice to see some examples of the types of bodyweight exercises you intend to complete with the participants.

Author response

Many thanks for this salient comment. We recognise the necessity to tailor exercise interventions to individual capabilities for safety, in this high risk group, and individual exercise preferences to maintain adherence. For this feasibility trial, we have selected brisk walking as the mode due to its popularity, accessibility and low risk of injury. Brisk walking is also cost-effective and versatile, allowing patients to progress readily by manipulating intensity and duration, and to enable us to constantly monitor and adjust exercise prescription to ensure gradual progression and adaptation. Additionally, the self-confidence and exercise experiences of the men in this trial are likely to be diminished post-diagnosis, so we have provided a familiar mode of exercise (which they are capable of doing) to enhance both. Patients will engage in follow up interviews at the trial conclusion, which will provide the forum for them to express any desires to alternative exercises, for the follow up randomised control trial. This information will be taken forward in the design of the downstream trial intervention. We have added our justification for selecting brisk walking as the exercise intervention in the revised manuscript, in the exercise prescription section, as follows:
Brisk walking was selected as the mode of exercise for this feasibility trial as it poses a low risk of injury and due to its popularity, accessibility, cost-effectiveness and ease in adjusting exercise intensity / demand.

In relation to the second part of your comment, we have included some examples of the strengthening exercises included in the programme. The following has been added to the revised manuscript within the exercise prescription section:

The program will consist of 12 weeks of moderate intensity aerobic (55-70% max HR; 12-14 Borg scale) and strengthening exercises (predominantly body weight; e.g. wall press, sit-to-stand; lateral raise and bicep curls, using household items for resistance).

Reviewer comment:

Pg 7, Line 35: Replace "determine" with "determined"

Author response

We have corrected this error.

Reviewer comment:

Pg 9: Lines 20-22: Please add more details on the accelerometer being used. Also, give an indication of some of the variables you will be assessing (i.e. sedentary behaviour, light physical activity, moderate-vigorous physical activity, step counts etc.)?

Author response

Many thanks for your comment. We have added the following to the revised manuscript, in the physical activity levels subsection, to clarify the accelerometer being used, the parameters set and the variables for analysis:

Objective physical activity will be captured the week prior to each outcome visit using an accelerometer (ActiGraph GT3X). The accelerometer will be worn for 7-days, capturing data at 10-second Epoch intervals. Analysis will be completed at 60-second Epoch intervals, in accordance with recommendations (41, 42). Moderate to vigorous physical activity and step counts will be assessed for each patient.
Reviewer comment:
Pg 11, Lines 60-61: Before re-submission, try to update this section with the latest information.

Author response
Many thanks for your recommendation; we have updated the trial status section in the revised manuscript, now reading:

This feasibility trial commenced recruitment in December 2018 and is currently ongoing. At the time of submission of this protocol, five patients have entered the trial.

Reviewer comment:
Pg 16: The abbreviations should be listed below the table. Also, in the example programme given in the Table, it would be good to highlight how many stations would be required to be completed during each week of the strength exercises (does Week 1 consist of 1 station, Week 2 two stations etc?).

Author response
Many thanks for this recommendation, we have moved the abbreviations to below the table in the revised manuscript. We have also added some clarification in table 2, regarding the number of exercises each week.

Reviewer comment:
Pg 18, Lines 43-44: Should be "3889-3895" not "3889-895". Other than that, references are very well formatted.

Author response
We have amended this reference as advised.

REVIEWER 2

We thank reviewer 2 for their positive comments and for highlighting the strengths in our manuscript. Please find below our responses to each of the comments raised, for your approval.
Reviewer comment:

Page 6 - Screening. Please provide further detail about how participants will be screened in relation to physical activity (i.e via the accelerometer data or questionnaire) Page 7 - Behavioural support. This appears an important component intervention. Please provide further detail that will demonstrate how fidelity of the behavioural intervention will be maintained. Details about this intervention within a structure (e.g Michie 2011 Psychology & Health, 26:11, 1479-1498, will be beneficial to the reader for reproducibility in clinical practice.

Author response

On page 6, we have clarified that a determination of physical activity level during screening, will be made using the International Physical Activity Questionnaire. We wish to point out, that this response is similar to one previously, as the other reviewer also queried this assessment. The International Physical Activity Questionnaire will be completed in the presence of an exercise physiologist, familiar in determining exercise intensity, should the patient required any assistance in estimating intensity. If required, the exercise physiologist can ask a number of questions (some below) to help the patient reach a decision:

- Is your walking speed casual or brisk?
- Do you typically walk uphill and for how long?
- How many steps would you typically take per minute (on average)?
- Is your breathing and heart rate elevated?
- Do you develop a sweat after approximately 10 minutes?
- During exercise, could you talk or sing?
- During your typical bouts of exercise, how would you categories your perceived exertion using the Borg scale?

Many thanks for your salient comment relating to fidelity. We appreciate the importance of behavioural intervention fidelity, to ensure the programme is delivered as intended and to enhance reliability and validity of the findings. The behaviour change component of this particular programme is based on the COM-B method, defined by Michie and colleagues (2011). The initial behaviour change consultation and weekly sessions will follow a scripted protocol of defined questioning. The questions will account for weekly exercise adherence, barriers and potential solutions, goal setting and confidence / self-efficacy, with all information recorded on a study specific template. Behavioural support sessions will provide the opportunity to reinforce
key aspects of the trial and a chance to provide positive feedback on progress at that time. The same researcher will conduct all aspects of the behavioural support to maintain reliability and will record call duration and suitability for the next appointment. The purpose of the support programme is to ensure continuity in the exercise prescribed, so all patients are completing the necessary exercise volume by study cessation, while receiving equal support throughout. We have revised the behavioural support section of the manuscript which now reads as follows:

The behaviour change component of this particular programme is based on the COM-B method (31). Behavioural support will comprise a behaviour change consultation at baseline and weekly, structured telephone contact. The behavioural support component will follow a scripted protocol of defined questioning, to maintain intervention fidelity. The same member of the research team will lead the behavioural consultations throughout, to maintain reliability. Information pertaining weekly exercise adherence, perceived barriers and potential solutions, weekly goal setting and self-confidence, will be recorded. Behavioural support sessions provide the opportunity to reinforce key aspects of the trial and a chance to provide positive feedback on progress. Records of call durations and patient availability will be stored. The behavioural support programme will ensure continuity in the exercise prescribed, so all patients receive equal support to meet the desired exercise volume by study cessation. The purpose of this communication is to maintain a close relationship with the patient and identify additional support required. Accurate recording of physical activity data is essential to enable associations with treatment-related adversities and the outcome markers. Participants will specify their preferred communication type (if not telephone), to ensure regular contact is maintained.

Reviewer comment:

Page 8 - Please clarify what is meant about exercise adherence. Will this be number of sessions attended?

Author response

You are indeed correct; it is the number of session attended. We have added this information to clarify this point in the revised manuscript as follows:

Recruitment and attrition rates, exercise adherence (number of sessions completed), general safety / adverse events and the patient experience will be a focus of determining feasibility.
Reviewer comment:

Page 8 - Secondary endpoints. As this is a feasibility trial, change wording that changes from baseline will provide an indication of efficacy (not effect). Following this sentence please also add after '...detect differences from baseline', 'or changes in effect'.

Author response

Many thanks for this comment; we have amended this section as requested:

Although the sample size is small and perhaps underpowered to definitely report causation, changes from baseline will be analysed, to provide an indication of efficacy and detect any differences. It should be noted that all secondary outcome measures are obtained principally for testing ability to undertake and complete measures and not to detect differences from baseline.

Reviewer comment:

Page 9 - Physical activity levels. Please provide further detail about physical activity monitoring using the accelerometer (eg. wear time, type etc. Consider referring to Migueles 2017 Sports Med (2017) 47:1821-1845)

Author response

Many thanks for your comment. We have revised this section of the manuscript to account for these key variables:

Objective physical activity will be captured the week prior to each outcome visit using an accelerometer (ActiGraph GT3X). The accelerometer will be worn for 7-days, capturing data at 10-second Epoch intervals. Analysis will be completed at 60-second Epoch intervals, in accordance with recommendations (41, 42). Moderate to vigorous physical activity and step counts will be assessed for each patient.

Reviewer comment:

Page 11 - You have stated that supervise exercise is unsustainable in the NHS. Provide further detail how so and how this may be resolved using home-based exercise as this is usually 1:1 and phone calls may also be resource intensive.

Author response

Many thanks for this opportunity to elaborate on this point. We believe, for an exercise strategy to be implemented as an adjuvant therapy, as part of standard of care in the NHS, a workforce of
experienced exercise practitioners is required to tailor interventions, given the complexities of cancer and its treatment. Furthermore, exercise-related resources and facilities (designated space and equipment) is a necessary and costly addition (e.g. purchase and maintenance of resistance equipment) to permit implementation of such trials, especially at a time when funding is restricted.

At this time, the evidence base advocating exercise in cancer is still accumulating, with a number of smaller randomised controlled trials, but momentum for incorporating exercise alongside established methods (e.g. radiotherapy, chemotherapy or hormone therapy), may not come to fruition until the conclusion of the INTERVAL GAP4 and CHALLENGE trails, if survival benefits are detected. We believe that supervised exercise, while enhancing safety and currently regarded as the ‘gold standard’, may prove inconvenient and impractical for different cancer patients and that a remotely supervised exercise intervention, with ongoing behavioural support, provides a potentially effective alternative. We have included the following in the revised manuscript within the discussion:

Yet despite the reported benefits such a regime, at this time, is economically unsustainable in current NHS settings, due to the limited number of specialist exercise professionals, equipment and resources, highlighting a necessity for establishing an alternative.

Implementing a remotely supervised walking and strengthening programme with sufficient, ongoing behavioural support is appealing and can overcome many perceived barriers, in terms of its practicality (incorporating into daily living) and cost-effectiveness (home-based with little investment in equipment or memberships). We hope this intervention caters for perceived patient preferences and will assist in uptake and adherence, but admittedly may prove resource intensive, with dedicated researcher time invested in weekly contact. Perhaps exercise provision for mCRPC patients could eventually be embedded in standard of care follow-up consultations between patients and trained, specialist nurses / physiotherapists, if feasible, to alleviate some of this time burden, while resulting in a coordinated effort to facilitate behavioural change.

- End of responses -