

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Rehabilitation interventions to improve patient reported outcomes and physical fitness in survivors of muscle invasive bladder cancer: a systematic review protocol
<b>AUTHORS</b>	Rammant, Elke; Bultijnck, Renée; Sundahl, Nora; Ost, Piet; Pauwels, Nele; Deforche, Benedicte; Pieters, Ronny; Decaestecker, Karel; Fonteyne, Valérie

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Bente Thoft Jensen Department of Urology, Aarhus University Hospital & Department of Clinical medicine; Center of Research in Rehabilitation (CORIR), Aarhus University Denmark
<b>REVIEW RETURNED</b>	10-Feb-2017

<b>GENERAL COMMENTS</b>	<p>he idea is absolutely relevant, but do not agree on why it should differ significantly from other attempts. I can not agree on the argument that bladder cancer soon will have a huge impact on public health because of significant increasing numbers. I do not agree on this, the incidence is marginal. This is clear in those countries who have national databases based on civil registration numbers. However, prevention should be promoted. A new study from authors already cited in the references have been published in January and should maybe be considered (Buffart et al 2017)</p> <p>Comments to the authors</p> <p>Congrats with the study proposal. Be aware of the study by Buffart et al from January 2017 which seems partly to cover your aims! Only a few comments</p> <p><b>Page 4:</b></p> <p>Line 8-1 : Relative much information concerning BC although the scope is MIBC. It seems not relevant. Moreover, it is difficult to imagine an enormous challenge considering the marginal increase in the <i>incidence</i>.</p> <p>Line 26-28: Health Related Quality of Life or Quality of Life? There is a difference as pr. definition.</p> <p>Line 41-43: An overall definition of rehabilitation may be useful?</p>
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	<p><b>Page 5:</b></p> <p>Line 13-14: Reference number 16 - Cunningham? The ref. is not Cunningham, but Buffart 2013 and looking into the reference Cunningham appears – use the original reference</p> <p>Line 57: Define supervised ,, by whom and where ?</p> <p><b>Page 7</b></p> <p>Line 31: Still difficult with Cunningham – where is the original work?</p> <p>Line 55: The second time you mention PRO – maybe define it earlier on page 6</p> <p><b>Page 8</b></p> <p>Why don't you add muscle capacity, which seems to be a very precise measurement and already reported to be effective and evident in the literature? Especially with regards to the MIBC patients</p> <p><b>Page 11</b></p> <p>Line 33: Moderator analysis? Another name for regression? You mention the lack of studies so maybe the list of analysis is very ambitious although it will be a break through</p>
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<b>REVIEWER</b>	Mohamed, NE Mount Sinai School of Medicine, New York, USA
<b>REVIEW RETURNED</b>	15-Feb-2017

<b>GENERAL COMMENTS</b>	<p>Manuscript: Rehabilitation intervention to improve patient reported outcomes in physical fitness in survivors of muscle invasive bladder cancer: a systematic review protocol.</p> <p>This is a very-well written protocol for a systematic review manuscript targeting physical fitness in survivors of muscle invasive bladder cancer patients. The authors did a very good job following standard recommendations for conducting a meta-analyses study. The overall approach is clearly written in a cohesive manner. The topic is important and addresses an understudied area. The manuscript could be further enhanced if the authors address the following weaknesses.</p> <p>The introduction section could use a theoretical model or a framework to justify the focus on physical fitness/rehabilitation, its importance for this specific cancer population, and potential pathways between physical fitness, quality of life and other selected psychosocial outcomes, and clinical outcomes. Additionally, challenges in recommending and pursuing programs targeting physical fitness in this specific population should be thoroughly discussed. These issues contribute to the significance of this manuscript. Additionally the introduction needs a general discussion of what rehabilitation programs/interventions might work and what</p>
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	<p>might not work for this specific population given the demographic and clinical characteristics of this population (i.e., elderly patients with co-morbid conditions). Anticipated barriers to such programs should also be discussed and how this review might help provide potential solutions to such barriers should be included. The analyses section should provide more information about the proposed “future” meta-analyses. The authors mentioned that there will be a moderator analyses to identify certain characteristics of the interventions (timing, frequency, and duration), it is not clear how this moderation analyses will be conducted and whether potential interactions might exist between participants’ characteristics (e.g., age, urinary diversion type) and intervention characteristics. The discussion section is rather brief. Given that the manuscript focuses on describing the protocol and no data is included, this section could be better used to describe potential problems and solution to address potential limitations in this study. The authors should also describe potential implications for this manuscript for health care, research, and cancer survivorship.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewer 1

Congrats with the study proposal. Be aware of the study by Buffart et al from January 2017 which seems partly to cover your aims! Only a few comments

Response: Thank you very much for your careful assessment of this work.

We have added the recent publication of Buffart in our text. However, the impact of exercise was not specifically evaluated for bladder cancer patients. Since the morbidity of surgical intervention in these patients is high we doubt if we can extrapolate data from other tumor sites to this specific group of cancer patients as was addressed in the introduction part.

Below you can find our answers to the other suggestions/corrections.

#### Page 4:

Line 8-1 : Relative much information concerning BC although the scope is MIBC. It seems not relevant.

Response: We removed following sentences: ‘Worldwide, the age-standardized incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women. In 2012, the age-standardized mortality rate (per 100,000 person/years) was 3.2 for men and 0.9 for women’.

Moreover, it is difficult to imagine an enormous challenge considering the marginal increase in the incidence.

Response: We changed the sentence in a less convincingly statement:

‘Due to the growth of an aging population, it can be expected that the incidence of BC will rise in the near future’.

Line 26-28: Health Related Quality of Life or Quality of Life? There is a difference as pr. definition.

Response: Thank you for this remark. The correct term was ‘health related quality of life (HRQoL)’ and we have changed the sentence to the following definition of HRQoL: ‘the patients’ own perceptions of their health and ability to function encompassing physical, psychological, social, and spiritual dimensions’.

Line 41-43: An overall definition of rehabilitation may be useful?

Response: We added the following definition of rehabilitation coming from the WHO: “the use of all means aimed at reducing the impact of disabling and handicapping conditions at enabling people with

disabilities to achieve optimal social integration”.

Page 5:

Line 13-14: Reference number 16 - Cunningham? The ref. is not Cunningham, but Buffart 2013 and looking into the reference Cunningham appears – use the original reference

Response: This was adjusted.

Line 57: Define supervised ,, by whom and where ?

Response: This comment made us think that maybe it would be interesting to include both supervised (by a physiotherapist for example in a hospital) and non supervised interventions (at home without a supervisor). This way, we do not exclude interventions at forehand. So we removed the word ‘supervised’.

Page 7

Line 31: Still difficult with Cunningham – where is the original work?

Response: We have replaced the reference by the publication of Buffart cfr the remark above.

Line 55: The second time you mention PRO – maybe define it earlier on page 6

Response: This was added as suggested.

Page 8

Why don't you add muscle capacity, which seems to be a very precise measurement and already reported to be effective and evident in the literature? Especially with regards to the MIBC patients

Response: This was added as suggested:

2. Body composition assessed by height, weight, body mass index, muscle capacity, fat mass, lean body mass, thickness of skin folds, body fat, arm circumference, waist circumference, hip circumference or waist-hip ratio.

Page 11

Line 33: Moderator analysis? Another name for regression? You mention the lack of studies so maybe the list of analysis is very ambitious although it will be a break through

Response: We agree that this section was not clearly described. By moderator analysis we meant actually that we would do a subgroup analysis to identify potential moderators. The list is indeed very ambitious. Therefore, we chose the most relevant patient characteristics (age and urinary diversion type) and intervention characteristics (only exercised-based interventions, only psychosocial interventions or a combination).

The reason why we will not do a subgroup analysis based on timing, frequency and duration of the interventions, is the fact that we will not pool interventions in a meta analysis if we think that there is too much heterogeneity (in for example timing, frequency and duration) between the different interventions.

Reviewer 2

This is a very-well written protocol for a systematic review manuscript targeting physical fitness in survivors of muscle invasive bladder cancer patients. The authors did a very good job following standard recommendations for conducting a meta-analyses study. The overall approach is clearly written in a cohesive manner. The topic is important and addresses an understudied area. The manuscript could be further enhanced if the authors address the following weaknesses.

Response: Thank you very much for your careful assessment of this work. Below you can find our answers to your suggestions/corrections.

The introduction section could use a theoretical model or a framework to justify the focus on physical fitness/rehabilitation, its importance for this specific cancer population, and potential pathways between physical fitness, quality of life and other selected psychosocial outcomes, and clinical outcomes.

Response: Thank you very much for this valuable suggestion. We have rewritten the introduction part including a framework to make it clearer. Below you can find the section that we added to the introduction (page 5)(we also removed several sentences from the previous version of the manuscript, which you can see in the track changes in the word document):

'In order to explain how cancer rehabilitation interventions might work, the revised Wilson and Cleary Model for HRQoL will be used as a conceptual framework. This can be a useful framework to help explain the pathways between different patient outcomes. The model proposes five types of patient outcome measurements (biological function, symptoms, functional status, health perception and overall QOL), which have a causal relationship. This five patient outcome measurements can be influenced by individual and environment characteristics.

In the context of bladder cancer, morbidity associated with the disease and its treatment can lead to complications related to urinary diversion, fatigue, urinary incontinence or constipation, sexual dysfunction and psychological distress (symptoms). This can potentially lead to a loss of physical, social, psychological and role function which affects activities in daily life. As a consequence, the general health perceptions of the patient can be damaged which can finally lead to an overall impaired QOL. All of these outcomes can be influenced by environment and individual characteristics.

The provision of cancer rehabilitation can be seen as a physical environment characteristic. Since it has been proven in other cancer populations that cancer rehabilitation interventions have a positive influence on for example aerobic fitness, muscle capacity, fatigue and emotional distress, we can conclude, according to the revised Wilson and Cleary Model for HRQoL, that cancer rehabilitation interventions can have a positive influence on other patient outcomes such as HRQoL.'

Additionally, challenges in recommending and pursuing programs targeting physical fitness in this specific population should be thoroughly discussed. These issues contribute to the significance of this manuscript.

Response: We fully agree that this should be discussed. We added the following section (page 5):

'Individual characteristics, such as age and the associated increased risk of co morbidities, are important factors to take into account in bladder cancer patients. These characteristics are associated with poorer health such as functional and psychosocial declines. Although this supports the need for cancer rehabilitation, the older age of bladder cancer patients creates challenges in recommending rehabilitation interventions. Potential difficulties are the lack of social support in older patients and the need for extra time and resources to enroll these patients. Additionally, the high prevalence of urinary complications and problems with body image in bladder cancer patients can act as potential barriers to participate in exercise interventions.'

Additionally the introduction needs a general discussion of what rehabilitation programs/interventions might work and what might not work for this specific population given the demographic and clinical characteristics of this population (i.e., elderly patients with co-morbid conditions).

Response: As suggested, we added the following section (page 5-6):

'According to Karvinen et al., exercise interventions aimed at bladder cancer survivors should focus

on offering enjoyable activities, education on the benefits of regular exercise, enhancing activity levels in important others and targeting perceived barriers. They also note that adjuvant therapy, age and invasiveness of the tumor may affect exercise participation. Furthermore, bladder cancer survivors seem to be most interested in walking and home-based, individual exercises that are not supervised.'

Anticipated barriers to such programs should also be discussed and how this review might help provide potential solutions to such barriers should be included.

Response: This is indeed very important.

We added following section in the section: Why is it important to do this review (page 6):

'It should also be noticed that the provision of cancer rehabilitation is an often-neglected facet of cancer care in terms of health policy and infrastructure. Frequently reported barriers to rehabilitation interventions are the lack of expertise, inappropriate referrals by physicians, funding issues and availability of rehabilitation resources. The results of this review may increase the awareness of physicians and funders of the importance of cancer rehabilitation.'

The analyses section should provide more information about the proposed "future" meta-analyses. The authors mentioned that there will be a moderator analyses to identify certain characteristics of the interventions (timing, frequency, and duration), it is not clear how this moderation analyses will be conducted and whether potential interactions might exist between participants' characteristics (e.g., age, urinary diversion type) and intervention characteristics.

Response: We agree that this section was not clearly described.

By moderator analysis we meant actually that we would do a subgroup analysis to identify potential moderators. The list was very ambitious. Therefore, we chose the most relevant patient characteristics (age and urinary diversion type) and intervention characteristics (only exercised-based interventions, only psychosocial interventions or a combination).

The reason why we will not do a subgroup analysis based on timing, frequency and duration of the interventions, is the fact that we will not pool interventions in a meta analysis if we think that there is too much heterogeneity (in for example timing, frequency and duration) between the different interventions.

This is the section we changed (page 11-12) and hope that it is clearer in the current form:

'There will be an attempt to identify significant moderators, based on the most important demographical and clinical characteristics in this population. In order to do this, there will be a subgroup analysis for age and urinary diversion type. To prevent co-intervention bias, there will also be a subgroup analysis based on the type of intervention (only exercised-based interventions, only psychosocial interventions or a combination).'

The discussion section is rather brief. Given that the manuscript focuses on describing the protocol and no data is included, this section could be better used to describe potential problems and solution to address potential limitations in this study.

Response: As suggested we added strengths and limitations of the manuscript (page 12).

'This systematic review has several strengths. First, the overall approach of this review is consistent with the methodology described in the Cochrane Handbook for Systematic reviews of Interventions. Secondly, rehabilitation interventions are an innovative topic in the field of bladder cancer so this review ensures an absolute value. A third potential strength is the fact that MIBC is an actual problem because of the potentially rising incidence of MIBC due to the aging population.'

The results of this systematic review could also have potential limitations in terms of biased results due to the nature of exercise and psychosocial interventions. It is impossible for such interventions to blind participants and personnel. Therefore, 'blinding of participants and personnel' will not be taken into account in the risk of bias assessment because of the thought that this will not necessarily affect the study quality. On the other hand, attrition and adherence biases and selective reporting biases are other common concerns around high risk of bias that would affect the study quality. Therefore, it's important that the risk of bias assessment will be carried out very carefully to detect potential biases. Another limitation of this review could be the possible paucity of studies meeting the inclusion criteria.'

The authors should also describe potential implications for this manuscript for health care, research, and cancer survivorship.

Response: We added this in the discussion section (page 13).

'In spite of these anticipated limitations, it's important to conduct this review because of the expected implications for health care, research and survivorship. To date, there are no specific guidelines for exercise-based or psychosocial rehabilitation interventions for MIBC survivors. This systematic review is expected to provide guidance to the development of specific guidelines and evidence-based rehabilitation or survivorship programs for MIBC survivors. Development of such programs could have further implications for health care if they will be translated into daily clinical practice.

By identifying which interventions have a positive effect on patient outcomes and what underlying factors ensure the success of such rehabilitation interventions, new interventions can be developed that can contribute to further research. The positive influence of physical activity on survivorship is already suggested in different tumor types. The results of this systematic review can contribute to patient survivorship from the hypothesis that this positive association is also applicable in MIBC.'

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Bente Thoft Jensen Aarhus University Hospital Department of Urology Denmark
<b>REVIEW RETURNED</b>	04-Apr-2017

<b>GENERAL COMMENTS</b>	Doing a quick literature search I found that muscle capacity already have been shown( in a RCT) to be significantly improved by early exercise intervention and by offering this, RC patients are significantly earlier mobilized and able to independently perform activity of daily living compared to those without a systematic exercise intervention (another RCT) (PUBMED Jensen et al 2015 , 2016) Not more to add except from good luck
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<b>REVIEWER</b>	Mohamed, NE Mount Sinai School of Medicine
<b>REVIEW RETURNED</b>	11-Apr-2017

<b>GENERAL COMMENTS</b>	This is a valuable study that will enhance understanding of factors that influence muscle invasive bladder cancer patients' quality of life and follow-up care. The review will provide evidence for the efficacy of programs and interventions that are likely to improve patient-centered outcomes following cystectomy and urinary diversion. I full-heartedly recommend this manuscript for publication.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dear authors

Doing a quick literature search I found that muscle capacity already have been shown( in a RCT) to be significantly improved by early exercise intervention and by offering this, RC patients are significantly earlier mobilized and able to independently perform activity of daily living compared to those without a systematic exercise intervention (another RCT) (PUBMED Jensen et al 2015 , 2016)  
Not more to add except from good luck

Answer: Dear reviewer, this is indeed a valuable finding that certainly will be included in the systematic review itself.

Reviewer 2

This is a valuable study that will enhance understanding of factors that influence muscle invasive bladder cancer patients' quality of life and follow-up care. The review will provide evidence for the efficacy of programs and interventions that are likely to improve patient-centered outcomes following cystectomy and urinary diversion. I full-heartedly recommend this manuscript for publication.

Answer: Dear reviewer, thank you for this recommendation.