PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Examining the effects of creatine supplementation in augmenting adaptations to resistance training in prostate cancer patients undergoing androgen deprivation therapy: a randomised, double-blind, placebo-controlled trial.
AUTHORS	Fairman, Ciaran; Kendall, Krissy; Newton, Robert; Hart, Nicolas; Taaffe, Dennis; Chee, Raphael; Tang, Colin; Galvão, Daniel

VERSION 1 – REVIEW

REVIEWER	Christina Dieli-Conwright University of Southern California
REVIEW RETURNED	22-Mar-2019

GENERAL COMMENTS	This paper addresses the ever-increasing problem of muscle and strength loss among prostate cancer survivors. The inclusion of foundational exercise modalities will generate substantial findings and the novelty of creatine supplementation in this population is appreciated. However, there are three flaws that must be addressed. First, the use of creatine versus other protein types was not rationalized thoroughly. If creatine is a superior amino acid compared to other options, rationale must be provided. Particularly as it pertains to muscle hypertrophy, creatine is a vital protein to aid in growth, but it is not the only or necessarily the "best" amino acid to consume. Second, to better assess the difference in response between creatine and creatine + resistance exercise, there needs to be additional arms for no exercise + creatine and no exercise + placebo. Perhaps consider discussing the lack of these study arms as a limitation. Lastly, creatine dosage should be prescribed relative to body weight, rather than an absolute dose of 5g/day; please provide justification for the dose used. Overall, this study design has the potential for successful and meaningful findings, but the aforementioned shortcomings must first be addressed. Page 4 Line 15: The term 'functional decline' is unclear. Please specify if it is referred to musculoskeletal, cardiovascular or others. Lines 36-37: The phrase 'accelerated trajectory toward a 'disability' condition and progressive decline in independence' is not clear. Please specify what 'disabilities' is referring to and how this pertains to muscle atrophy. Page 5 Lines 9-10: Has creatine supplementation been utilized in non-cancer male populations with low testosterone? If so, this may be more related to the problem at hand, as the mechanisms by which

	HIV and muscular dystrophy lose muscle is different than low testosterone/ADT. METHODS: Page 5 It is understood that a pure control group (no exercise or supplement) is not included in the study. Please provide justification for why this 3rd arm was not included. Line 51-52: Creatine loading has been established in other populations (i.e., performance or body building) to improve efficacy. However, this needs to be substantiated with evidence for this study perhaps in the supplement protocol section. Page 6 Line 25: 'eligible to enrol' is misspelled. Lines 32-33: Will participants currently participating in aerobic exercise will be excluded? Given the interest in altering body composition, excluding aerobically active participants should be considered. Page 8 Line 6: 4 hours does not seem like enough time to fast prior to a DEXA scan. Is this the recommended protocol by Hologic? Page 9 Line 10-29: The tenses of verb in this paragraph are not consistent. Please revise here and throughout the manuscript to ensure consistent verb tenses. Other measures- Are these included because they are confounding measures? If so, this needs to be specified. Diet recall- Due to alterations in the outcomes by changes in dietary patterns, consider using 3-day food records each week during the intervention, perhaps with compensation? Exercise program- What load will each resistance exercise progress to by the end of the program? Page 12 Lines 58-59: Since glucose consumption promotes muscle hypertrophy by replenishing stored glycogen, it seems the consumption of juice will confound any hypertrophy seen due to resistance exercise and/or creatine. What specific type of juice will be consumed? Page 13 Line 18: It is unclear how FFM of 1.4kg was calculated/determined. Page 15 Lines 59-60: Please provide justification that creatine improves physical function. Tables and Figures: Table 3-

	Please specify how the push-ups are loaded as the program progresses. With bodyweight exercises, eliciting hypertrophy is difficult because the load cannot be increased unless repetitions are increased, which goes against the current program characteristics

REVIEWER	Erik Hanson University of North Carolina at Chapel Hill, USA
REVIEW RETURNED	14-May-2019

GENERAL COMMENTS	This is a well-designed study by a research group who are extremely well-versed in this population. The design includes familiarsation prior to baseline testing, a battery of clinically relevant tests, and a training and supplementation program that is consistent with best practice. The use of creatine in conjunction with resistance training is practical and offers significant potential benefit with low apparent risk to the participants. I am quite keen to see the final results of this project, as it may help prevent (or even reverse) lean mass loss with ADT. Below are a few points for the authors to consider. In the strengths and weakness, consider adding dietary analyses as either a strength or a weakness. The 3d dietary recall at pre/post will give some insight into the dietary habits of the participants that may influence muscle hypertrophy with RT (i.e. total protein intake). Would a dietary recall each month or even just adding at the midpoint allow for the researchers to better dissect the role of diet in this study, given its potentially confounding role? Moreover, having more frequent dietary recalls would give insight into the natural creatine intake of the non-supplemented group. While these men would need to be eating 400-500g of red meat/fish per day to ingest significant creatine from food, the authors would be in better position to eliminate this potential issue, even if rather unlikely. Did the authors consider including RMR at baseline and comparing vs. estimating daily caloric intake based on dietary recall? This information may be useful in reducing the variability in the responses to RT likely to be seen within this population. Exclusion criteria say 2-3 days of structured RT. Are you using 2 or 3? This criterion seems to be vaguely applied. The study is powered on a group difference of 1.4 kg of lean mass. As studies have reported anywhere from 0.5 – 1.5 kg increases in lean mass with RT, this would imply that the supplement group would need to increase lean mass by 1.9 – 2.9 kg, which currently exceeds any reported increases in lean mass I am aware of, which makes me concerned about the power to detect differences with the current sample size (which is to be commended on its own). P4 line 32, “potent exercise medicine” comes across as awkward.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Christina Dieli-Conwright
Institution and Country: University of Southern California
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This paper addresses the ever-increasing problem of muscle and strength loss among prostate cancer survivors. The inclusion of foundational exercise modalities will generate substantial findings and the novelty of creatine supplementation in this population is appreciated. However, there are three flaws that must be addressed.

First, the use of creatine versus other protein types was not rationalized thoroughly. If creatine is a superior amino acid compared to other options, rationale must be provided. Particularly as it pertains to muscle hypertrophy, creatine is a vital protein to aid in growth, but it is not the only or necessarily the "best" amino acid to consume.

We appreciate the reviewers time in reviewing this manuscript and offering insightful comments on how we can improve this paper. As we recently reviewed (Fairman et al., Crit Rev Oncol Hematol 2019), despite the numerous studies examining the mechanisms of and potential for creatine supplementation combined with exercise in apparently healthy populations, the research is quite sparse in cancer populations. Because of this, it is too early to suggest that one supplement is superior to the other. We have chosen to examine the potential benefits of creatine in this population, not because we believe it to be the best amino acid (or supplement) to consume, but because of its suggested actions in assisting with energy provision during exercise. These mechanisms are different to the ingestion of protein or amino acids in an attempt to increase overall protein intake and/or muscle protein synthesis. As a result, the following has been added to the introduction to better support our inclusion of creatine:

"Creatine supplementation increases intramuscular stores of phosphocreatine (PCr), a high-energy phosphate that plays a critical role in energy provision during exercise [1]. It is hypothesised that Cr uptake by skeletal muscle is modulated by muscle activity [2]. Importantly, the ability to sustain exercise effort is dependent on PCr availibity, which diminishes with intense exercise. Increases in PCr stores may contribute to an accelerated resynthesis of ATP during exercise [3, 4]. Consequently, the ergogenic effects of Cr supplementation are likely a result from an increase in overall training volume and/or quality,[3, 4] due to increases in intramuscular PCr stores[2, 5] enhancing exercise capacity. Taken collectively, there is the potential that Cr supplementation may enhance the quantity and/or quality of resistance training in patients with PCa, leading to augmented adaptations in FFM, muscle strength and/or function.[6] Given the overwhelming evidence of Cr supplementation in other populations, there is large therapeutic potential for its use in patients with PCa.[6]"

Second, to better assess the difference in response between creatine and creatine + resistance exercise, there needs to be additional arms for no exercise + creatine and no exercise + placebo. Perhaps consider discussing the lack of these study arms as a limitation

We appreciate the reviewers insight into the study design. However, this is a state-funded trial from the Cancer Council Western Australia, that included oncologists, clinical trialists, epidemiologists etc. on the review panel. As such, substantial modifications to the study protocol are no longer possible. However, this trial is an extension of numerous prior trials from this group investigating exercise during androgen deprivation therapy in prostate cancer (eg., Galvão et al., J Clin Oncol 2010; Cormie

et al., BJU Int 2015). In these trials, we have demonstrated that usual care groups (i.e. no exercise) typically see declines in muscular strength, lean body mass and /or physical function. Comparatively, we have previously demonstrated that men with prostate cancer undergoing ADT who participate in resistance exercise see improvements in physical function, lean body mass and muscular strength (eg., Galvão et al., Med Sci Sports Exerc 2006; Galvão et al., J Clin Oncol 2010; Cormie et al., BJU Int 2015). Thus, the goal of this trial is to extend this work and investigate the ability to enhance those gains with the addition of a creatine supplement. The basis for this rationale has been recently published by our team (Fairman et al., Crit Rev Oncol Hematol 2019). After thorough discussion with clinicians and the study team we have elected not to include this as a limitation to the trial.

Lastly, creatine dosage should be prescribed relative to body weight, rather than an absolute dose of 5g/day; please provide justification for the dose used. Line 51-52: Creatine loading has been established in other populations (i.e., performance or body building) to improve efficacy. However, this needs to be substantiated with evidence for this study perhaps in the supplement protocol section.

There are no studies that have directly compared a standard 5g/day versus doses relative to bodyweight to determine if one is superior to the other. Morover, using 20g (loading)/ 5g (maintenance) is well supported in the literature and has been reported to be safe in older adults (Brose et al., 2003; Gualano et al., Med Sci Sports Exerc, 2011; Devries & Phillips, Med Sci Sports Exerc, 2014; Pinto et al., J Cachexia Sarcopenia Muscle, 2016). As a result, we have added these references to our protocol which now reads as below:

“Participants in the SUPP group will receive 20g/day of Cr monohydrate for 5 days, beginning on day 4 of the familiarisation/testing phase (immediately after randomisation, approximately 7 days prior to first training session), divided into four equal doses throughout the day. Participants will then be given single daily doses of 5 grams for the duration of the 12-week training program. This dosing protocol has been previously demonstrated to be safe and efficacious in older adults.[7-10]”

Page 4
Line 15: The term ‘functional decline’ is unclear. Please specify if it is referred to musculoskeletal, cardiovascular or others.

We thank the reviewer for highlighting this. We have revised this term to state “In turn, these adverse effects of ADT are linked with functional decline (i.e. reduced walking speed, ability to rise from a chair or climb stairs etc. that impact ability to perform activites of daily living), frailty, and increased risk for cardiovascular disease, metabolic syndrome, and osteoporosis."

Lines 36-37: The phrase ‘accelerated trajectory toward a ‘disability’ condition and progressive decline in independence’ is not clear. Please specify what ‘disabilities’ is referring to and how this pertains to muscle atrophy.

We thank the reviewer for directing us towards this. The “disability” condition refers to limitations in abilities to carry out daily tasks. We have rephrased this paragraph to make this more clear and the sentence in question now reads (page 4):

“In turn, these adverse effects of ADT are linked with functional decline (i.e. reduced walking speed, ability to rise from a chair or climb stairs etc.), frailty, and increased risk for cardiovascular disease, metabolic syndrome, and osteoporosis.[11]”

Page 5
Lines 9-10: Has creatine supplementation been utilized in non-cancer male populations with low testosterone? If so, this may be more related to the problem at hand, as the mechanisms by which HIV and muscular dystrophy lose muscle is different than low testosterone/ADT.

Thank you for the suggestion. To our knowledge, there are no studies examining the effects of creatine supplementation in non-cancer male populations with low testosterone. In any case, this is likely due to the fact that creatine does not have an affect on hormone production or secretion—rather its main function is to serve as an energy substrate. Whilst we understand that the mechanisms of muscle loss can vary across a wide range of populations, we believe the mechanisms of increasing strength and hypertrophy via a progressive resistance training program combined with creatine will remain consistent among these populations. We have updated the introduction to better reflect this in response to point 1, which reads:

“Creatine supplementation increases intramuscular stores of phosphocreatine (PCr), a high-energy phosphate that plays a critical role in energy provision during exercise [1]. It is hypothesised that Cr uptake by skeletal muscle is modulated by muscle activity [2]. Importantly, the ability to sustain exercise effort is dependent on PCr availibity, which diminishes with intense exercise. Increases in PCr stores may contribute to an accelerated resynthesis of ATP during exercise [3, 4]. Consequently, the ergogenic effects of Cr supplementation are likely a result from an increase in overall training volume and/or quality,[3, 4] due to increases in intramuscular PCr stores[2, 5] enhancing exercise capacity. Taken collectively, there is the potential that Cr supplementation may enhance the quantity and/or quality of resistance training in patients with PCa, leading to augmented adaptations in FFM, muscle strength and/or function.[6] Given the overwhelming evidence of Cr supplementation in other populations, there is large therapeutic potential for its use in patients with PCa.[6]”

METHODS:
Page 5
It is understood that a pure control group (no exercise or supplement) is not included in the study. Please provide justification for why this 3rd arm was not included.

In our prior trials in this patient group, we have included control groups (e.g., Galvão et al., J Clin Oncol, 2010; Cormie et al., BJU Int 2015) to compare the effects of exercise versus usual care on meausures of physical function, strength and body composition. We and others have demonstrated that individuals who do not participate in exercise experience demonstrable reductions in physical function and muscle strength. As in response to point 2, the purpose of this trial is to examine if creatine supplementation has additive effects with resistance training on body composition and muscular strength, rather than comparing these effects to individuals who do not exercise.

Page 6
Line 25: ‘eligible to enrol’ is misspelled.

This has been revised.

Lines 32-33: Will participants currently participating in aerobic exercise will be excluded? Given the interest in altering body composition, excluding aerobically active participants should be considered.

We agree that aerobic exercise can alter body composition. Prior work from our team has demonstrated that men with prostate cancer in Australia typically have low levels of participation in aerobic and resistance activity (Galvão et al., Psychooncology 2015). Individuals currently participating in aerobic exercise will not be excluded from the trial but will be asked to maintain current levels of activity throughout the trial to avoide any dramatic increases in activity. We will record the

individual's level of activity at the beginning and end of the trial. Our primary outcomes are lean body mass and muscle strength, which will require an anabolic stimulus. This is a process we have used in prior trials despite not excluding people who are aerobically active demonstrating significant improvements in lean body mass, muscular strength an physical function.

Page 8
Line 6: 4 hours does not seem like enough time to fast prior to a DEXA scan. Is this the recommended protocol by Hologic?

Hologic currently has no standardized protocol for pre-testing conditions related to fasting. Moreover, among the many studies that incorporate DXA scanning for body composition there is often no mention regarding food consumption prior to testing in order to standardise conditions or times may vary. Consequently, as patients will likely come at different times of the day to undertake DXA scanning we have elected to incoporate a 4-hour fast (as compared to for instance an overnight fast) to standardise testing considitions. Further, repeat testing will be undertaken at the same time of day to facilitate the standardisation of conditions.Additionally, we will be using 3-day dietary recall to standardize pre-post testing diet in order to control for these factors.

Page 9
Line 10-29: The tenses of verb in this paragraph are not consistent. Please revise here and throughout the manuscript to ensure consistent verb tenses.

This section and the manuscript has been revised for consistency in verb tenses.

Other measures- Are these included because they are confounding measures? If so, this needs to be specified.
These measures are included as descriptives (demographic information), fidelity (diet-recall) and safety (adverse events).

Diet recall- Due to alterations in the outcomes by changes in dietary patterns, consider using 3-day food records each week during the intervention, perhaps with compensation?

We have discussed this as a team and have opted against weekly diet records in an effort to minimize participant burden. However, we have opted for a midpoint 3-day food record at 6 weeks in an attempt to gain additional information on any changes in dietary patterns. We have included this revision on pages 9/10

"Further, a 3-day diet recall will be completed at mid-point to gain further information about dietary changes that may occur throughout the study."

Exercise program-
What load will each resistance exercise progress to by the end of the program?
The load will be progressed to ~80% 1RM (4 sets of 8). We have included this in the revised manuscript as well as additional detail regarding the intervention. This revised section now reads:

"The initial loading will be equivalent to ~65% 1RM (3 sets of 12 reps), progressing towards ~80% 1RM (4 sets of 8 reps). Loading will be progressed throughout the program using the "2 for 2 rule", whereby if a participant can complete 2 additional reps on the last set of an exercise for 2 consecutive sessions, the weight for an exercise (~5-10% for upper body; ~10-15% for lower body) will be increased. Concurrently, repetitions will gradually decrease across the program to match the increase in weight. This type of resistance training protocol (i.e. exercises that stimulate large muscle groups, multiple sets, short rest) has been recommended to enhance the hypertrophic response to

training.[12, 13] The program will be autoregulated where variations in participants' fatigue, recovery, energy and physical capacity will be used to adjust each training session. This model of autoregulation has been previously proposed and currently being utilized in other exercise oncology trials. Moreover, any deviations to the protocol will be recorded in detail and reported in the final manuscript. Specific details of the program are outlined in Table 3."

Page 12
Lines 58-59: Since glucose consumption promotes muscle hypertrophy by replenishing stored glycogen, it seems the consumption of juice will confound any hypertrophy seen due to resistance exercise and/or creatine. What specific type of juice will be consumed?

We agree that replenishment of glycogen can play a role in muscle hypertrophy. However, we don't agree that ~30g of carbohydrates in 300ml of orange or apple juice is sufficient to wash out any hypertrophic effects of creatine supplementation and resistance training. Morover, this mode of supplementation protocol is standard with prior trials investigating creatine supplementation and resistance training on hypertrophy and/or strength. [8]

We have clarified in the text that individuals will consume apple or orange juice and the section in question in the revised manuscript now reads:

"Participants will be asked to dissolve the supplements in 200-300 mL of juice (orange or apple) to mask the solubility of Cr and taste of dextrose."

Page 13
Line 18: It is unclear how FFM of 1.4kg was calculated/determined.

We have based this value on two factors. In analysis of our recent trial in men receiving ADT, men who participated in resistance training gained 0.7 kg following 6 months of training (Newton et al, Med Sci Sports Exerc 2019) and prior research in apparently healthy older men (Brose et al., J Gerontol A Biol Sci Med Sci 2003) demonstrated gains of about 1.7 kg in men who supplemented with creatine for 14 weeks in addition to resistance training, whereas men who participated in resistance training alone gained ~ 0.4 kg. Taken collectively, we assumed that men who participate in resistance training would see gains of 0.3-0.5 kg in the 12 weeks of training with gains in the creatine supplemented group of ~1.7-1.9 kg. As a result, we used this information to power the trial based on a net difference between groups of ~1.4 kg. We have amended the statement in the revised manuscript to reflect this that reads:

"To achieve 80% power at an alpha-level of $p<0.05$ (two tailed), 25 participants per group would be required to detect a mean difference in change between the two groups for FFM of 1.4 kg at the end of the 12-week intervention, based on our previous work in men receiving ADT [14] and work by Brose et al. [8] investigating changes in body composition and muscle strength with Cr supplementation and resistance training in older adults. To account for an attrition rate of ~10% seen in prior trials [15, 16], we aim to recruit 56 participants (SUPP n=28; PLA n=28)."

Page 15
Lines 59-60: Please provide justification that creatine improves physical function.

We have included the following reference in lines 59-60, supporting the use of creatine in improving physical function.

"Devries, M. C., & Phillips, S. M. (2014). Creatine supplementation during resistance training in older adults—a meta-analysis. Medicine & Science in Sports & Exercise, 46(6), 1194-1203."

Tables and Figures:
Table 3-
Please specify how the push-ups are loaded as the program progresses. With bodyweight exercises, eliciting hypertrophy is difficult because the load cannot be increased unless repetitions are increased, which goes against the current program characteristics.

Participants will begin with incline push ups on a Smith machine, where the bar will be lowered to increase the resistance across the program. If participants can get to a point where they are successfully performing all push-ups on the ground with good technique, they will be progressed to a free weight bench press to allow for further progression if necessary. We have included a statement to this effect below Table 3 which reads:

“Push-ups will be performed on a Smith machine, where the initial height of the bar will be adjusted to a point where individuals can perform 12 repetitions. The exercise will be progressed by lowering the bar (15 cm intervals) when participants can successfully complete all repetitions. When participants can complete all repetitions on the floor with good technique, they will be progressed to a free weight bench press movement.”

Reviewer: 2
Reviewer Name: Erik Hanson
Institution and Country: University of North Carolina at Chapel Hill, USA
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This is a well-designed study by a research group who are extremely well-versed in this population. The design includes familiarsation prior to baseline testing, a battery of clinically relevant tests, and a training and supplementation program that is consistent with best practice. The use of creatine in conjunction with resistance training is practical and offers significant potential benefit with low apparent risk to the participants. I am quite keen to see the final results of this project, as it may help prevent (or even reverse) lean mass loss with ADT.

Thank you for your favourable review of our manuscript. We appreciate your time and effort and have worked to respond to your comments below.

In the strengths and weakness, consider adding dietary analyses as either a strength or a weakness. The 3d dietary recall at pre/post will give some insight into the dietary habits of the participants that may influence muscle hypertrophy with RT (i.e. total protein intake).

Thank you, we have included a statement to this effect in the strengths/limitations section, which reads as follows:

“The inclusion of dietary analysis at baseline, 6 wk mid-point and 12-wk follow-up will offer additional insight into dietary habits of participants that may influence muscle hypertrophy (i.e. protein intake).”

Would a dietary recall each month or even just adding at the midpoint allow for the researchers to better dissect the role of diet in this study, given its potentially confounding role? Moreover, having more frequent dietary recalls would give insight into the natural creatine intake of the non-supplemented group. While these men would need to be eating 400-500g of red meat/fish per day to ingest significant creatine from food, the authors would be in better position to eliminate this potential issue, even if rather unlikely.

We have discussed this as a team and have opted to include a 3d recall at midpoint to obtain more information on changes in dietary patterns. We have included this revision on pages 9/10

“Further, a 3-day diet recall will be completed at mid-point to gain further information about dietary changes that may occur throughout the study .”

Did the authors consider including RMR at baseline and comparing vs. estimating daily caloric intake based on dietary recall? This information may be useful in reducing the variability in the responses to RT likely to be seen within this population.

We agree with the reviewer that a RMR test would be helpful in determining energy requirements. RMR would be valuable if dietary modifications were being made in order to more accurately determine caloric needs. We are currently conducting this in a separate study in which men on ADT are receiving exercise with dietary modifications. However, the purpose of this study is to investigate the addition of a supplement to resistance training, thus we don’t anticipate knowledge of RMR providing further insight into changes in our outcomes of interest.

Exclusion criteria say 2-3 days of structured RT. Are you using 2 or 3? This criterion seems to be vaguely applied.

We have revised this criterion to > 2 days/week.

The study is powered on a group difference of 1.4 kg of lean mass. As studies have reported anywhere from 0.5 – 1.5 kg increases in lean mass with RT, this would imply that the supplement group would need to increase lean mass by 1.9 – 2.9 kg, which currently exceeds any reported increases in lean mass I am aware of, which makes me concerned about the power to detect differences with the current sample size (which is to be commended on its own).

As in our response to reviewer 1, the study was based on our prior work in men receiving ADT, who experience improvements of ~ 0.7 kg following 6 months of training (Newton et al, Med Sci Sports Exerc 2019). Additionally, in an investigation of creatine supplementation in older men (Brose et al., J Gerontol A Biol Sci Med Sci 2003), those who participated in resistance training alone gained ~ 0.4 kg and those who received supplementation experienced gains of ~1.7 kg after 14 weeks of training. Taken collectively, we assumed that men who participate in resistance training would see gains of 0.3-0.5 kg in the 12 weeks of training and those who received supplementation experience improvements in ~1.7-1.9 kg. As a result, we used this information to power the trial based on a net difference between groups of ~1.4 kg.

We have amended the statement in the revised manuscript to reflect this that reads:

“To achieve 80% power at an alpha-level of $p<0.05$ (two tailed), 25 participants per group would be required to detect a mean difference in change between the two groups for FFM of 1.4 kg at the end of the 12-week intervention, based on our previous work in men receiving ADT [14] and work by Brose et al. [8] investigating changes in body composition and muscle strength with Cr supplementation and resistance training in older adults. To account for an attrition rate of ~10% seen in prior trials [15, 16], we aim to recruit 56 participants (SUPP n=28; PLA n=28).”

P4 line 32, “potent exercise medicine” comes across as awkward.

We have revised this sentence to “promising strategy”

VERSION 2 – REVIEW

REVIEWER	Christina Dieli-Conwright University of Southern California
REVIEW RETURNED	20-Jul-2019

GENERAL COMMENTS	Overall Comments: The revisions do provide more clarity to superiorly explain this study. However, there are still many comments that were not addressed by the authors. These comments highlight many potential flaws that could greatly affect the results of the study if not addressed now. METHODS: Page 5 It is understood that a pure control group (no exercise or supplement) is not included in the study. Please provide justification for why this 3rd arm was not included. - The exclusion of a control was not addressed. Line 51-52: Creatine loading has been established in other populations (i.e., performance or body building) to improve efficacy. However, this needs to be substantiated with evidence for this study perhaps in the supplement protocol section. - Creatine loading needs to be justified based upon prior evidence. Page 6 Lines 32-33: Will participants currently participating in aerobic exercise will be excluded? Given the interest in altering body composition, excluding aerobically active participants should be considered. - Please specify if participants currently participating in aerobic exercise will be excluded. Page 8 Line 6: 4 hours does not seem like enough time to fast prior to a DEXA scan. Is this the recommended protocol by Hologic? - Please provide rationale for the 4-hour fasting parameters Page 12 Lines 58-59: Since glucose consumption promotes muscle hypertrophy by replenishing stored glycogen, it seems the consumption of juice will confound any hypertrophy seen due to resistance exercise and/or creatine. What specific type of juice will be consumed? - This is confounder that will likely greatly influence the results of this study. As such, the inclusion of juice post-exercise must be thoroughly validated.

REVIEWER	Erik Hanson University of North Carolina at Chapel Hill, USA
REVIEW RETURNED	15-Jul-2019

GENERAL COMMENTS	The authors have sufficiently addressed all of my comments at this time.

VERSION 2 – AUTHOR RESPONSE

It is understood that a pure control group (no exercise or supplement) is not included in the study. Please provide justification for why this 3rd arm was not included.
- The exclusion of a control was not addressed.

The consequences of androgen deprivation therapy in men with prostate cancer as standard of care (pure control group) has been well documented by members of our team and others.[1, 2] The beneficial effects of resistance training on body composition and physical function outcomes in men with prostate cancer receiving ADT is also well documented. [3-6] In this study, we are specifically interested in the additive effects of creatine supplementation with resistance training in targeting lean body mass in men with prostate cancer receiving androgen deprivation therapy. Consequently, the resistance training + placebo group will act as a "control group" for the purpose of this study. As we stated in the study design section of the protocol paper (page 6), this is a double-blind, placebo-controlled trial. Moreover, this type of study design is regularly employed in studies examining the additive effects of creatine supplementation and exercise training in older adults. [7] Finally, this research has been funded through a competitive funding scheme with the Cancer Council Western Australia. The funding permitted a two group design that enabled the comparison of two active cohorts.

Line 51-52: Creatine loading has been established in other populations (i.e., performance or body building) to improve efficacy. However, this needs to be substantiated with evidence for this study perhaps in the supplement protocol section.
- Creatine loading needs to be justified based upon prior evidence.

In research investigating the effects of Cr supplementation on intramuscular creatine stores, it is understood that protocols using a loading protocol (20 g day for 7 days) followed by a maintenance phase (5 g/day thereafter) and those using a maintenance phase alone (i.e. 5 g per day throughout) yield similar levels of saturation of intramuscular Cr after ~28 days.[8] However, in some of the trials of Cr supplementation with resistance training that have yielded null results, one of the hypotheses has been that Cr stores weren't fully saturated prior to the beginning of resistance training. [9] We are limited in our ability to perform muscle biopsies to accurately determine intramuscular Cr stores. Consequently, the loading phase prior to the beginning of the resistance training program was included to ensure intramuscular creatine stores were saturated prior to resistance training to "maximise" the likihood of seeing an effect of supplementation. [8] Loading protocols are regularly employed in studies investigating Cr supplementation with resistance training in older adults.[7, 10-13]

We have added this rationale to the supplement section of the protocol paper, as below:

Consequently, the loading phase prior to the beginning of the resistance training program was included to ensure intramuscular creatine stores were saturated prior to resistance training to "maximise" the likihood of seeing an effect of supplementation. [8]

Page 8, Lines 32-33: Will participants currently participating in aerobic exercise will be excluded? Given the interest in altering body composition, excluding aerobically active participants should be considered.
- Please specify if participants currently participating in aerobic exercise will be excluded.

We agree that aerobic exercise can alter body composition. Prior work from our team has demonstrated that men with prostate cancer in Australia typically have low levels of participation in aerobic and resistance activity.[14] As a result, this will likely to be a minimal proportion of potential participants enrolled in our trial. We feel the critical element of the eligibility criteria is the exclusion of individuals who are currently participating in >2 days a week of resistance training, which will likely have a larger impact on our outcomes of interest.

Individuals currently participating in aerobic exercise will not be excluded from the trial but will be asked to maintain current levels of activity throughout the trial to avoid any dramatic increases in activity. We will record the individual's level of activity at the beginning and end of the trial. Our primary outcomes are lean body mass and muscle strength, which will require an anabolic stimulus. This is a process that has been used in prior trials (not excluding people who are aerobically active) of individuals with cancer and have demonstrated significant improvements in lean body mass, muscular strength and physical function.[6, 15, 16] We have included a statement to this effect on page 7 that reads:

"Individuals who are participating in regular structured aerobic training (>2 days a week) will not be excluded from the study. Baseline physical activity will be recorded and participants enrolled in the study will be asked not to modify outside activity."

Page 8, Line 6: 4 hours does not seem like enough time to fast prior to a DEXA scan. Is this the recommended protocol by Hologic?
- Please provide rationale for the 4-hour fasting parameters

We acknowledge the reviewer's comments on fasting. We have not used a fasting protocol in our previous protocols using DXA and have still demonstrated sensitivity to minor changes in LBM.[5, 17] Further, an overnight fast is not part of Hologic's recommended practices for whole body DXA scans.

The fasting protocol prior to DXA is a process of standardisation for the purposes of validity and repeatability. While hydration status and prior meal intake may be a confounding factor - this is accounted for by reproducing the same conditions at the post-intervention DXA scan that were provided to the patient at the baseline DXA scan. The variability in DXA is minimal under such a standardisation process. If patients replicate the same dietary practices in the lead-up to their follow-up DXA scan as their baseline DXA scan, this potential confounding factor is minimised. In our experience working with individuals with cancer, constraints related to scheduling, travel, conflicting appointments and work commitments often preclude their ability to arrive at the lab early morning in an overnight fasted state. Consequently, we elected to choose a 4-hour fast to limit the influence of acute changes in hydration or energy intake on the results. As a result, this protocol, standardises our pre-/post-testing procedures while also respecting the participants' time and autonomy. In addition, we will be performing repeated scans on a subset of patients to calculate coeeficients of variations for these scans and will report this information in the final manuscript.[18]
In order to standarise test conditions, participants will be asked to avoid strenuous exercise for 24 hours prior to testing. Further, they will be instructed to avoid the consumption of food and water 4 hours and 1 hour prior to testing, respectively.

Page 12, Lines 58-59: Since glucose consumption promotes muscle hypertrophy by replenishing

stored glycogen, it seems the consumption of juice will confound any hypertrophy seen due to resistance exercise and/or creatine. What specific type of juice will be consumed?
- This is confounder that will likely greatly influence the results of this study. As such, the inclusion of juice post-exercise must be thoroughly validated.

The juice is not consumed post-training. Rather, participants are given packets of supplement and/or placebo to take home with them and consume with juice. We agree that replenishment of glycogen can play a role in muscle hypertrophy. However, it's unlikely that ~30g of carbohydrates in 300ml of orange or apple juice is sufficient to wash out any hypertrophic effects of creatine supplementation and resistance training. We will use dietary logs taken at baseline, 6 weeks and post-testing to analyse any changes in dietary habits, which will include additional consumption of juice. Any significant changes in dietary habits will be discussed in the context of the results. Moreover, this mode of supplementation protocol is standard with prior trials investigating creatine supplementation and resistance training on hypertrophy and/or strength. [19]

We have clarified in the text that individuals will consume apple or orange juice and the section in question in the revised manuscript now reads (page 13):

"Participants will be asked to dissolve the supplements in 200-300 mL of juice (orange or apple) to mask the solubility of Cr and taste of dextrose."

References

1. Owen, P.J., et al., Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: an update. Prostate Cancer Prostatic Dis, 2017. 20(2): p. 137-145.
2. Galvao, D.A., et al., Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int, 2008. 102(1): p. 44-7.
3. Focht, B.C., et al., Effects of a Group-Mediated Exercise and Dietary Intervention in the Treatment of Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: Results From the IDEA-P Trial. Ann Behav Med, 2018. 52(5): p. 412-428.
4. Galvao, D.A., 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): p. 856-64.
5. Galvao, D.A., et al., Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. Prostate Cancer Prostatic Dis, 2007. 10(4): p. 340-6.
6. Winters-Stone, K.M., et al., Resistance training reduces disability in prostate cancer survivors on androgen deprivation therapy: evidence from a randomized controlled trial. Arch Phys Med Rehabil, 2015. 96(1): p. 7-14.
7. Stares, A. and M. Bains, The Additive Effects of Creatine Supplementation and Exercise Training in an Aging Population: A Systematic Review of Randomized Controlled Trials. J Geriatr Phys Ther, 2019.
8. Kreider, R.B., et al., International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr, 2017. 14: p. 18.
9. Lonbro, S., et al., Feasibility and efficacy of progressive resistance training and dietary supplements in radiotherapy treated head and neck cancer patients--the DAHANCA 25A study. Acta Oncol, 2013. 52(2): p. 310-8.
10. Bemben, M.G., et al., The effects of supplementation with creatine and protein on muscle strength following a traditional resistance training program in middle-aged and older men. J Nutr Health Aging, 2010. 14(2): p. 155-9.
11. Chilibeck, P.D., et al., Creatine monohydrate and resistance training increase bone mineral content and density in older men. J Nutr Health Aging, 2005. 9(5): p. 352-3.

12. Chrusch, M.J., et al., Creatine supplementation combined with resistance training in older men. Med Sci Sports Exerc, 2001. 33(12): p. 2111-7.
13. Gualano, B., et al., Creatine supplementation and resistance training in vulnerable older women: a randomized double-blind placebo-controlled clinical trial. Exp Gerontol, 2014. 53: p. 7-15.
14. Galvao, D.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): p. 1241-1249.
15. Winters-Stone, K.M., et al., Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial. Breast Cancer Res Treat, 2011. 127(2): p. 447-56.
16. Courneya, K.S., et al., Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol, 2007. 25(28): p. 4396-404.
17. Newton, R.U., et al., Body composition, fatigue and exercise in patients with prostate cancer undergoing androgen-deprivation therapy. BJU Int, 2018. 122(6): p. 986-993.
18. Hart, N.H., et al., Segmental Musculoskeletal Examinations using Dual-Energy X-Ray Absorptiometry (DXA): Positioning and Analysis Considerations. J Sports Sci Med, 2015. 14(3): p. 620-6.
19. Brose, A., G. Parise, and M.A. Tarnopolsky, Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. J Gerontol A Biol Sci Med Sci, 2003. 58(1): p. 11-9.

VERSION 3 – REVIEW

REVIEWER	Christina Dieli-Conwright City of Hope National Medical Center, US
REVIEW RETURNED	26-Aug-2019

GENERAL COMMENTS	We thank the authors for a thorough and complete response to the concerns. The concerns have been appropriately addressed.