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Protocol for evaluating cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021936
Article Type:	Protocol
Date Submitted by the Author:	26-Jan-2018
Complete List of Authors:	Withers, Thomas; University of Bedfordshire, Institute for Sport Science and Physical Activity Research, School of Sport Science and Physical Activity Croft, Louise; University of Bedfordshire, Institute for Sport Science and Physical Activity Research, School of Sport Science and Physical Activity Goosey-Tolfrey, Victoria L; Loughborough University, School of Sport, Exercise and Health Sciences, The Peter Harrison Centre for Disability Sport Dunstan, David; Baker Heart and Diabetes Institute; Australian Catholic University, Mary MacKillop Institute for Health Research Leicht, Christof; Loughborough University, School of Sport, Exercise and Health Sciences, The Peter Harrison Centre for Disability Sport Bailey, Daniel; University of Bedfordshire, Institute for Sport and Physical Activity Research, School of Sport Science and Physical Activity
Keywords:	physical activity, sedentary lifestyle, activity breaks, glucose, cardiovascular disease, spinal cord injury

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Manuscripts

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3 **Protocol for evaluating cardiovascular disease risk marker responses to breaking up**
4 **prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move**
5 **More (SCIMM) study**
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42
43 **Word count:** 2676

44
45 **Sources of funding:** This work is supported by Heart Research UK grant number
46 RG2655/17/18.

47
48 **Conflicts of interest:** None of the authors have declared any conflicts of interest.

49
50 **Study start date:** 19th May 2017

51 **Study end date:** 18th January 2019

1 **Abstract**

2 **Introduction:** Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD)
3 and could partly explain the increased prevalence of CVD in people with spinal cord injury
4 (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely
5 suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute
6 CVD risk marker response to breaking up prolonged sedentary time in people with SCI has
7 not been investigated. **Methods and analysis:** A randomised two-condition crossover trial
8 will compare: 1) breaking up prolonged sedentary time with 2 min moderate-intensity arm
9 crank activity every 20 min with 2) uninterrupted prolonged sedentary time (control) in people
10 with SCI. Outcomes will include acute effects on postprandial glucose, insulin, lipids and
11 blood pressure. Blood samples will be collected and blood pressure measured at regular
12 intervals during each 5.5 h condition. **Ethics and dissemination:** This study was approved
13 by the Cambridge South NHS Research Ethics Committee. The research will help determine
14 if breaking up prolonged sedentary time could be effective in lowering CVD risk in people
15 with SCI. The findings of the research will be published in a peer reviewed journal and
16 disseminated to relevant user groups. **Trial registration:** The study is registered as a clinical
17 trial on the ISRCTN register (trial ID: ISRCTN51868437).

19 **Strengths and limitations of this study**

- 20 • This is the first study to investigate cardiovascular disease risk marker responses to
21 breaking up prolonged sedentary time in individuals with paraplegia.
- 22 • This study adds to the limited literature on the acute cardiovascular disease risk
23 marker responses to intermittent physical activity in individuals with paraplegia.
- 24 • Due to the acute nature of the study, the long-term cardiovascular disease risk
25 marker responses to a chronic intervention will remain unknown.
- 26 • The cardiovascular disease risk marker responses to breaking up prolonged
27 sedentary time in people with tetraplegia still requires investigation.

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28 **Keywords:** physical activity; sedentary lifestyle; activity breaks; glucose; cardiovascular
29 disease; spinal cord injury

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30 Introduction

31 There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year
32 with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading
33 cause of death in individuals with SCI [3]. Traditional risk factors for CVD include impaired
34 glucose tolerance, central obesity, high triglycerides, low high-density lipoprotein cholesterol
35 (HDL), and high blood pressure. The clustering of ≥ 2 and ≥ 3 risk factors is prevalent in 87%
36 and 72% of SCI individuals, respectively [4], which is markedly higher compared with the
37 able-bodied population [5].

38
39 Postprandial glucose and lipid concentrations are strong independent predictors of future
40 CVD incidence, even in those without diabetes [6]. There is a dose-response relationship
41 between postprandial glucose area under the curve (AUC) and CVD risk, while progression
42 of carotid atherosclerosis can be prevented by control of postprandial glucose
43 concentrations [7, 8]. It is thus pertinent to identify interventions to reduce postprandial
44 glucose and lipid responses in individuals with SCI to reduce their CVD risk.

45
46 Physical activity guidelines have been developed specifically for this population that
47 recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA)
48 three times per week for CVD health benefits [9]. Reduced levels of physical activity are
49 proposed to largely account for the increased CVD risk in SCI [10]; it is estimated that 50%
50 of this population engage in no leisure-time physical activity whatsoever [11]. However,
51 sedentary behaviour (i.e. any waking behaviour in a sitting, reclining or lying posture with low
52 energy expenditure [12]), is now recognised as being a significant CVD risk factor in the
53 able-bodied population, independent of MVPA [13]. Experimental studies in able-bodied
54 individuals have reported an acute reduction in postprandial glucose, insulin, triglycerides
55 and blood pressure in response to breaking up prolonged sedentary time with 2 min bouts of
56 light or moderate-intensity walking every 20 min [14-17]. No research has examined whether

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3 57 postprandial CVD risk marker responses are attenuated in response to breaking up
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5 58 prolonged sedentary time in individuals with SCI.
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9 60 The primary aim of this study is therefore to compare the acute CVD risk marker responses
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11 61 in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted
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13 62 sedentary time. It is hypothesised that breaking up prolonged sedentary time will result in
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15 63 favourable CVD risk marker responses compared with uninterrupted sedentary time in
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17 64 individuals with paraplegia.
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20 66 **Methods and analysis**

21 67 *Study design*

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24 68 A randomised two-condition crossover design will be used in accordance with the SPIRIT
25
26 69 statement [18]. The study is registered as a clinical trial on the ISRCTN register (trial ID:
27
28 70 ISRCTN51868437). The study schedule can be seen in Table 1. All research will take place
29
30 71 at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary
31
32 72 measures, participants will complete two experimental conditions in randomised order. The
33
34 73 conditions will be separated by ≥ 6 days to eliminate any potential carryover effects.
35
36 74 Condition order will be randomised by a researcher independent from the study using
37
38 75 computer generated random numbers (block randomisation with balanced block sizes).
39

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42 77 Insert Table 1 about here.
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45 79 *Participants*

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47
48 80 *Inclusion criteria:* Males and females aged 18-60 years; chronic SCI (≥ 1 year since injury);
49
50 81 individuals with a traumatic SCI below Thoracic level 6 (mid to low level paraplegia);
51
52 82 individuals with a non-traumatic SCI (as defined within the International Spinal Cord Injury
53
54 83 Data Sets for non-traumatic SCI [19]) that present with mid to low level paraplegia.
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56 84 Individuals who express an interest in taking part in the study will be required to indicate their
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85 spinal cord lesion level and completeness of injury via a questionnaire prior to preliminary
86 measures. Participants will be encouraged to obtain relevant information from a medical
87 professional if they are unaware of their injury level.

88

89 *Exclusion criteria:* individuals who regularly engage in >300 min/week of MVPA; history of
90 severe cardiovascular complications; hypotension (resting blood pressure <90/60 mmHg);
91 body mass index >45 kg/m², a history of autonomic dysreflexia; pregnancy; taking glucose
92 lowering medication; smokers; diagnosed diabetes, renal failure, liver disease, major illness,
93 or other health issues that may limit ability to perform the physical activity protocols.

94

95 *Recruitment*

96 Participants will be recruited through organisations and charities that promote physical
97 activity, health and wellbeing for individuals with SCI; the National Spinal Injuries Centre,
98 Stoke Mandeville Hospital, Buckinghamshire NHS Healthcare Trust; and local sport and
99 activity clubs. Mail outs, social media, information on websites, posters, flyers, and visits
100 from the research team will be used to provide information on the study to potentially eligible
101 individuals who can then express their interest to the research team in taking part in the
102 study. Written informed consent will be obtained by a member of the research team prior to
103 participation in any testing protocols. As an incentive, participants will received a £25
104 shopping gift voucher for each main condition they complete and will have all travel
105 expenses paid.

106

107 *Preliminary measures*

108 Participants will attend a preliminary testing session where they will have body mass
109 measured using wheelchair double beam scales (300 series; Marsden, London, UK) and
110 body fat% measured using dual-energy x-ray absorptiometry (DXA; GE Medical Systems;
111 Chalfont St Giles, UK) in line with previous research [20]. During DXA measures,

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3 112 participants will be positioned as closely as possible to standard protocols and Velcro
4
5 113 restraints will be fastened around the participant's knees and ankles to maintain correct
6
7 114 position of the legs during scanning. Participants will be offered a wedge to be used as a
8
9 115 pillow for comfort. Waist circumference will be measured using International Standards for
10
11 116 Anthropometric Assessment (ISAK) guidelines [21, 22]. These measures will be taken in the
12
13 117 standing position for participants who are able to maintain this posture and in a supine
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15 118 position for participants who are not able to stand [23]. Resting blood pressure will be
16
17 119 measured on the left arm, while seated, three times after the participant has rested for 5 min
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19 120 with the lowest readings being recorded. Following this, participants will be familiarised with
20
21 121 use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [24]. They will then cycle
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23 122 using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power
24
25 123 output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour
26
27 124 research [14, 25]. Participants will be asked to cycle at ~70 rpm during the test. The test will
28
29 125 start at a low intensity (~20 Watts), which will gradually increase until an RPE of 13 has been
30
31 126 attained. The test is expected to take no longer than 15 min. The intensity that corresponds
32
33 127 to an RPE of 13 during the test will be recorded for each participant and used for the
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35 128 physical activity breaks described in the respective main condition below. The use of the
36
37 129 Borg 6-20 RPE scale is highly reproducible in individuals with SCI to determine physical
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39 130 activity intensity [26].

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42 132 *Experimental protocol*

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44 133 **Error! Reference source not found.** shows the experimental protocol. Participants will be
45
46 134 instructed to refrain from caffeine, alcohol and exercise for 48 h prior to each experimental
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48 135 condition. They will also be provided with a food diary and digital weighing scales to record
49
50 136 volume and timings of all food and liquids consumed in the 24 h period prior to the first
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52 137 experimental condition. Participants will be asked to replicate their diet the day prior to the
53
54 138 subsequent experimental condition [27]. On condition days, participants will attend in the
55
56 139 morning following an overnight fast and avoid active travel to the laboratory. Upon arrival,

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3 140 resting blood pressure will be measured after 5 min rest; two measures will be taken and the
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5 141 lowest of these recorded. A fasting capillary blood sample will then be collected. Participants
6
7 142 will commence the 5.5 h condition period following consumption of a standardised breakfast.
8
9 143 The two experimental conditions are as follows:

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13 145 1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their
14
15 146 wheelchair or a standard chair at a desk during this condition.

16
17 147 2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will
18
19 148 complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using
20
21 149 the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical
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23 150 activity.

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27 152 Figure 1 about here.

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30
31 154 An RPE of 13 for the physical activity intensity was selected in line with previous research
32
33 155 [14, 28] and the Borg 6-20 RPE scale may be used to assess and regulate upper-body
34
35 156 physical activity at moderate-to-vigorous intensity in adults with chronic SCI [26]. Moderate-
36
37 157 intensity physical activity was selected as it is well-tolerated, can be performed safely, and is
38
39 158 recommended for health risk reduction in individuals with SCI [9, 29].

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43 160 Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during
44
45 161 each condition. Except during the activity bouts, participants will remain inactive and only
46
47 162 leave their desk to void and consume standardised meals in a kitchen adjacent to the test
48
49 163 laboratory; participants will be aided by a member of the research team when moving to
50
51 164 these locations so that they remain inactive. A researcher will be present to ensure
52
53 165 compliance with protocols throughout all conditions.

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57 167 *Meal and water consumption*

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3 168 Standardised meals will be consumed immediately prior to the start of each experimental
4
5 169 condition and at 3 h, each providing 30% of estimated daily energy requirements for each
6
7 170 participant [30]. Participants will be asked to consume each meal within a 15 min time
8
9 171 period. The time taken to consume the meals will be recorded for the first condition and
10
11 172 participants will be asked to replicate this time as closely as possible in the subsequent
12
13 173 condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice
14
15 174 (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted
16
17 175 crisps and apple (54% carbohydrate, 34% fat, 13% protein). This macronutrient composition
18
19 176 of meals was chosen as it is generally representative of UK guidelines for a balanced diet
20
21 177 [31]. The glycaemic index for these breakfast and lunch meals is 43 and 72, respectively.
22
23 178 Glycaemic index values for each food item were obtained from the International Tables of
24
25 179 Glycaemic Index and Glycaemic Load Values 2008 [32] and meal glycaemic index was
26
27 180 calculated using weighted means of the glycaemic index values for the component foods
28
29 181 [33]. Water will be available ad libitum during the first condition and this volume of intake will
30
31 182 be provided at standardised regular intervals in the subsequent condition.

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34 184 *Blood collection and biochemistry*

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36 185 Finger prick blood samples will be collected into two EDTA-containing microvettes
37
38 186 (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120,
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40 187 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity
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42 188 bouts in SED-ACT. At each time point, approximately 600 μ L of whole blood will be
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44 189 collected. Blood glucose concentrations will be analysed immediately using the YSI 2300
45
46 190 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μ L of
47
48 191 blood from one microvette. Additional 30 μ L volumes of whole blood will be aliquoted onto
49
50 192 two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the
51
52 193 measurement of triglyceride and HDL concentrations using the Reflotron Plus system
53
54 194 (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood (\sim 490 μ L) will be

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3 195 centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK)
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5 196 and the plasma then stored at -80°C. An enzyme-linked immunosorbent assay kit will be
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7 197 used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).
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10 199 *Blood pressure*

12 200 Blood pressure will be measured at baseline as described above followed by single readings
13
14 201 taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly
15
16 202 activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory
17
18 203 blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).
19
20 204

22 205 *Study outcomes*

24 206 *Primary outcome:* the primary outcome for the study is within-participant, between condition
25
26 207 postprandial glucose net incremental area under the curve (iAUC) [6]. *Secondary outcomes:*
27
28 208 these include within-participant, between condition mean systolic and diastolic blood
29
30 209 pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC and
31
32 210 total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit
33
34 211 comparisons across previous studies. *Feasibility measures:* to assess feasibility of the trial,
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36 212 participant dropout, number of experimental sessions completed, fatigue at the beginning
37
38 213 and end of each day rated on an 11 point (0-10) Visual Analogue Scale (VAS), and the
39
40 214 degree of difficulty in completing the experimental conditions rated on an 11 point (0-10)
41
42 215 VAS will be recorded. Participants will also complete the Physical Activity Enjoyment Scale
43
44 216 [34] at the end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [35]
45
46 217 (“Enjoyment”) 20 min after the last activity bout in the SED-ACT condition. Participants will
47
48 218 also report on the same scale how enjoyable they would find it to engage in this form of
49
50 219 physical activity most days of the week in the coming month (“Expected enjoyment”).
51
52 220 *Psychological outcomes:* determinants of sedentary behaviour will be measured based on
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54 221 the COM-B [36] and the theory of planned behaviour using standardised wording formats
55
56 222 [37] that will include overcoming barriers (self-efficacy/perceived behavioural control),
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3 223 attitudes, intentions and action planning. The following questionnaires will be completed by
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5 224 participants at baseline and at the end of each experimental condition: sedentary behaviour
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7 225 self-efficacy using an adapted version of the Schwarzer et al. [38] Physical Exercise Self-
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9 226 Efficacy Scale; current mood using the short Positive and Negative Affect Scale [39];
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11 227 psychological wellbeing using the National Wellbeing Measurement [40]; and the Warwick
12
13 228 Edinburgh Mental Well-Being Scale [41].

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16 230 *Sample size calculations*

17
18 231 Sample size calculations were performed using GPower [42]. Previous research reported a
19
20 232 16% reduction (effect size, $F=0.61$) in 5 h postprandial glucose total AUC when breaking up
21
22 233 prolonged sedentary time with 2 min light-intensity walking every 20 min versus
23
24 234 uninterrupted sitting in able-bodied participants [16]. As this study will use arm cranking
25
26 235 (localised muscular contractions) as opposed to walking where a larger muscle mass is
27
28 236 required, a smaller effect may be observed. Based on this, it was estimated that 14
29
30 237 participants would be required for this complete two-treatment crossover design to detect a
31
32 238 smaller minimum intervention effect of 10% with a within-person correlation of 0.6, 80%
33
34 239 power, and an α of 0.05. To allow for potential withdrawals, a total of 20 participants will be
35
36 240 recruited.

37
38 241

39 242 *Statistical analysis*

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41
42 243 Linear mixed models will be used to determine differences in the primary and secondary
43
44 244 outcome variables between the conditions. All models will adjust for potential covariates
45
46 245 explaining residual outcome variances. Statistical significance will be accepted as $p<0.05$.
47
48 246 Cohens' d effect sizes will be calculated to describe the magnitude of differences between
49
50 247 conditions [43].

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3 249 **Ethics and dissemination**

4 250 This study was approved on the 19th May 2017 by the Cambridge South NHS Research
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6 251 Ethics Committee (reference 17/EE/0076).
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10 253 The findings of this research will be disseminated to lay, academic, practice, and policy-
11
12 254 based audiences via presentation at conference proceedings; publication in a peer review
13
14 255 journal; websites, newsletters, and social media; and summary reports to policy makers and
15
16 256 clinical care partners.
17

18 257

19
20 258 **Acknowledgements:** The authors would like to thank Dr Jan van der Scheer for providing
21
22 259 his advice on the design of the study protocol.
23

24 260

25
26 261 **Author contributions**

27 262 DB and LC conceptualised the study.

28
29 263 TW, LC, VT, DD, CL, and DB contributed to the design of the study protocol.

30
31 264 TW drafted the manuscript.

32
33 265 TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and
34
35 266 approved the final version.
36
37

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39
40 268 **Funding statement**

41 269 This work is supported by Heart Research UK grant number RG2655/17/18.

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44
45 271 **Conflicts of interest**

46 272 None of the authors have declared any conflicts of interest.

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Table 1. Study schedule

Visit	Over phone/ email	1		2		3
Activity	Eligibility screening	Preliminary visit and randomisation to experimental condition order	≥6 day washout	Experimental condition A or B	≥6 day washout	Experimental condition A or B

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3 **Figure captions**
4

5 **Figure 1** Schematic of experimental protocol.
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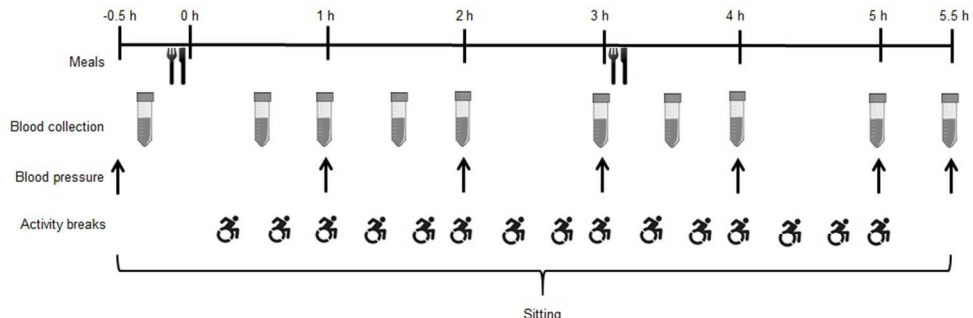


Figure 1

259x96mm (96 x 96 DPI)

Peer review only



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___2___
	2b	All items from the World Health Organization Trial Registration Data Set	___2___
Protocol version	3	Date and version identifier	___NA___
Funding	4	Sources and types of financial, material, and other support	___1___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___12___
	5b	Name and contact information for the trial sponsor	___NA___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___12___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___NA___

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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8

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3	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____11_____
4				
5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____6_____
6				
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8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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12	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____5_____
13				
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17	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____5_____
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____5_____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____NA_____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
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31 **Methods: Data collection, management, and analysis**

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33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____7-11_____
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____6_____
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3 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality _____11_____

4 (eg, double data entry; range checks for data values). Reference to where details of data management

5 procedures can be found, if not in the protocol

6

7 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the _____11_____

8 statistical analysis plan can be found, if not in the protocol

9

10 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) _____NA_____

11

12 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any

13 statistical methods to handle missing data (eg, multiple imputation) _____NA_____

14

15 **Methods: Monitoring**

16

17 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of _____NA_____

18 whether it is independent from the sponsor and competing interests; and reference to where further details

19 about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not

20 needed

21

22 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim _____NA_____

23 results and make the final decision to terminate the trial

24

25 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse _____NA_____

26 events and other unintended effects of trial interventions or trial conduct

27

28 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent _____NA_____

29 from investigators and the sponsor

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31

32 **Ethics and dissemination**

33

34 Research ethics 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval _____12_____

35 approval

36

37 Protocol 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, _____5_____

38 amendments analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,

39 regulators)

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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____6_____
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
7				
8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____NA_____
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____12_____
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____NA_____
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____12_____
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA_____
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____5_____
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29	Appendices			
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31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____9_____
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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BMJ Open

Cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) randomised crossover laboratory trial protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021936.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Apr-2018
Complete List of Authors:	Withers, Thomas; University of Bedfordshire, Institute for Sport Science and Physical Activity Research, School of Sport Science and Physical Activity Croft, Louise; University of Bedfordshire, Institute for Sport Science and Physical Activity Research, School of Sport Science and Physical Activity Goosey-Tolfrey, Victoria L; Loughborough University, School of Sport, Exercise and Health Sciences, The Peter Harrison Centre for Disability Sport Dunstan, David; Baker Heart and Diabetes Institute; Australian Catholic University, Mary MacKillop Institute for Health Research Leicht, Christof; Loughborough University, School of Sport, Exercise and Health Sciences, The Peter Harrison Centre for Disability Sport Bailey, Daniel; University of Bedfordshire, Institute for Sport and Physical Activity Research, School of Sport Science and Physical Activity
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Public health
Keywords:	physical activity, sedentary lifestyle, activity breaks, glucose, cardiovascular disease, spinal cord injury

SCHOLARONE™
Manuscripts

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3 **Cardiovascular disease risk marker responses to breaking up prolonged sedentary**
4 **time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM)**
5 **randomised crossover laboratory trial protocol**
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43 **Word count:** 3531

44
45 **Sources of funding:** This work is supported by Heart Research UK grant number
46 RG2655/17/18.

47
48 **Conflicts of interest:** None of the authors have declared any conflicts of interest.
49

50 **Study start date:** 19th May 2017

51 **Study end date:** 18th January 2019
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1 **Abstract**

2 **Introduction:** Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD)
3 and could partly explain the increased prevalence of CVD in people with spinal cord injury
4 (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely
5 suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute
6 CVD risk marker response to breaking up prolonged sedentary time in people with SCI has
7 not been investigated. **Methods and analysis:** A randomised two-condition laboratory
8 crossover trial will compare: 1) breaking up prolonged sedentary time with 2 min moderate-
9 intensity arm crank activity every 20 min, with 2) uninterrupted prolonged sedentary time
10 (control) in people with SCI. Outcomes will include acute effects on postprandial glucose,
11 insulin, lipids and blood pressure. Blood samples will be collected and blood pressure
12 measured at regular intervals during each 5.5 h condition. **Ethics and dissemination:** This
13 study was approved by the Cambridge South NHS Research Ethics Committee. This
14 research will help determine if breaking up prolonged sedentary time could be effective in
15 lowering CVD risk in people with SCI. The findings of the research will be published in a peer
16 review journal and disseminated to relevant user groups. **Trial registration:** The study is
17 registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437).

19 **Strengths and limitations of this study**

- 20 • This study uses a randomised crossover design to investigate, for the first time,
21 cardiovascular disease risk marker responses to breaking up prolonged sedentary
22 time in individuals with paraplegia.
- 23 • Regular collection of blood samples will permit robust time course and incremental
24 area under the curve calculations for primary and secondary outcomes.
- 25 • Due to the acute nature of the study, the long-term cardiovascular disease risk
26 marker responses to a chronic intervention will remain unknown.

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27 • The cardiovascular disease risk marker responses to breaking up prolonged
28 sedentary time in people with tetraplegia still requires investigation.

29
30 **Keywords:** physical activity; sedentary lifestyle; activity breaks; glucose; cardiovascular
31 disease; spinal cord injury

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32 Introduction

33 There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year
34 with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading
35 cause of death in individuals with SCI [3] and this population have a significantly increased
36 risk of heart disease and stroke compared with able-bodied individuals [4]. Traditional risk
37 factors for CVD include impaired glucose tolerance, central obesity, high triglycerides, low
38 high-density lipoprotein cholesterol (HDL), and high blood pressure. These risk factors often
39 exacerbate significantly as a consequence of SCI [5] and a plethora of research has
40 documented impaired glucose tolerance and adverse lipid profiles in individuals with SCI [5,
41 6]. The clustering of ≥ 2 and ≥ 3 risk factors is prevalent in 87% and 72% of SCI individuals,
42 respectively [7], which is markedly higher compared with the able-bodied population [8]. This
43 milieu of metabolic disturbances after SCI may be due to increases in body fat resulting from
44 an imbalance in energy intake and expenditure [5]. Excess fat accumulation, particularly in
45 the visceral region, is associated with inflammation that is causal in glucose intolerance and
46 dyslipidaemia [5, 9] thus promoting atherogenesis that would increase the risk of CVD in this
47 population [10].

48
49 Postprandial glucose and lipid concentrations are strong independent predictors of future
50 CVD incidence, even in those without diabetes [11]. There is a dose-response relationship
51 between postprandial glucose area under the curve (AUC) and CVD risk, while progression
52 of carotid atherosclerosis can be prevented by attenuation of postprandial glucose
53 concentrations [12, 13]. Impaired postprandial glucose metabolism was observed in 50%
54 and 62% of individuals with paraplegia and tetraplegia, respectively, compared with 18% in
55 able-bodied individuals [6]. This impaired glucose intolerance in SCI is characterised by
56 hyperinsulinaemia, which suggests that there is tissue level resistance to insulin [14]. In
57 paraplegic individuals, there appears to be no difference in postprandial glucose responses
58 between those with complete versus incomplete lesions [15, 16]. Although postprandial
59 lipaemic responses have not been compared between individuals with complete and

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3 60 incomplete lesions, fasting lipid levels do not differ between these groups [17]. There does,
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5 61 however, appear to be an exaggerated postprandial lipaemic response in individuals with
6
7 62 paraplegia compared with able-bodied individuals [18]. These observations are of potential
8
9 63 concern as the high dietary intake of carbohydrate and fat in individuals with SCI [19] may
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11 64 lead to repeated exaggerated elevations in glucose and lipids following food intake. It is thus
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13 65 pertinent to identify interventions to reduce postprandial glucose and lipid responses in
14
15 66 individuals with SCI to reduce their CVD risk.

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17 67
18
19 68 Physical activity guidelines have been developed specifically for this population that
20
21 69 recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA)
22
23 70 three times per week for CVD health benefits [20]. However, it is estimated that 37 to 50% of
24
25 71 this population engage in no leisure-time physical activity whatsoever [21, 22]. Reduced
26
27 72 levels of physical activity are proposed to largely account for the increased CVD risk in SCI
28
29 73 with reduced levels of leisure-time physical activity associated with increased body fat,
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31 74 insulin resistance, and systolic blood pressure [22, 23]. However, sedentary behaviour (i.e.
32
33 75 any waking behaviour in a sitting, reclining or lying posture with low energy expenditure
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35 76 [24]), is now recognised as being a significant CVD risk factor in the able-bodied population,
36
37 77 independent of MVPA [25]. Experimental studies in able-bodied individuals have reported an
38
39 78 acute reduction in postprandial glucose, insulin, triglycerides and blood pressure in response
40
41 79 to breaking up prolonged sedentary time with 2 min bouts of light or moderate-intensity
42
43 80 walking every 20 min [26-29]. However, no research has examined whether postprandial
44
45 81 CVD risk marker responses are attenuated in response to breaking up prolonged sedentary
46
47 82 time in individuals with SCI.

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50
51 84 The primary aim of this study is therefore to compare the acute CVD risk marker responses
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53 85 in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted
54
55 86 sedentary time. The CVD risk markers that will be studied include postprandial glucose
56
57 87 (primary outcome), insulin and lipids, and systolic and diastolic blood pressure (secondary

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2
3 88 outcomes) based on evidence that these markers predict CVD outcomes and are adversely
4
5 89 affected by SCI. It is hypothesised that breaking up prolonged sedentary time will result in
6
7 90 favourable CVD risk marker responses compared with uninterrupted sedentary time in
8
9 91 individuals with paraplegia. This could identify a novel strategy for the prevention of CVD in
10
11 92 SCI that would warrant further evaluation.

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14 94 **Methods and analysis**

15 95 *Study design*

16
17 96 A randomised two-condition crossover design will be used in accordance with the SPIRIT
18
19 97 statement [30]. The study is registered as a clinical trial on the ISRCTN register (trial ID:
20
21 98 ISRCTN51868437). The study schedule can be seen in Figure 1. All research will take place
22
23 99 at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary
24
25 100 measures, participants will complete two experimental conditions in a randomised order. The
26
27 101 conditions will be separated by ≥ 6 days to eliminate any potential carryover effects.
28
29 102 Condition order will be randomised by a researcher independent from the study using
30
31 103 computer generated random numbers (block randomisation with balanced block sizes).
32
33 104

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35
36 105 Figure 1 about here.

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38 106

39 107 *Participants*

40
41 108 *Inclusion criteria:* Males and females aged 18-60 years; chronic SCI (≥ 1 year since injury);
42
43 109 individuals with a traumatic SCI below T5 (mid to low level paraplegia); individuals with a
44
45 110 non-traumatic SCI (as defined by the International Spinal Cord Injury Data Sets for non-
46
47 111 traumatic SCI [31]) that present with mid to low level paraplegia. Including only individuals
48
49 112 with injuries below T5 will ensure sympathetic innervation to the major organs at the T5 level
50
51 113 so that heart rate and catecholamine responses would be unaffected by injury [32] and thus
52
53 114 minimise the potential that innervation variations could have on the study outcomes.
54
55 115 Paraplegic individuals who have complete or incomplete lesions will be included based on
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2
3 116 evidence that these groups do not differ with respect to postprandial glucose metabolism
4
5 117 (primary outcome) [15, 16]. Individuals who express an interest in taking part in the study will
6
7 118 be required to indicate their spinal cord lesion level and completeness of injury via a
8
9 119 questionnaire and asked to provide the research team with a copy of medical records to
10
11 120 confirm injury level and ASIA impairment scale classification prior to preliminary measures.

12
13 121

14 122 *Exclusion criteria:* individuals who regularly engage in >300 min/week of MVPA as such high
15
16 123 levels of physical activity may offset the detrimental association of sedentary time with health
17
18 124 outcomes [33]; history of severe cardiovascular complications; hypotension (resting blood
19
20 125 pressure <90/60 mmHg); body mass index >45 kg/m²; a history of autonomic dysreflexia;
21
22 126 pregnancy; taking glucose lowering medication; smokers; diagnosed diabetes, renal failure,
23
24 127 liver disease, major illness, or other health issues that may limit ability to perform the
25
26 128 physical activity protocols.

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30 130 *Recruitment*

31
32 131 Participants will be recruited through organisations and charities relevant to individuals with
33
34 132 SCI, including the National Spinal Injuries Centre, Stoke Mandeville Hospital,
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36 133 Buckinghamshire NHS Healthcare Trust; local sport and activity clubs; and local community
37
38 134 groups. Mail outs, social media, information on websites, posters, flyers, and visits from the
39
40 135 research team will be used to provide information on the study to potentially eligible
41
42 136 individuals who can then express their interest to the research team in taking part in the
43
44 137 study. Written informed consent will be obtained by a member of the research team prior to
45
46 138 participation in any testing protocols (see supplementary file). As an incentive, participants
47
48 139 will receive a £25 shopping gift voucher for each main condition they complete and will have
49
50 140 all travel expenses paid.

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52 141

53 54 142 *Preliminary measures*

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3 143 Participants will attend a preliminary testing session where they will have body mass
4
5 144 measured using wheelchair double beam scales (300 series; Marsden, London, UK).
6
7 145 They will also have body fat and lean tissue mass (and percent) determined for the
8
9 146 whole body and regionally via whole-body scans using dual-energy x-ray absorptiometry
10
11 147 (DXA; GE Medical Systems; Chalfont St Giles, UK) in line with previous research [34-36].
12
13 148 During DXA measures, participants will be positioned as closely as possible to standard
14
15 149 protocols and Velcro restraints will be fastened around the participants' knees and ankles to
16
17 150 maintain correct position of the legs during scanning. Participants will be offered a wedge to
18
19 151 be used as a pillow for comfort. Waist circumference will be measured using International
20
21 152 Standards for Anthropometric Assessment (ISAK) guidelines [37, 38]. These measures will
22
23 153 be taken in the standing position for participants who are able to maintain this posture and in
24
25 154 a supine position for participants who are not able to stand [38]. Resting blood pressure will
26
27 155 be measured on the left arm, while seated, three times after the participant has rested for 5
28
29 156 min with the lowest readings being recorded. Following this, participants will be familiarised
30
31 157 with use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [39]. They will then cycle
32
33 158 using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power
34
35 159 output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour
36
37 160 research [26, 40]. Participants will be asked to cycle at ~70 rpm during the test. The test will
38
39 161 start at a low intensity (~20 Watts) and the participants will then indicate their RPE at 1 min
40
41 162 intervals. The resistance will then be increased by 5-20 Watts based on the participants'
42
43 163 RPE until an RPE of 13 has been achieved, at which point the test will be terminated. The
44
45 164 test is expected to take no longer than 15 min. The intensity that corresponds to an RPE of
46
47 165 13 during the test will be recorded for each participant and used for the physical activity
48
49 166 breaks described in the respective main condition below. The use of the Borg 6-20 RPE
50
51 167 scale has acceptable validity in individuals with SCI to determine physical activity intensity
52
53 168 [41]. This method is also suggested as a practical approach for health care professionals
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3 169 and scientists as oxygen consumption testing equipment is costly and not available in many
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5 170 rehabilitation centres and community settings [41].
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8
9 172 *Experimental protocol*

10
11 173 Figure 2 shows the experimental protocol. Participants will be instructed to refrain from
12
13 174 caffeine, alcohol and exercise for 48 h prior to each experimental condition. They will also be
14
15 175 provided with a food diary and digital weighing scales to record volume and timings of all
16
17 176 food and liquids consumed in the 24 h period prior to the first experimental condition.
18
19 177 Participants will be asked to replicate their diet the day prior to the subsequent experimental
20
21 178 condition [42]. On condition days, participants will attend in the morning following an
22
23 179 overnight fast and avoid active travel to the laboratory. Upon arrival, resting blood pressure
24
25 180 will be measured after 5 min rest; two measures will be taken and the lowest of these
26
27 181 recorded. A fasting capillary blood sample will then be collected. Participants will commence
28
29 182 the 5.5 h condition period following consumption of a standardised breakfast. The two
30
31 183 experimental conditions are as follows:

32 184

- 34 185 1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their
35
36 186 wheelchair or a standard chair at a desk during this condition.
37
38 187 2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will
39
40 188 complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using
41
42 189 the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical
43
44 190 activity.
45

46 191

48 192 Figure 2 about here.
49

50 193

52 194 The SED-ACT protocol was selected based on previous research that reported a significant
53
54 195 reduction in 5 h postprandial glucose in response to breaking up prolonged sitting time with 2
55
56 196 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied
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2
3 197 participants [28]. An RPE of 13 for the physical activity intensity was selected in line with
4
5 198 previous research [26, 42] and the Borg 6-20 RPE scale may be used to assess and
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7 199 regulate upper-body physical activity at moderate-to-vigorous intensity in adults with chronic
8
9 200 SCI [41]. Moderate-intensity physical activity was selected as it is well-tolerated, can be
10
11 201 performed safely, and is recommended for health risk reduction in individuals with SCI [20,
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13 202 43].

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15 203

16
17 204 Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during
18
19 205 each condition. This will be standardised by asking participants to engage in the same
20
21 206 activities during each of the two experimental conditions. Except during the activity bouts,
22
23 207 participants will remain inactive and only leave their desk to void and consume standardised
24
25 208 meals in a kitchen adjacent to the test laboratory; participants will be aided by a member of
26
27 209 the research team when moving to these locations so that they remain inactive. A researcher
28
29 210 will be present to ensure compliance with the protocols throughout all conditions.

30
31 211

32 212 *Meal and water consumption*

33
34 213 Standardised meals will be consumed immediately prior to the start of each experimental
35
36 214 condition and at 3 h, each providing 30% of estimated daily energy requirements for each
37
38 215 participant [44]. Participants will be asked to consume each meal within a 15 min time
39
40 216 period. The time taken to consume the meals will be recorded for the first condition and
41
42 217 participants will be asked to replicate this time as closely as possible in the subsequent
43
44 218 condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice
45
46 219 (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted
47
48 220 crisps and apple (54% carbohydrate, 34% fat, 13% protein). The macronutrient composition
49
50 221 of meals in the current study was selected as it is generally representative of UK guidelines
51
52 222 for a balanced diet [45]. The glycaemic index for these breakfast and lunch meals is 43 and
53
54 223 72, respectively. Glycaemic index values for each food item were obtained from the
55
56 224 International Tables of Glycaemic Index and Glycaemic Load Values 2008 [46] and meal

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2
3 225 glycaemic index was calculated using weighted means of the glycaemic index values for the
4
5 226 component foods [47]. Water will be available ad libitum during the first condition and this
6
7 227 volume of intake will be provided at standardised regular intervals in the subsequent
8
9 228 condition.

10
11 229

12 230 *Blood collection and biochemistry*

13
14 231 Finger prick blood samples will be collected into two EDTA-containing microvettes
15
16 232 (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120,
17
18 233 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity
19
20 234 bouts in SED-ACT. At each time point, approximately 600 μL of whole blood will be
21
22 235 collected. Blood glucose concentrations will be analysed immediately using the YSI 2300
23
24 236 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μL of
25
26 237 blood from one microvette. Additional 30 μL volumes of whole blood will be aliquoted onto
27
28 238 two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the
29
30 239 measurement of triglyceride and HDL concentrations using the Reflotron Plus system
31
32 240 (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood ($\sim 490 \mu\text{L}$) will be
33
34 241 centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK)
35
36 242 and the plasma then stored at -80°C . An enzyme-linked immunosorbent assay kit will be
37
38 243 used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).

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41 244

42 245 *Blood pressure*

43
44 246 Blood pressure will be measured at baseline as described above followed by single readings
45
46 247 taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly
47
48 248 activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory
49
50 249 blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).

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54 251 *Study outcomes*

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3 252 *Primary outcome:* the primary outcome for the study is within-participant, between condition
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5 253 postprandial glucose net incremental area under the curve (iAUC) [11]. *Secondary*
6
7 254 *outcomes:* these include within-participant, between condition mean systolic and diastolic
8
9 255 blood pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC
10
11 256 and total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit
12
13 257 comparisons with previous studies. *Feasibility measures:* to assess feasibility of the trial,
14
15 258 participant dropout, number of experimental sessions completed, fatigue at the beginning
16
17 259 and end of each day rated on an 11-point (0 “not fatigued at all” to 10 “extremely fatigued”)
18
19 260 Visual Analogue Scale (VAS), and the degree of difficulty in completing each experimental
20
21 261 condition rated on an 11-point VAS (0 “not difficult at all” to 10 “extremely difficult”) will be
22
23 262 recorded. Participants will also complete the Physical Activity Enjoyment Scale [48] at the
24
25 263 end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [49]
26
27 264 (“Enjoyment”) 20 min after the last activity bout in the SED-ACT condition. Participants will
28
29 265 also report on the same scale how enjoyable they would find it to engage in this form of
30
31 266 physical activity most days of the week in the coming month (“Expected enjoyment”).
32
33 267 *Psychological outcomes:* correlates of sedentary behaviour will be measured immediately
34
35 268 before and after each experimental condition to explore whether participants’ mood, affect,
36
37 269 wellbeing, and social cognitions regarding their ability to overcome being sedentary may
38
39 270 differ in response to the SED-ACT condition compared with the SED condition. These
40
41 271 measures will be based on the COM-B framework [50] using standardised wording formats
42
43 272 [51] that will include overcoming barriers (self-efficacy/perceived behavioural control),
44
45 273 attitudes, intentions and action planning. The following questionnaires will be used: an
46
47 274 adapted version of the Schwarzer and Renner [52] Physical Exercise Self-Efficacy Scale to
48
49 275 measure self-efficacy to avoid long periods of sedentary time; current mood using the short
50
51 276 Positive and Negative Affect Scale [53]; psychological wellbeing using the National
52
53 277 Wellbeing Measurement [54]; and the Warwick Edinburgh Mental Well-Being Scale [55].
54
55 278 These measures will be taken within 45 min following the last bout of activity in the SED-

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3 279 ACT condition, which is an appropriate time frame based on evidence that mood and affect
4
5 280 is enhanced for 3-4 hours following a single session of exercise [56].
6

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9 282 *Sample size calculations*

10 283 Sample size calculations were performed using GPower [57]. Previous research reported a
11
12 284 16% reduction (effect size, $F=0.61$) in 5 h postprandial glucose total AUC when breaking up
13
14 285 prolonged sedentary time with 2 min light-intensity walking every 20 min versus
15
16 286 uninterrupted sitting in able-bodied participants [28]. As this study will use arm cranking
17
18 287 (localised muscular contractions) as opposed to walking where a larger muscle mass is
19
20 288 required, a smaller effect may be observed. Based on this, it was estimated that 14
21
22 289 participants would be required for this complete two-treatment crossover design to detect a
23
24 290 medium effect size ($F=0.4$) with a within-person correlation of 0.6, 80% power, and an α of
25
26 291 0.05. To allow for potential withdrawals, a total of 20 participants will be recruited.
27

28 292

29
30 293 *Statistical analysis*

31
32 294 Linear mixed models will be used to determine differences in the primary and secondary
33
34 295 outcome variables between the conditions. All models will adjust for potential covariates
35
36 296 explaining residual outcome variances (age, body fat% gender, lesion level, completeness of
37
38 297 lesion and pre-prandial outcome values). Statistical significance will be accepted as $p<0.05$.
39
40 298 Cohens' d effect sizes will be calculated to describe the magnitude of differences between
41
42 299 conditions [58]. Individuals' responses for CVD risk marker outcomes will also be compared
43
44 300 between the conditions to determine the number of participants who respond to the
45
46 301 experimental protocols.
47

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50 303 *Patient and Public Involvement*

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52 304 Patients and public were not involved with the development of the research question,
53
54 305 outcome measures or study design, nor will they be involved with the conduct of the study.
55

1
2
3 306 The recruitment plan was informed based on feedback from patients and public. A summary
4
5 307 of the study results will be provided to each of the study participants.
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For peer review only

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2
3 308 **Ethics and dissemination**

4 309 This study was approved on the 19th May 2017 by the Cambridge South NHS Research
5
6 310 Ethics Committee (reference 17/EE/0076). Personal information about potential and enrolled
7
8 311 participants will be stored in electronic format on password protected computers or in hard
9
10 312 copy format in locked filing cabinets at the University of Bedfordshire. Only members of the
11
12 313 research team will have access to this information. All personal information will be destroyed
13
14 314 after a period of five years. Individuals will be referred to in anonymised fashion in any
15
16 315 published data.
17

18
19 316

20 317 The findings of this research will be disseminated to lay, academic, practice, and policy-
21
22 318 based audiences via presentation at conference proceedings; publication in a peer review
23
24 319 journal; websites, newsletters, and social media; and summary reports to policy makers and
25
26 320 clinical care partners. The final trial dataset will be made available as supplementary
27
28 321 material when the findings of the study are published in a peer review journal. Any protocol
29
30 322 modifications will be communicated to the Cambridge South NHS Research Ethics
31
32 323 Committee, recorded in the study's ISRCTN clinical trials registry, and detailed in a journal
33
34 324 publication of the study findings.
35

36 325

37
38 326 **Acknowledgements:** The authors would like to thank Dr Jan van der Scheer for providing
39
40 327 his advice on the design of the study protocol. We would also like to thank the patients and
41
42 328 public who helped to inform the recruitment strategy for this study.
43

44 329

45
46 330 **Author contributions**

47 331 DB and LC conceptualised the study.

48 332 TW, LC, VT, DD, CL, and DB contributed to the design of the study protocol.

49 333 TW drafted the manuscript.

50 334 TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and
51
52 335 approved the final version.
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4
5 337 **Funding statement**

6
7 338 This work is supported by Heart Research UK grant number RG2655/17/18. The funder has
8
9 339 no role in the study design; collection, management, analysis, and interpretation of data;
10
11 340 writing of any reports; and the decision to submit any reports for publication, and will not
12
13 341 have authority over any of these activities.

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16
17 343 **Conflicts of interest**

18
19 344 None of the authors have declared any conflicts of interest.

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3 **Figure captions**
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5 **Figure 1** Study schedule.
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8 **Figure 2** Schematic of experimental protocol.
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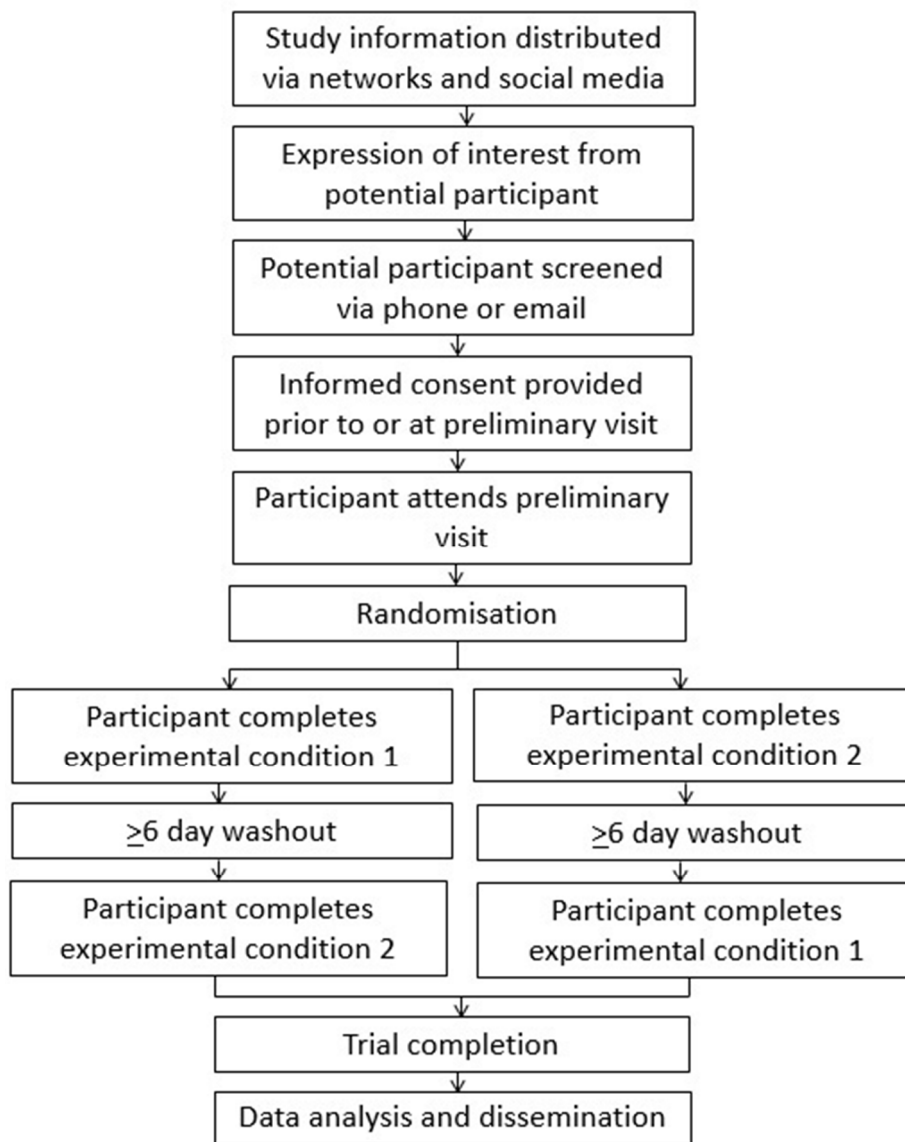


Figure 1 Study schedule.

43x56mm (300 x 300 DPI)

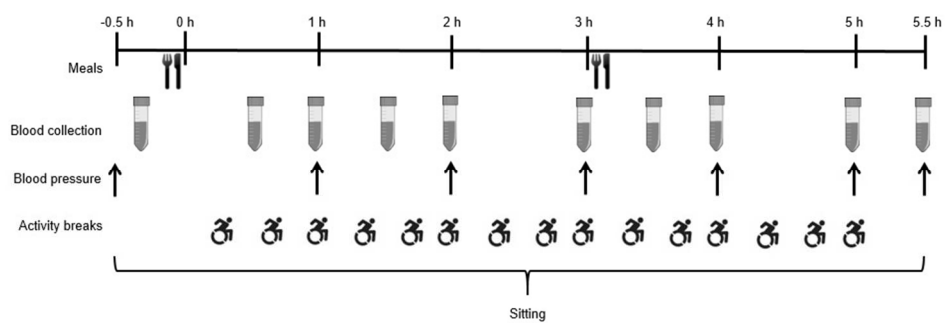


Figure 2 Schematic of experimental protocol.

85x30mm (300 x 300 DPI)

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University of
Bedfordshire

Version 2 (14/03/2017)

Participant Identification Number for this trial:____

CONSENT FORM

Title of Project: The Spinal Cord Injury Move More (SCIMM) study: The benefits of breaking up prolonged sedentary time on cardiovascular disease risk markers in people with spinal cord injury

Please initial box

1. I confirm that I have read and understand the information sheet dated [07/08/2017] (version 9) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of my data collected during the study may be looked at by individuals from the University of Bedfordshire or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. In the event that the results from the DXA bone scan show that I have low bone mineral density I agree to being notified of this in a letter that will advise me to contact my GP for further investigation about the results.
5. I agree to my GP being notified of my taking part in this study.
6. I agree to take part in the above study.

Name of Participant

Date

Signature

Email

Mobile

GP Name

GP Address

Researcher

Date

Signature

Please return this form to: Thomas Withers, Institute for Sport and Physical Activity Research, University of Bedfordshire, Polhill Avenue, Bedford, MK41 9EA.

Email: thomas.withers@beds.ac.uk



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 2 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ 2 ___
Protocol version	3	Date and version identifier	___ NA ___
Funding	4	Sources and types of financial, material, and other support	___ 1 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 14 ___
	5b	Name and contact information for the trial sponsor	___ NA ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 14 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ NA ___

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47**Introduction**

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-10

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3	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____13_____
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5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____7_____
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8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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12	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____6_____
13				
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17	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____6_____
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____6_____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____NA_____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
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31 **Methods: Data collection, management, and analysis**

32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____8-12_____
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____7_____
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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____ 14 _____
4				
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7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____ 13 _____
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ 13 _____
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____ NA _____
13				
14				
15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____ NA _____
18				
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____ NA _____
23				
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____ NA _____
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ NA _____
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 14 _____
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ 14 _____
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____7_____
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
7				
8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____14_____
9				
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____15_____
12				
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____14_____
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
18				
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____14_____
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA_____
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____14_____
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____N/A_____
35				
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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BMJ Open

Cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) randomised crossover laboratory trial protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021936.R2
Article Type:	Protocol
Date Submitted by the Author:	16-May-2018
Complete List of Authors:	Withers, Thomas; University of Bedfordshire, Institute for Sport Science and Physical Activity Research, School of Sport Science and Physical Activity Croft, Louise; University of Bedfordshire, Institute for Sport Science and Physical Activity Research, School of Sport Science and Physical Activity Goosey-Tolfrey, Victoria L; Loughborough University, School of Sport, Exercise and Health Sciences, The Peter Harrison Centre for Disability Sport Dunstan, David; Baker Heart and Diabetes Institute; Australian Catholic University, Mary MacKillop Institute for Health Research Leicht, Christof; Loughborough University, School of Sport, Exercise and Health Sciences, The Peter Harrison Centre for Disability Sport Bailey, Daniel; University of Bedfordshire, Institute for Sport and Physical Activity Research, School of Sport Science and Physical Activity
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Public health
Keywords:	physical activity, sedentary lifestyle, activity breaks, glucose, cardiovascular disease, spinal cord injury

SCHOLARONE™
Manuscripts

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3 **Cardiovascular disease risk marker responses to breaking up prolonged sedentary**
4 **time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM)**
5 **randomised crossover laboratory trial protocol**
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43 **Word count:** 3531

44
45 **Sources of funding:** This work is supported by Heart Research UK grant number
46 RG2655/17/18.
47

48 **Conflicts of interest:** None of the authors have declared any conflicts of interest.
49

50 **Study start date:** 19th May 2017

51 **Study end date:** 18th January 2019
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1 **Abstract**

2 **Introduction:** Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD)
3 and could partly explain the increased prevalence of CVD in people with spinal cord injury
4 (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely
5 suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute
6 CVD risk marker response to breaking up prolonged sedentary time in people with SCI has
7 not been investigated. **Methods and analysis:** A randomised two-condition laboratory
8 crossover trial will compare: 1) breaking up prolonged sedentary time with 2 min moderate-
9 intensity arm crank activity every 20 min, with 2) uninterrupted prolonged sedentary time
10 (control) in people with SCI. Outcomes will include acute effects on postprandial glucose,
11 insulin, lipids and blood pressure. Blood samples will be collected and blood pressure
12 measured at regular intervals during each 5.5 h condition. **Ethics and dissemination:** This
13 study was approved by the Cambridge South NHS Research Ethics Committee. This
14 research will help determine if breaking up prolonged sedentary time could be effective in
15 lowering CVD risk in people with SCI. The findings of the research will be published in a peer
16 review journal and disseminated to relevant user groups. **Trial registration:** The study is
17 registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437).

19 **Strengths and limitations of this study**

- 20 • This study uses a randomised crossover design to investigate, for the first time,
21 cardiovascular disease risk marker responses to breaking up prolonged sedentary
22 time in individuals with paraplegia.
- 23 • Regular collection of blood samples will permit robust time course and incremental
24 area under the curve calculations for primary and secondary outcomes.
- 25 • Due to the acute nature of the study, the long-term cardiovascular disease risk
26 marker responses to a chronic intervention will remain unknown.

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27 • The cardiovascular disease risk marker responses to breaking up prolonged
28 sedentary time in people with tetraplegia still requires investigation.

29
30 **Keywords:** physical activity; sedentary lifestyle; activity breaks; glucose; cardiovascular
31 disease; spinal cord injury

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32 Introduction

33 There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year
34 with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading
35 cause of death in individuals with SCI [3] and this population have a significantly increased
36 risk of heart disease and stroke compared with able-bodied individuals [4]. Traditional risk
37 factors for CVD include impaired glucose tolerance, central obesity, high triglycerides, low
38 high-density lipoprotein cholesterol (HDL), and high blood pressure. These risk factors often
39 exacerbate significantly as a consequence of SCI [5] and a plethora of research has
40 documented impaired glucose tolerance and adverse lipid profiles in individuals with SCI [5,
41 6]. The clustering of ≥ 2 and ≥ 3 risk factors is prevalent in 87% and 72% of SCI individuals,
42 respectively [7], which is markedly higher compared with the able-bodied population [8]. This
43 milieu of metabolic disturbances after SCI may be due to increases in body fat resulting from
44 an imbalance in energy intake and expenditure [5]. Excess fat accumulation, particularly in
45 the visceral region, is associated with inflammation that is causal in glucose intolerance and
46 dyslipidaemia [5, 9] thus promoting atherogenesis that would increase the risk of CVD in this
47 population [10].

48
49 Postprandial glucose and lipid concentrations are strong independent predictors of future
50 CVD incidence, even in those without diabetes [11]. There is a dose-response relationship
51 between postprandial glucose area under the curve (AUC) and CVD risk, while progression
52 of carotid atherosclerosis can be prevented by attenuation of postprandial glucose
53 concentrations [12, 13]. Impaired postprandial glucose metabolism was observed in 50%
54 and 62% of individuals with paraplegia and tetraplegia, respectively, compared with 18% in
55 able-bodied individuals [6]. This impaired glucose intolerance in SCI is characterised by
56 hyperinsulinaemia, which suggests that there is tissue level resistance to insulin [14]. In
57 paraplegic individuals, there appears to be no difference in postprandial glucose responses
58 between those with complete versus incomplete lesions [15, 16]. Although postprandial
59 lipaemic responses have not been compared between individuals with complete and

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3 60 incomplete lesions, fasting lipid levels do not differ between these groups [17]. There does,
4
5 61 however, appear to be an exaggerated postprandial lipaemic response in individuals with
6
7 62 paraplegia compared with able-bodied individuals [18]. These observations are of potential
8
9 63 concern as the high dietary intake of carbohydrate and fat in individuals with SCI [19] may
10
11 64 lead to repeated exaggerated elevations in glucose and lipids following food intake. It is thus
12
13 65 pertinent to identify interventions to reduce postprandial glucose and lipid responses in
14
15 66 individuals with SCI to reduce their CVD risk.

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17 67
18 68 Physical activity guidelines have been developed specifically for this population that
19
20 69 recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA)
21
22 70 three times per week for CVD health benefits [20]. However, it is estimated that 37 to 50% of
23
24 71 this population engage in no leisure-time physical activity whatsoever [21, 22]. Reduced
25
26 72 levels of physical activity are proposed to largely account for the increased CVD risk in SCI
27
28 73 with reduced levels of leisure-time physical activity associated with increased body fat,
29
30 74 insulin resistance, and systolic blood pressure [22, 23]. However, sedentary behaviour (i.e.
31
32 75 any waking behaviour in a sitting, reclining or lying posture with low energy expenditure
33
34 76 [24]), is now recognised as being a significant CVD risk factor in the able-bodied population,
35
36 77 independent of MVPA [25]. Experimental studies in able-bodied individuals have reported an
37
38 78 acute reduction in postprandial glucose, insulin, triglycerides and blood pressure in response
39
40 79 to breaking up prolonged sedentary time with 2 min bouts of light or moderate-intensity
41
42 80 walking every 20 min [26-29]. However, no research has examined whether postprandial
43
44 81 CVD risk marker responses are attenuated in response to breaking up prolonged sedentary
45
46 82 time in individuals with SCI.

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48 83
49
50 84 The primary aim of this study is therefore to compare the acute CVD risk marker responses
51
52 85 in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted
53
54 86 sedentary time. The CVD risk markers that will be studied include postprandial glucose
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56 87 (primary outcome), insulin and lipids, and systolic and diastolic blood pressure (secondary

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3 88 outcomes) based on evidence that these markers predict CVD outcomes and are adversely
4
5 89 affected by SCI. It is hypothesised that breaking up prolonged sedentary time will result in
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7 90 favourable CVD risk marker responses compared with uninterrupted sedentary time in
8
9 91 individuals with paraplegia. This could identify a novel strategy for the prevention of CVD in
10
11 92 SCI that would warrant further evaluation.
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14 94 **Methods and analysis**

15 95 *Study design*

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17
18 96 A randomised two-condition crossover design will be used in accordance with the SPIRIT
19
20 97 statement [30]. The study is registered as a clinical trial on the ISRCTN register (trial ID:
21
22 98 ISRCTN51868437). The study schedule can be seen in Figure 1. All research will take place
23
24 99 at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary
25
26 100 measures, participants will complete two experimental conditions in a randomised order. The
27
28 101 conditions will be separated by ≥ 6 days to eliminate any potential carryover effects.
29
30 102 Condition order will be randomised by a researcher independent from the study using
31
32 103 computer generated random numbers (block randomisation with balanced block sizes).
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34 104

35
36 105 Figure 1 about here.
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38 106

39 107 *Participants*

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41
42 108 *Inclusion criteria:* Males and females aged 18-60 years; chronic SCI (≥ 1 year since injury);
43
44 109 individuals with a traumatic SCI below T5 (mid to low level paraplegia); individuals with a
45
46 110 non-traumatic SCI (as defined by the International Spinal Cord Injury Data Sets for non-
47
48 111 traumatic SCI [31]) that present with mid to low level paraplegia. Including only individuals
49
50 112 with injuries below T5 will ensure sympathetic innervation to the major organs at the T5 level
51
52 113 so that heart rate and catecholamine responses would be unaffected by injury [32] and thus
53
54 114 minimise the potential that innervation variations could have on the study outcomes.
55
56 115 Paraplegic individuals who have complete or incomplete lesions will be included based on
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3 116 evidence that these groups do not differ with respect to postprandial glucose metabolism
4
5 117 (primary outcome) [15, 16]. Individuals who express an interest in taking part in the study will
6
7 118 be required to indicate their spinal cord lesion level and completeness of injury via a
8
9 119 questionnaire and asked to provide the research team with a copy of medical records to
10
11 120 confirm injury level and ASIA impairment scale classification prior to preliminary measures.

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13 121

14 122 *Exclusion criteria:* individuals who regularly engage in >300 min/week of MVPA as such high
15
16 123 levels of physical activity may offset the detrimental association of sedentary time with health
17
18 124 outcomes [33]; history of severe cardiovascular complications; hypotension (resting blood
19
20 125 pressure <90/60 mmHg); body mass index >45 kg/m²; a history of autonomic dysreflexia;
21
22 126 pregnancy; taking glucose lowering medication; smokers; diagnosed diabetes, renal failure,
23
24 127 liver disease, major illness, or other health issues that may limit ability to perform the
25
26 128 physical activity protocols.

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29 129

30 130 *Recruitment*

31
32 131 Participants will be recruited through organisations and charities relevant to individuals with
33
34 132 SCI, including the National Spinal Injuries Centre, Stoke Mandeville Hospital,
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36 133 Buckinghamshire NHS Healthcare Trust; local sport and activity clubs; and local community
37
38 134 groups. Mail outs, social media, information on websites, posters, flyers, and visits from the
39
40 135 research team will be used to provide information on the study to potentially eligible
41
42 136 individuals who can then express their interest to the research team in taking part in the
43
44 137 study. Written informed consent will be obtained by a member of the research team prior to
45
46 138 participation in any testing protocols (see supplementary file). As an incentive, participants
47
48 139 will receive a £25 shopping gift voucher for each main condition they complete and will have
49
50 140 all travel expenses paid.

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52 141

53 54 142 *Preliminary measures*

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3 143 Participants will attend a preliminary testing session where they will have body mass
4
5 144 measured using wheelchair double beam scales (300 series; Marsden, London, UK).
6
7 145 They will also have body fat and lean tissue mass (and percent) determined for the
8
9 146 whole body and regionally via whole-body scans using dual-energy x-ray absorptiometry
10
11 147 (DXA; GE Medical Systems; Chalfont St Giles, UK) in line with previous research [34-36].
12
13 148 During DXA measures, participants will be positioned as closely as possible to standard
14
15 149 protocols and Velcro restraints will be fastened around the participants' knees and ankles to
16
17 150 maintain correct position of the legs during scanning. Participants will be offered a wedge to
18
19 151 be used as a pillow for comfort. Waist circumference will be measured using International
20
21 152 Standards for Anthropometric Assessment (ISAK) guidelines [37, 38]. These measures will
22
23 153 be taken in the standing position for participants who are able to maintain this posture and in
24
25 154 a supine position for participants who are not able to stand [38]. Resting blood pressure will
26
27 155 be measured on the left arm, while seated, three times after the participant has rested for 5
28
29 156 min with the lowest readings being recorded. Following this, participants will be familiarised
30
31 157 with use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [39]. They will then cycle
32
33 158 using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power
34
35 159 output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour
36
37 160 research [26, 40]. Participants will be asked to cycle at ~70 rpm during the test. The test will
38
39 161 start at a low intensity (~20 Watts) and the participants will then indicate their RPE at 1 min
40
41 162 intervals. The resistance will then be increased by 5-20 Watts based on the participants'
42
43 163 RPE until an RPE of 13 has been achieved, at which point the test will be terminated. The
44
45 164 test is expected to take no longer than 15 min. The intensity that corresponds to an RPE of
46
47 165 13 during the test will be recorded for each participant and used for the physical activity
48
49 166 breaks described in the respective main condition below. The use of the Borg 6-20 RPE
50
51 167 scale has acceptable validity in individuals with SCI to determine physical activity intensity
52
53 168 [41]. This method is also suggested as a practical approach for health care professionals
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3 169 and scientists as oxygen consumption testing equipment is costly and not available in many
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5 170 rehabilitation centres and community settings [41].
6

7 171

8
9 172 *Experimental protocol*

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11 173 Figure 2 shows the experimental protocol. Participants will be instructed to refrain from
12
13 174 caffeine, alcohol and exercise for 48 h prior to each experimental condition. They will also be
14
15 175 provided with a food diary and digital weighing scales to record volume and timings of all
16
17 176 food and liquids consumed in the 24 h period prior to the first experimental condition.
18
19 177 Participants will be asked to replicate their diet the day prior to the subsequent experimental
20
21 178 condition [42]. On condition days, participants will attend in the morning following an
22
23 179 overnight fast and avoid active travel to the laboratory. Upon arrival, resting blood pressure
24
25 180 will be measured after 5 min rest; two measures will be taken and the lowest of these
26
27 181 recorded. A fasting capillary blood sample will then be collected. Participants will commence
28
29 182 the 5.5 h condition period following consumption of a standardised breakfast. The two
30
31 183 experimental conditions are as follows:

32 184

- 34 185 1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their
35
36 186 wheelchair or a standard chair at a desk during this condition.
37
38 187 2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will
39
40 188 complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using
41
42 189 the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical
43
44 190 activity.

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46 191

47
48 192 Figure 2 about here.
49

50 193

51
52 194 The SED-ACT protocol was selected based on previous research that reported a significant
53
54 195 reduction in 5 h postprandial glucose in response to breaking up prolonged sitting time with 2
55
56 196 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied
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2
3 197 participants [28]. An RPE of 13 for the physical activity intensity was selected in line with
4
5 198 previous research [26, 42] and the Borg 6-20 RPE scale may be used to assess and
6
7 199 regulate upper-body physical activity at moderate-to-vigorous intensity in adults with chronic
8
9 200 SCI [41]. Moderate-intensity physical activity was selected as it is well-tolerated, can be
10
11 201 performed safely, and is recommended for health risk reduction in individuals with SCI [20,
12
13 202 43].

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15 203

16
17 204 Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during
18
19 205 each condition. This will be standardised by asking participants to engage in the same
20
21 206 activities during each of the two experimental conditions. Except during the activity bouts,
22
23 207 participants will remain inactive and only leave their desk to void and consume standardised
24
25 208 meals in a kitchen adjacent to the test laboratory; participants will be aided by a member of
26
27 209 the research team when moving to these locations so that they remain inactive. A researcher
28
29 210 will be present to ensure compliance with the protocols throughout all conditions.

30
31 211

32 212 *Meal and water consumption*

33
34 213 Standardised meals will be consumed immediately prior to the start of each experimental
35
36 214 condition and at 3 h, each providing 30% of estimated daily energy requirements for each
37
38 215 participant [44]. Participants will be asked to consume each meal within a 15 min time
39
40 216 period. The time taken to consume the meals will be recorded for the first condition and
41
42 217 participants will be asked to replicate this time as closely as possible in the subsequent
43
44 218 condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice
45
46 219 (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted
47
48 220 crisps and apple (54% carbohydrate, 34% fat, 13% protein). The macronutrient composition
49
50 221 of meals in the current study was selected as it is generally representative of UK guidelines
51
52 222 for a balanced diet [45]. The glycaemic index for these breakfast and lunch meals is 43 and
53
54 223 72, respectively. Glycaemic index values for each food item were obtained from the
55
56 224 International Tables of Glycaemic Index and Glycaemic Load Values 2008 [46] and meal

1
2
3 225 glycaemic index was calculated using weighted means of the glycaemic index values for the
4
5 226 component foods [47]. Water will be available ad libitum during the first condition and this
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7 227 volume of intake will be provided at standardised regular intervals in the subsequent
8
9 228 condition.

10 229

11 230 *Blood collection and biochemistry*

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13
14 231 Finger prick blood samples will be collected into two EDTA-containing microvettes
15
16 232 (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120,
17
18 233 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity
19
20 234 bouts in SED-ACT. At each time point, approximately 600 μ L of whole blood will be
21
22 235 collected. Blood glucose concentrations will be analysed immediately using the YSI 2300
23
24 236 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μ L of
25
26 237 blood from one microvette. Additional 30 μ l volumes of whole blood will be aliquoted onto
27
28 238 two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the
29
30 239 measurement of triglyceride and HDL concentrations using the Reflotron Plus system
31
32 240 (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood (\sim 490 μ L) will be
33
34 241 centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK)
35
36 242 and the plasma then stored at -80° C. An enzyme-linked immunosorbent assay kit will be
37
38 243 used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).

39 244

40 245 *Blood pressure*

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42
43 246 Blood pressure will be measured at baseline as described above followed by single readings
44
45 247 taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly
46
47 248 activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory
48
49 249 blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).

50 250

51 251 *Study outcomes*

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3 252 *Primary outcome:* the primary outcome for the study is within-participant, between condition
4
5 253 postprandial glucose net incremental area under the curve (iAUC) [11]. *Secondary*
6
7 254 *outcomes:* these include within-participant, between condition mean systolic and diastolic
8
9 255 blood pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC
10
11 256 and total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit
12
13 257 comparisons with previous studies. *Feasibility measures:* to assess feasibility of the trial,
14
15 258 participant dropout, number of experimental sessions completed, fatigue at the beginning
16
17 259 and end of each day rated on an 11-point (0 “not fatigued at all” to 10 “extremely fatigued”)
18
19 260 Visual Analogue Scale (VAS), and the degree of difficulty in completing each experimental
20
21 261 condition rated on an 11-point VAS (0 “not difficult at all” to 10 “extremely difficult”) will be
22
23 262 recorded. Participants will also complete the Physical Activity Enjoyment Scale [48] at the
24
25 263 end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [49]
26
27 264 (“Enjoyment”) 20 min after the last activity bout in the SED-ACT condition. Participants will
28
29 265 also report on the same scale how enjoyable they would find it to engage in this form of
30
31 266 physical activity most days of the week in the coming month (“Expected enjoyment”).
32
33 267 *Psychological outcomes:* correlates of sedentary behaviour will be measured immediately
34
35 268 before and after each experimental condition to explore whether participants’ mood, affect,
36
37 269 wellbeing, and social cognitions regarding their ability to overcome being sedentary may
38
39 270 differ in response to the SED-ACT condition compared with the SED condition. These
40
41 271 measures will be based on the COM-B framework [50] using standardised wording formats
42
43 272 [51] that will include overcoming barriers (self-efficacy/perceived behavioural control),
44
45 273 attitudes, intentions and action planning. The following questionnaires will be completed in
46
47 274 this order: psychological wellbeing using the National Wellbeing Measurement [52]; the
48
49 275 Warwick Edinburgh Mental Well-Being Scale [53]; current mood using the short Positive and
50
51 276 Negative Affect Scale [54]; and an adapted version of the Schwarzer and Renner [55]
52
53 277 Physical Exercise Self-Efficacy Scale to measure self-efficacy to avoid long periods of
54
55 278 sedentary time. These measures will be taken at the end of each experimental condition
56
57 279 (330 min) meaning that each questionnaire will be completed within 45 min following the last

1
2
3 280 bout of activity in the SED-ACT condition. This is an appropriate time frame based on
4
5 281 evidence that mood and affect is enhanced for 3-4 hours following a single session of
6
7 282 exercise [56]. Although between-participant variation in the time taken to complete each
8
9 283 questionnaire is anticipated, within-participant variation is expected to be limited therefore
10
11 284 permitting valid between-condition comparisons.

12 285

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14 286 *Sample size calculations*

15
16 287 Sample size calculations were performed using GPower [57]. Previous research reported a
17
18 288 16% reduction (effect size, $F=0.61$) in 5 h postprandial glucose total AUC when breaking up
19
20 289 prolonged sedentary time with 2 min light-intensity walking every 20 min versus
21
22 290 uninterrupted sitting in able-bodied participants [28]. As this study will use arm cranking
23
24 291 (localised muscular contractions) as opposed to walking where a larger muscle mass is
25
26 292 required, a smaller effect may be observed. Based on this, it was estimated that 14
27
28 293 participants would be required for this complete two-treatment crossover design to detect a
29
30 294 medium effect size ($F=0.4$) with a within-person correlation of 0.6, 80% power, and an α of
31
32 295 0.05. To allow for potential withdrawals, a total of 20 participants will be recruited.

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36 297 *Statistical analysis*

37
38 298 Linear mixed models will be used to determine differences in the primary and secondary
39
40 299 outcome variables between the conditions. All models will adjust for potential covariates
41
42 300 explaining residual outcome variances (age, body fat% gender, lesion level, completeness of
43
44 301 lesion and pre-prandial outcome values). Statistical significance will be accepted as $p<0.05$.
45
46 302 Cohens' d effect sizes will be calculated to describe the magnitude of differences between
47
48 303 conditions [58]. Individuals' responses for CVD risk marker outcomes will also be compared
49
50 304 between the conditions to determine the number of participants who respond to the
51
52 305 experimental protocols.

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56 307 *Patient and Public Involvement*

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2
3 308 Patients and public were not involved with the development of the research question,
4
5 309 outcome measures or study design, nor will they be involved with the conduct of the study.
6
7 310 The recruitment plan was informed based on feedback from patients and public. A summary
8
9 311 of the study results will be provided to each of the study participants.
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For peer review only

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3 312 **Ethics and dissemination**

4 313 This study was approved on the 19th May 2017 by the Cambridge South NHS Research
5
6 314 Ethics Committee (reference 17/EE/0076). Personal information about potential and enrolled
7
8 315 participants will be stored in electronic format on password protected computers or in hard
9
10 316 copy format in locked filing cabinets at the University of Bedfordshire. Only members of the
11
12 317 research team will have access to this information. All personal information will be destroyed
13
14 318 after a period of five years. Individuals will be referred to in anonymised fashion in any
15
16 319 published data.
17

18
19 320

20 321 The findings of this research will be disseminated to lay, academic, practice, and policy-
21
22 322 based audiences via presentation at conference proceedings; publication in a peer review
23
24 323 journal; websites, newsletters, and social media; and summary reports to policy makers and
25
26 324 clinical care partners. The final trial dataset will be made available as supplementary
27
28 325 material when the findings of the study are published in a peer review journal. Any protocol
29
30 326 modifications will be communicated to the Cambridge South NHS Research Ethics
31
32 327 Committee, recorded in the study's ISRCTN clinical trials registry, and detailed in a journal
33
34 328 publication of the study findings.
35

36
37 329

38 330 **Acknowledgements:** The authors would like to thank Dr Jan van der Scheer for providing
39
40 331 his advice on the design of the study protocol. We would also like to thank the patients and
41
42 332 public who helped to inform the recruitment strategy for this study.
43

44
45 333

46 334 **Author contributions**

47
48 335 DB and LC conceptualised the study.

49
50 336 TW, LC, VT, DD, CL, and DB contributed to the design of the study protocol.

51
52 337 TW drafted the manuscript.

53
54 338 TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and
55
56 339 approved the final version.
57

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4
5 341 **Funding statement**

6
7 342 This work is supported by Heart Research UK grant number RG2655/17/18. The funder has
8
9 343 no role in the study design; collection, management, analysis, and interpretation of data;
10
11 344 writing of any reports; and the decision to submit any reports for publication, and will not
12
13 345 have authority over any of these activities.

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16
17 347 **Conflicts of interest**

18
19 348 None of the authors have declared any conflicts of interest.

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3 **Figure captions**
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5 **Figure 1** Study schedule.
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8 **Figure 2** Schematic of experimental protocol.
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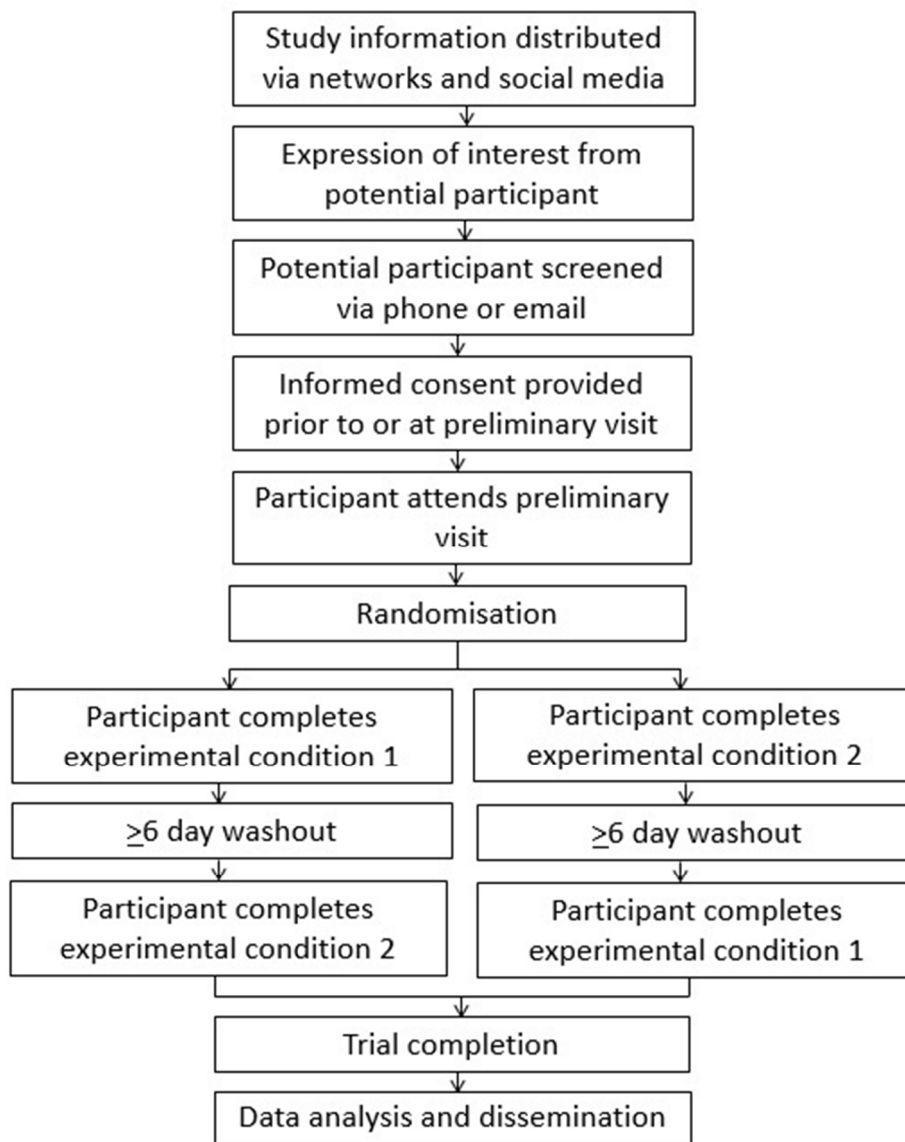


Figure 1 Study schedule.

43x56mm (300 x 300 DPI)

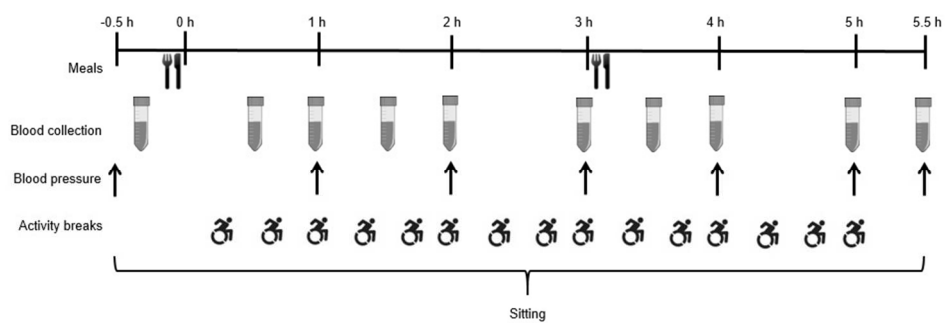


Figure 2 Schematic of experimental protocol.

85x30mm (300 x 300 DPI)

peer review only

University of
Bedfordshire

Version 2 (14/03/2017)

Participant Identification Number for this trial: _____

CONSENT FORM

Title of Project: The Spinal Cord Injury Move More (SCIMM) study: The benefits of breaking up prolonged sedentary time on cardiovascular disease risk markers in people with spinal cord injury

Please initial box

1. I confirm that I have read and understand the information sheet dated [07/08/2017] (version 9) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of my data collected during the study may be looked at by individuals from the University of Bedfordshire or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. In the event that the results from the DXA bone scan show that I have low bone mineral density I agree to being notified of this in a letter that will advise me to contact my GP for further investigation about the results.
5. I agree to my GP being notified of my taking part in this study.
6. I agree to take part in the above study.

Name of Participant

Date

Signature

Email

Mobile

GP Name

GP Address

Researcher

Date

Signature

Please return this form to: Thomas Withers, Institute for Sport and Physical Activity Research, University of Bedfordshire, Polhill Avenue, Bedford, MK41 9EA.

Email: thomas.withers@beds.ac.uk



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 2 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ 2 ___
Protocol version	3	Date and version identifier	___ NA ___
Funding	4	Sources and types of financial, material, and other support	___ 1 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 14 ___
	5b	Name and contact information for the trial sponsor	___ NA ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 14 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ NA ___

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47**Introduction**

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____4-6_____
	6b	Explanation for choice of comparators	_____NA_____
Objectives	7	Specific objectives or hypotheses	_____5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____6_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____6-7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____9_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____NA_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____NA_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____12_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____7-10_____

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3	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____13_____
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5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____7_____
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8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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12	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____6_____
13				
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17	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____6_____
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____6_____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____NA_____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
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31 **Methods: Data collection, management, and analysis**

32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____8-12_____
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____7_____
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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____ 14 _____
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7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____ 13 _____
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ 13 _____
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12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____ NA _____
13				
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15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____ NA _____
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____ NA _____
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____ NA _____
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ NA _____
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 14 _____
35				
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37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ 14 _____
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____7_____
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
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8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____14_____
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____15_____
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____14_____
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____14_____
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA_____
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____14_____
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____N/A_____
35				
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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