PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Health promotion and cardiovascular risk reduction in people with spinal cord injury - physical activity, healthy diet and maintenance after discharge: study protocol for a prospective national cohort study and pre-post intervention study
AUTHORS	Holm, Nicolaj; Møller, Tom; Adamsen, Lis; Dalsgaard, Line; Biering-Sorensen, Fin; Schou, Lone

VERSION 1 - REVIEW

REVIEWER	Jasmin Ma Arthritis Research Canada/University of British Columbia, Canada
REVIEW RETURNED	16-May-2019

GENERAL COMMENTS	The authors present an ambitious project to evaluate the effects of a pragmatic education intervention on multiple health outcomes. As sub-studies, a prospective national survey of BMI will be conducted, in addition to test-retest reliability evaluations of VO2 peak and combined use of accelerometry and heart rate to measure PA. Of note, it is impressive the authors are accessing an in-patient population, which is greatly understudied in this population. Perhaps a product of the multiple studies included in this paper, my major concern is the current level of detail provided in the methods precludes the ability to understand the evidence-based rationale and rigour of the methods. Please see below for specific comments. Please note Page number references are to those provided in the footer of the PDF Introduction • As mentioned previously, perhaps a product of the admirable yet broad scope of the project, the introduction didn't lead me to understand what has been done to date in each of these areas and provide sufficient evidence or rationale that there is a gap. Specifically, how this addresses an area of need in PA and diet interventions in SCI (which there are a good number of; see Tomasone et al., 2018 in Psychology of Sport and Exercise) and measurement in SCI (there is certainly work to be done in this area but reference to what has been done and what the shortcomings are have not been made). I agree, that there are few studies that have evaluated the effects of PA interventions in the clinical setting, but would recommend reading van der Scheer et al., 2018 in Neurology for a recent list of exercise interventions and their effects on cardiometabolic health in SCI.

	Page 5: Patient involvement I commend you for involving end-users in your intervention design. It is unclear though, how end-users were specifically involved. How were interviews conducted (e.g., structured, semi-structured, focus group)? What was the general content of the questions asked? How was the interview data interpreted and analyzed, etc. Page 6: Participants and eligibility criteria • Sample size calculation? • What methods of recruitment will be used? Page 6: Primary Study • What factors did you consider in coming to the number 50-60 patients out of an approximate 70 possible participants? • Intervention: "patients will receive all the multimodal components, or parts of them" how will you record and assess fidelity to the intervention? The fidelity to which the practitioners administer the intervention and adherence to the intervention would be important to assess (I see in your discussion you mention using a checklist for participation in the education elements). • Is this intervention guided by theory or how did you decide upon the intervention content and delivery (i.e., rationale)? • Line 22: what is meant by 'targeted and strategic' • Line 29: what are these pre-determined time points? Page 8: Sub study 1 • Will participants in the historical control group be matched by e.g. level of injury, sex, previous PA levels, etc to the intervention group? Or what factors will you control for in your statistical analyses? Page 8: Sub Study 2 • Why is the testing equipment used selected based on completeness of injury and not level of injury as well or using their ASIA score? The Nu Step can be quite cumbersome and difficult to grade intensity, especially for high level tetraplegics (including incomplete). I understand the rationale for whole body exercise vs. solely upper body as is the case with the arm ergometer, however, it does not ensure completion of the test as results can still be peripherally limited using the Nustep. • What is the VO2 peak protocol? (for example, ramp, stage, W increase, stage duration, etc.) • Which pre-defined criteria are you using to support reaching VO2 peak? • What if participants don't reach VO2 peak in the second test? See Au et al., 2018 in Archives of Physical Medicine & Rehab- many participants with tetraplegia don't reach VT. Study 3 • What are the specifics of the set up for your accelerometers e.g., sampling frequency, epoch, minimum wear time, etc. • Individuals with level of injury at T6 and above have compromised sympathetic innervation of the heart (e.g., peak heart rate is affected), how will you account for this in your analyses? • What are the specifics of the calibration? Are you applying cutpoints to a given vector magnitude? What is the calibration procedure e.g., what activities will they be performing under what conditions?

	• How will this data between HR and accelerometry be triangulated? Page 9: • Line 27: There are international SCI-specific evidence-based guidelines now available that suggest for cardiometabolic health improvements, individuals with SCI should engage in 3x30 minutes of MVPA; see van der Scheer et al., 2018 in Neurology and Martin Ginis et al., 2018 in Spinal Cord. General Abstract Line 17-19: Unclear sentence Study design: what is meant by multi-modal?

REVIEWER	Armin Gemperli University of Lucerne, Switzerland
REVIEW RETURNED	18-May-2019

GENERAL COMMENTS	The protocol is well elaborated and extensive on the study conduct and its related operations. Since it observes effectiveness in a standard of care program, it is fair to refrain from many clinical trial elements; e.g. sample size determination. The protocol is strong on the outcomes, but rather weak on how these outcomes were finally synthesized into statistical evidence. The statistical approaches were determined and reproducible us such. Hence, the requirements of a study protocol were fulfilled. However, the statistical analysis were describe so superficially, that there is doubt that a competent study team will adhere to such a rudimental approach, once the rich data are available. E.g. the pre-post test design is composed of a simple paired t-test, that cannot account for the control group nor any other confounding factors. Here a ANCOVA approach is recommended (see Bonate: Analysis of the Pretest-Posttest Designs). The psychometric properties were hardly analyzed in a full statistical approach. If the approach will be conducted as explained, then it is a pity to go though all the efforts for such a minor analysis. An ITT analysis is suggested, but it is not clear how it could be conducted without attrition bias when no imputation is foreseen and considering the long duration between measurement time points. A note on data monitoring and that (or why) no interim analysis is planned is recommended to be added. The protocol is properly versioned; for the future I recommend to include more information on the current and previous versions in order to be able to follow the stage of the versions and recognize the specific changes made between amendments to the protocol.

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 1.

Page 5: Patient involvement I commend you for involving end-users in your intervention design. It is unclear though, how end-users were specifically involved. How were interviews conducted (e.g., structured, semi-structured, focus group)? What was the general content of the questions asked? How was the interview data interpreted and analyzed, etc. RESPONSE: SEE PAGE 8, Line 11-20 IN THE MAIN DOCUMENT

Page 6: Participants and eligibility criteria

 Sample size calculation? RESPONSE: SEE PAGE 8, line 27 and comment from reviewer 2.

 What methods of recruitment will be used? RESPONSE: SEE PAGE 8 line 23.

Page 6: Primary Study

 What factors did you consider in coming to the number 50-60 patients out of an approximate 70 possible participants? RESPONSE: SEE PAGE 9, line 13-14.

 Intervention: “patients will receive all the multimodal components, or parts of them” how will you record and assess fidelity to the intervention? The fidelity to which the practitioners administer the intervention and adherence to the intervention would be important to assess (I see in your discussion you mention using a checklist for participation in the education elements). RESPONSE: SEE PAGE 9, line 27-31

 Is this intervention guided by theory or how did you decide upon the intervention content and delivery (i.e., rationale)? RESPONSE: SEE PAGE 9.line 16-24

 Line 22: what is meant by ‘targeted and strategic’ RESPONSE: SEE PAGE 10,line 6-8

 Line 29: what are these pre-determined time points? RESPONSE: SEE PAGE 10, line 9-12

Page 8: Sub study 1

 Will participants in the historical control group be matched by e.g. level of injury, sex, previous PA levels, etc to the intervention group? Or what factors will you control for in your statistical analyses? RESPONSE: SEE PAGE 14, line 13-15

Page 8: Sub Study 2

 Why is the testing equipment used selected based on completeness of injury and not level of injury as well or using their ASIA score? The Nu Step can be quite cumbersome and difficult to grade intensity, especially for high level tetraplegics (including

incomplete). I understand the rationale for whole body exercise vs. solely upper body as

is the case with the arm ergometer, however, it does not ensure completion of the test

as results can still be peripherally limited using the Nustep. RESPONSE: SEE PAGE 11,line 29-33. I agree with your comment and the rationale is more as described i line 29-33 than ensuring completion of the test as previously stated.

 What is the VO2 peak protocol? (for example, ramp, stage, W increase, stage duration,

etc.)RESPONSE: SEE PAGE 11,line 12-22

 Which pre-defined criteria are you using to support reaching VO2 peak? RESPONSE: SEE PAGE 11, line 8

 What if participants don't reach VO2 peak in the second test? See Au et al., 2018 in

Archives of Physical Medicine & Rehab- many participants with tetraplegia don't reach

VT. RESPONSE: SEE PAGE 11, line 24-25. We do not believe it is feasible with more attempts in the clinical setting and we believe that two attempts will be sufficient to correct the wrong choice of protocol in the first attempt.

Study 3

 What are the specifics of the set up for your accelerometers e.g., sampling frequency,

epoch, minimum wear time, etc. RESPONSE: SEE PAGE 12, line 9-12

 Individuals with level of injury at T6 and above have compromised sympathetic

innervation of the heart (e.g., peak heart rate is affected), how will you account for this

in your analyses? RESPONSE: SEE PAGE 12,line 6-7

 What are the specifics of the calibration? Are you applying cutpoints to a given vector

magnitude? What is the calibration procedure e.g., what activities will they be

performing under what conditions?RESPONSE: SEE PAGE 12, line 2-6

 How will this data between HR and accelerometry be triangulated? RESPONSE: SEE PAGE 11, line 38-39

Page 9:

 Line 27: There are international SCI-specific evidence-based guidelines now available

that suggest for cardiometabolic health improvements, individuals with SCI should

engage in 3x30 minutes of MVPA; see van der Scheer et al., 2018 in Neurology and

Martin Ginis et al., 2018 in Spinal Cord. RESPONSE: We are familiar with them and will use them consequently SEE PAGE 7, line 1-3 and 12, 22-24.

General

Abstract Line 17-19: Unclear sentence

Study design: what is meant by multi-modal? We use several different methods to motivate/ facilitate behavioral changes trough for example feedback on VO2peak, BMI, blood samples, DXA etc.

RESPONSE TO REVIEWER 2

The psychometric properties were hardly analyzed in a full statistical approach. If the approach will be conducted as explained, then it is a pity to go though all the efforts for such a minor analysis.
RESPONSE: SEE PAGE 14, line 15-18 and line, 9-13.

An ITT analysis is suggested, but it is not clear how it could be conducted without attrition bias when no imputation is foreseen and considering the long duration between measurement time points.
RESPONSE: SEE PAGE 14, line 18-20

A note on data monitoring and that (or why) no interim analysis is planned is recommended to be added RESPONSE: SEE PAGE 14, line RESPONSE: SEE PAGE 14, line 26-28

VERSION 2 – REVIEW

REVIEWER	Jasmin Ma University of British Columbia/Arthritis Research Canada Canada
REVIEW RETURNED	13-Oct-2019

GENERAL COMMENTS	I am satisfied with the authors' responses to my comments. My only comment is the minimum wear time defined at 80% may be uncomfortable or unnecessary given the increased risk for skin breakdown in this population. It might be worth it to give them the option of taking the accelerator off at night and using standard criteria of minimum wear time of at least 10 hours/day. Note: It would be appreciated if you included in the response to reviewers specifically how you addressed the comments (e.g., copy and paste) rather than referring to page and line numbers. The referrals you made to the document didn't match.

VERSION 2 – AUTHOR RESPONSE

Response to reviewer 1.

Regarding comment on "Continuous measurements of the amount and intensity of PA will occur over 48 hours with sampling epochs every 15 seconds and a minimum wear-time of 80% [47]"

We appreciate your comment on the minimum wear time and acknowledge your point about the increased risk of skin break down in this population. Therefore we agree that it will be appropriate to offer the participants the opportunity to take off the accelerometer at night (or any other time) if it is uncomfortable. The 48 hours monitoring and minimum wear time of 80% is based on the work by Nightingale et al (2017) who found that a minimum of two consecutive days was required to estimate

moderate to vigorous physical activity intensities reliably in people with SCI using a wheelchair. In this study they also describe wear time to have a significant impact on total energy expenditure measured . When data obtained during a wear time of >80% was analyzed this impact was non-significant. In addition they believe that the strict wear time criteria used in their study can explain the few days required to reliably measure physical activity variables.

In our study the minimum wear time of 80% is not an absolute criterion. If wear time is less (e.g. due to discomfort), data will be analyzed anyway.

Our revision to the document (on p.12) is copy pasted below.

In order to reliably measure total energy expenditure (kcal/min) and the amount and intensity of PA the patients are instructed to wear the equipment for 48 hours. They are informed to take off the sensor (not the adhesive part) when bathing, but if they experience discomfort or skin irritation related to the equipment they can as well remove the adhesive part of the electrode. If they have impaired or absent sensation, they are recommended to take off the equipment when sleeping, and to check for skin irritation regularly, alternatively asking a nurse for help if they are not able to do this themselves. A period of 48 hours with sampling epochs every 15 seconds and a minimum wear-time of 80% is aimed for, and considered an appropriate wear time as described by Nightingale et al [47]. However, data from recordings with < 80% wear time will be analyzed as well.