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)	EffectiveNess of a multimodal preHAbilitation program in patieNts with bladder canCEr undergoing radical cystectomy: protocol of the ENHANCE multicenter randomized controlled trial
AUTHORS	Akdemir, Emine; Sweegers, Maike; Vrieling, Alina; Rundqvist, Helene; Meijer, Richard; Leliveld-Kors, Annemarie; van der Heijden, Toine; Rutten, Vera; Koldewijn, Evert; Bos, Siebe; Wijburg, Carl; Marcelissen, Tom; Bongers, Bart; Retèl, Valesca; Van Harten, Wim; May, Anne; Groen, Wim; Stuiver, Martijn

VERSION 1 – REVIEW

REVIEWER	Jensen, Bente Aarhus Universitet
REVIEW RETURNED	27-Jan-2023

GENERAL COMMENTS	Dear authors It was with great pleasurer I read your protocol proposal. The study is a very important and I am looking forward to follow it!! My only comment is you should perhaps pay attention to the type of diversion while the complication profile differ substantially and perhaps also the surgical approach (robot assisted / intra -extra corporal creation of urine-diversion / open surgery

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Bente Jensen, Aarhus Universitet
Comments to the Author:
Dear authors
It was with great pleasurer I read your protocol proposal. The study is a very important and I am looking forward to follow it!! My only comment is you should perhaps pay attention to the type of diversion while the complication profile differ substantially and perhaps also the surgical approach (robot assisted / intra -extra corporal creation of urine-diversion / open surgery

We thank the reviewer for the compliment and for raising these important points. We have included the type of surgery (open vs robot-assisted) as a stratification factor during minimization and therefore this will be evenly distributed between the control and intervention groups. We will collect data on type of diversion and will consider exploring differences in effectiveness of prehabilitation between types of urine-diversion, if our results show differences in rate or type of complications. We have made the following changes to Table 1 (clean version p. 9) to specify the collection of data on type of urinary diversion.

Medical records: birth month and year, date of diagnosis, date and type of treatment, type of urinary diversion, tumor characteristics, ASA score, WHO score

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Alongside the changes we have made in response to the comments of the editor and reviewer, we have also corrected statements regarding eligibility and intervention duration, to be 3 to 6 weeks (instead of 4 to 6 weeks). In addition, we have added the exclusion criterion that patients will be excluded if they express an intention to follow an exercise program similar to the exercise intervention that is provided in the prehabilitation program, regardless of group assignment, to avoid contamination:

- *Patients are recruited from eight hospitals in The Netherlands and will be randomly (1:1) allocated to the intervention group receiving a structured multimodal prehabilitation program of approximately **3-6 weeks**, or to the control group receiving standard-of-care. (clean version p. 3)*
- *The intervention starts as soon as possible after baseline measurements and randomization, approximately **3-6 weeks** before surgery, and is continued until surgery. (clean version p. 10)*
- *Patients receive the physical exercise training program as described above for the remaining **3-6 weeks** before surgery. (clean version p. 12)*
- *Nutritional support starts at **3-6 weeks** before surgery for all patients. (clean version p. 12)*
- *Intensive counselling and nicotine replacement therapy is offered to all smoking patients in the **3-6 weeks** before surgery. (clean version p. 12)*
- ***Patients who express the intention to follow a similar exercise training program regardless of randomization outcome**, patients with severe cognitive or psychiatric disorders, patients with a contraindication to perform physical exercise training or a cardiopulmonary exercise test (CPET), and patients unable to read or understand the Dutch language will also be excluded. (clean version p. 7)*

We made the following changes to Figure 1:
- *Patients operated within **3 weeks***
- *Exclusion: **Intention to follow an exercise training program regardless of randomization outcome***

We have also added information on a planned exploratory moderation analysis regarding the impact of intervention duration on the outcome, by including an interaction term to the Poisson regression model. Currently, limited evidence is available regarding the optimal duration of a prehabilitation program and our study may provide preliminary results on this topic (clean version p. 16):

Exploratory analysis
Exploratory analyses will be performed to explore the moderating effect of intervention duration, and differences in effectiveness of the physical exercise training program between those who received neo-adjuvant chemotherapy and those who did not.

In addition, we included an acknowledgment to funders of our research institute (clean version p. 21):

Research at the Netherlands Cancer Institute is supported by institutional grants of the Dutch Cancer Society and of the Dutch Ministry of Health, Welfare and Sport.

Due to the changes we have made in response to the editor's and reviewer's comments, the manuscript now exceed the 4000-word count limit with 213 words, but we believe this has improved the quality of the manuscript. We hope that this will be acceptable.