PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	SUpervised exercise-therapy and Patient Education Rehabilitation (SUPER) versus minimal intervention for young adults at risk of knee osteoarthritis after ACL reconstruction: SUPER-Knee randomised controlled trial protocol
AUTHORS	Culvenor, Adam; West, Tom; Bruder, AM; Scholes, Mark; Barton, Christian; Roos, Ewa; Oei, Edwin; McPhail, Steven; Souza, Richard; Lee, Jusuk; Patterson, Brooke; Girdwood, Michael; Couch, Jamon L; Crossley, Kay

VERSION 1 – REVIEW

REVIEWER	Rhim, Hye Chang Harvard Medical School, Physical Medicine and Rehabilitation
REVIEW RETURNED	30-Oct-2022

GENERAL COMMENTS	The authors described the study very well and thoroughly, and here below are some suggestions/comments. Introduction -Recommend adding hypothesis at the end of the introduction based on previous literature: the following link is an example that is related with the current study. https://pubmed.ncbi.nlm.nih.gov/33379403/ Methods and Analysis Line 141: Any rationale for 4 months? Table 1: 9-36 months following ACLR seem like a wide range. Also, I understand the authors are interested in recruiting participants who are less likely to make improvements but I feel at 9 months, there might be room to make improvements depending on concomitant pathologies with ACL tear. Please comment on this. Line 210-211: Please describe in more detail about this predefined criteria - seems little vague Table 3: In participant characteristics, along with history of sport participation, current level of physical activity or sports participation (elite versus recreational) may be worth considering Line 358: Please describe Tampa scale of kinesiophobia just as the authors did for other outcome measures Line 364-365: If the devices are different, how would the objective measure be comparable? Adherence: What would be considered poor adherence/compliance? Any monitoring plans? Analysis: please describe in detail on how the authors are planning to conduct cost-effective analysis Discussion: please describe potential limitations

REVIEWER	Capin, Jacob Marquette University, Physical Therapy
REVIEW RETURNED	07-Nov-2022

GENERAL COMMENTS	Thank you for inviting me to review 'SUpervised exercise-therapy and Patient Education Rehabilitation (SUPER) versus minimal intervention for young adults at risk of knee osteoarthritis after ACL reconstruction: SUPER-Knee randomised controlled trial protocol'. This protocol describes a funded, registered, and adequately powered randomized controlled trial comparing rehabilitation consisting of supervised and independent exercise and patient education versus current best practice (i.e., minimal intervention control) for patients aged 18-40 years old who are 9-36 months after ACLR and have persistent knee symptoms. The authors/investigators are highly qualified and have the expertise in diverse backgrounds to perform the proposed work. The manuscript is well written, and the study is sufficiently rigorous and powered to answer the proposed questions. The study is novel, is needed, and has strong potential to be highly impactful. Below I offer several questions and comments that I hope will help the authors clarify or justify aspects of the study that were not clear in the original submission. Comments/Questions: 1. INCLUSION/EXCLUSION CRITERIA: Are patients with multiple ACL injuries (graft rupture and/or contralateral injury) eligible? If so, what (if any) adjustments will be made when rehabilitating (intervention group) and/or evaluating them (e.g., comparing symmetry indexes, completing surveys [for which knee or more symptomatic knee?])? a. Notably, it is unclear from the exclusion criteria language (i.e., 'Have had another knee injury/surgery or knee injection in the past 3 months') whether those with another knee injury/surgery at any timepoint or just within the past 3 months will be excluded. 2. INCLUSION/EXCLUSION CRITERIA: While I appreciate that the purpose of the study is to investigate this intervention among young adults, ACL injuries are highly prevalent among adolescents. Please comment on why adolescents are excluded. 3. RANDOMIZATION: It appears that the randomization algorithm does not include covariates that could affect outcomes (e.g., sex, age, graft type). Would the authors please comment on why this randomization method was selected including potentially the pros/cons of various approaches? 4. Table 2: When describing interventions, I recommend using the same terminology and order throughout (i.e., manuscript text, tables, and supplemental files). For example, in Table 2 under '4. What procedures' point 3 (iii) is stated as knee flexion whereas in the sample exercises, Exercise 3 is Plyometric Power (Jumping/Hopping) while Exercise 5 is labeled 'Hamstrings' (not knee flexion). There are several other similar minor inconsistencies that could be updated to improve readability. 5. DESIGN/COMPARATOR: The 'minimal intervention control' group receives a 'best practice' intervention that is likely better than the care most patients in the real world (outside of a clinical trial) would receive, at least in the United States where many patients would have to pay out-of-pocket for these services and many generic clinics may not have the resources or expertise to provide the quality of evaluation and education. Therefore, there is a strong possibility that the minimal intervention control group may

	(also) improve. Please discuss more thoroughly why the present design was selected and why a wait-list control group was not also included. 6. OUTCOMES: Please explain a bit more thoroughly why the timepoints are selected and why only patient reported outcomes (i.e., no physical performance tests) are analyzed at 2 months. 7. OUTCOMES: Lines 363-365 state: 'Objective physical activity will be captured using a Garmin vívofit® 4 actvity tracker (Garmin® International Inc., KS, USA) or participant's own device, if appropriate.' This non-research grade, wrist-mounted activity monitor may not be the most accurate method at capturing activity (e.g., step counts), and comparing to other devices has limitations. Please comment. a. There is also a typographical error on line 364 (actvity should be activity). Thank you for including the detailed study description including many supplemental files that thoroughly describe the study and will be immensely helpful for readers/clinicians. I commend the authors for designing and conducting this study and look forward to reading the results in a few years.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
The authors described the study very well and thoroughly, and here below are some suggestions and comments.

Author Response: We thank the reviewer for the positive comments regarding our paper.

Introduction
-Recommend adding hypothesis at the end of the introduction based on previous literature: the following link is an example that is related with the current study.
https://pubmed.ncbi.nlm.nih.gov/33379403/

Author Response: Our hypothesis was stated in our original submission at the end of the introduction, and copied here for clarity (page 5, line 123-5):
We hypothesise that the SUPER intervention will result in greater improvements in knee-related pain, symptoms, function and quality of life after 4 months (primary endpoint) and 12 months (secondary endpoint) compared to a minimal intervention control.

Methods and Analysis
Line 141: Any rationale for 4 months?

Author Response: The primary endpoint will be at 4 months following baseline as this aligns with the end of the intensive supervised exercise-therapy intervention period (i.e., Phase 1 of SUPER programme). Based on preliminary data in people with, or at risk of, osteoarthritis (Munukka et al., Osteoarthritis Cartilage 2016;24:1708; PubMed Roos et al., Arthritis Rheum 2005;52:3507),
4 PubMed months is also sufficient time for exercise-therapy to invoke a significant effect on joint structure (i.e., knee cartilage composition), which is an important secondary outcome.

Author Action: We have clarified in the paper that the primary endpoint of 4 months aligns with the end of the intensive supervised rehabilitation (page 6, line 142-3):
The primary endpoint will be at 4 months (immediately following the intensive supervised exercise-therapy phase), with…

Table 1: 9-36 months following ACLR seem like a wide range. Also, I understand the authors are interested in recruiting participants who are less likely to make improvements but I feel at 9 months, there might be room to make improvements depending on concomitant pathologies with ACL tear. Please comment on this.

Author Response: We discussed the inclusion criterion of "duration following ACLR" at length when designing this clinical trial.

Firstly, we had initially planned to include participants between 9-24 months following ACLR. However, due to recruitment commencing right at the beginning of the COVID-19 pandemic, we needed to increase the eligibility range to allow for recruitment of sufficient participants and trial completion within the grant funding window. In Australia, elective surgeries (e.g., ACLR) were suspended for many months during the COVID-19 pandemic, with the flow on effect of fewer participants being eligible in the smaller window of time post-ACLR.

Secondly, a minimum of 9 months post-ACLR was chosen because, in Australia, most patients with an ACLR are discharged from formal rehabilitation at that point and are expected to have returned to sport – only 5% of Australians with an ACLR participate in rehabilitation beyond 6 months (Ebert et al., KSSTA 2018;26:2353). We ensured that any potential participant still undertaking rehabilitation (and more likely to continue to improve) was excluded from our trial (as per exclusion criteria in Table 1).

Author Action: None required.

Line 210-211: Please describe in more detail about this predefined criteria - seems little vague

Author Response: Thank you for this suggestion. We have now included further detail to clarify these predefined criteria (page 9, line 212-6):
The intervention provided in Phase 2 will depend on whether the following predefined criteria are met at the 4-month follow-up assessment: goals are met (i.e., goals set with treating physiotherapist at start of Phase 1), participant satisfied with current symptoms/function (i.e., responded 'yes' to patient acceptable symptom state question (see Outcomes for details)) and GROC reported as at least 'better').

Table 3: In participant characteristics, along with history of sport participation, current level of physical activity or sports participation (elite versus recreational) may be worth considering

Author Response: The questions regarding sports participation do ask about level of sport (i.e., recreational vs elite). This table serves as an overview – specific details for all outcomes would make it very cumbersome. We have reworded the outcome slightly to "Sport/activity participation".

Line 358: Please describe Tampa scale of kinesiophobia just as the authors did for other outcome measures

Author Response: Thanks for this suggestion. We have added content for the Tampa scale (page 17, line 363-4):
This scale has established reliability and validity in musculoskeletal pain populations[52 53].

Line 364-365: If the devices are different, how would the objective measure be comparable?

Author Response: We agree that this commercial wrist-worn activity tracker may not be as accurate as research-grade activity monitors (e.g., Actigraph accelerometers). However, the Garmin vivofit 4 device we use in our trial is one of the most accurate on the market, reported to only underestimate step counts by 1% (i.e., 10 steps for eery 1,000 steps) compared to research-grade accelerometers (Modave et al., JMIR Mhealth Uhealth 2017; doi:10.2196/mhealth.7870). Other varieties of activity trackers from a number of different companies also only under-/over-estimate step counts by <4% compared to research-grade accelerometers (Modave et al., JMIR Mhealth Uhealth 2017; doi:10.2196/mhealth.7870). However, we acknowledge that this is a limitation compared to giving every participant an identical research-grade accelerometer).

Author Action: We have added content to the discussion section acknowledging this limitation (page 23, line 524-6):
We also acknowledge that the wrist-worn activity tracker (Garmin vívofit® 4) or other commercial devices that participants wear may under-/over-estimate daily step counts, however the differences with research-grade accelerometers appear minimal[69].

Adherence: What would be considered poor adherence/compliance? Any monitoring plans?

Author Response: We have multiple monitoring plans to be able to assess adherence to the supervised and unsupervised exercise-therapy sessions and adverse events etc., including:
i) Clinic logbooks (completed by treating physiotherapists at each session);
ii) Home logbooks (completed by participants after each unsupervised exercise session);
iii) Fortnightly questionnaire (electronic) asking about the number of supervised and unsupervised exercise sessions completed each fortnight; and
iv) Open probe questioning at each in-person follow-up.

These plans are detailed in the “treatment-related outcomes” section of our protocol paper.

Inadequate adherence is defined as participating in less than 13 (80%) of a minimum 16 (i.e., once per week) Phase 1 supervised sessions.

Author Action: We have revised the methods to clarify this definition (page 18, line 390-5):
Adherence with the supervised exercise-therapy sessions (i.e., number of sessions attended out of 32 possible Phase 1 sessions) and intensity/progression of the exercises will be recorded by treating physiotherapists and participants. Inadequate adherence is defined as participating in <22 (70%) supervised sessions. Participants in both groups will record adherence to home exercises and any co-interventions received in a logbook and via fortnightly (Phase 1) and monthly (Phase 2) online questionnaires.

Analysis: please describe in detail on how the authors are planning to conduct cost-effective analysis

Author Response: We plan on reporting the details of cost-effectiveness analysis in a separate publication, as this requires lots of additional content beyond the scope of the current main protocol paper.

Author Action: We have added content to the methods section to explain this (page 21, line 466-7): Methods of cost-effectiveness analysis will be reported elsewhere.

Discussion: please describe potential limitations

Author Action: We have added content to the discussion describing potential limitations as suggested (page 23, line 516-20):
While outcome assessors are blinded to group allocation and physiotherapists delivering the intervention are blinded to the control intervention, owing to the type of interventions (i.e., exercise-therapy and education), blinding of participants is not possible. Also, the difference in frequency of physiotherapy sessions between the two groups means that the contextual effects related to supervised physiotherapy treatment can not be isolated.

Reviewer #2:
Thank you for inviting me to review 'SUpervised exercise-therapy and Patient Education Rehabilitation (SUPER) versus minimal intervention for young adults at risk of knee osteoarthritis after ACL reconstruction: SUPER-Knee randomised controlled trial protocol'. This protocol describes a funded, registered, and adequately powered randomized controlled trial comparing rehabilitation consisting of supervised and independent exercise and patient education versus current best practice (i.e., minimal intervention control) for patients aged 18-40 years old who are 9-36 months after ACLR and have persistent knee symptoms. The authors/investigators are highly qualified and have the expertise in diverse backgrounds to perform the proposed work. The manuscript is well written, and the study is sufficiently rigorous and powered to answer the proposed questions. The study is novel, is needed, and has strong potential to be highly impactful. Below I offer several questions and comments that I hope will help the authors clarify or justify aspects of the study that were not clear in the original submission.

Author Response: We thank the reviewer for the positive comments regarding our paper. We have addressed each of the specific questions and comments in response to each one below.

1. INCLUSION/EXCLUSION CRITERIA: Are patients with multiple ACL injuries (graft rupture and/or contralateral injury) eligible? If so, what (if any) adjustments will be made when rehabilitating (intervention group) and/or evaluating them (e.g., comparing symmetry indexes, completing surveys [for which knee or more symptomatic knee?])?

Author Response: Patients with multiple ACL injuries or other knee injury history are eligible. This includes participants with more than one ACL reconstruction on their index knee or participants with an injury/surgery history on the contralateral knee. However, participants with an ACL graft rupture (i.e., ACL deficient knee) on the baseline MRI scan of their index knee will be excluded (as per exclusion criteria listed in Table 1). In the rare instance that both knees are eligible (i.e., both knees have had an ACL reconstruction 9-36 months prior and meet our symptomatic criteria), the most

symptomatic knee will be included as the ‘index knee’ to be evaluated in the RCT. The SUPER rehabilitation program will not be specifically modified for participants with multiple injuries, but treating physiotherapists are able to make small adjustments to individual programs based on clinical reasoning.

Author Action: We have added a sentence to the methods section clarifying inclusion (page 8, line 168-9):
If both knees are eligible, the most symptomatic knee will be considered as the index knee for the trial.

a. Notably, it is unclear from the exclusion criteria language (i.e., ‘Have had another knee injury/surgery or knee injection in the past 3 months’) whether those with another knee injury/surgery at any timepoint or just within the past 3 months will be excluded.

Author Response: Thanks for picking this up. We have revised the wording in Table 1 for clarity (page 6):
Any of the following in the past 3 months: knee re-injury, surgery or injection (either knee)

2. INCLUSION/EXCLUSION CRITERIA: While I appreciate that the purpose of the study is to investigate this intervention among young adults, ACL injuries are highly prevalent among adolescents. Please comment on why adolescents are excluded.

Author Response: We agree that ACL injuries are common in adolescents as well as young adults. We did not include adolescents in the SUPER-Knee clinical trial to reduce heterogeneity in our study sample, particularly in regard to cartilage structure. Knee cartilage continues to develop and thicken in athletic 16-18 year olds (Eckstein et al., 2014; https://doi.org/10.1016/j.aanat.2013.11.001). Furthermore, the ability of adolescents to access the SUPER intervention (i.e., drive to physiotherapy clinics for treatment) may be restricted due to not having the capacity to get to the clinic independently (i.e., lack of driver’s license).

3. RANDOMIZATION: It appears that the randomization algorithm does not include covariates that could affect outcomes (e.g., sex, age, graft type). Would the authors please comment on why this randomization method was selected including potentially the pros/cons of various approaches?

Author Response: The reviewer is correct – our randomisation schedule did not stratify by any variable. We discussed this during trial design phases but ultimately decided not to stratify our randomisation schedule because there is no strong evidence or clinical reasoning to suggest that factors (e.g., sex, age, graft type) influence the response to exercise-therapy and education. In other words, we hypothesised that men and women would respond similarly to the interventions, as would people with different graft types etc.

4. Table 2: When describing interventions, I recommend using the same terminology and order throughout (i.e., manuscript text, tables, and supplemental files). For example, in Table 2 under ‘4. What procedures’ point 3 (iii) is stated as knee flexion whereas in the sample exercises, Exercise 3 is Plyometric Power (Jumping/Hopping) while Exercise 5 is labeled ‘Hamstrings’ (not knee flexion). There are several other similar minor inconsistencies that could be updated to improve readability.

Author Response: Thanks for picking up this inconsistency. We have changed the order of the exercises in Table 2 to be consistent with the text, and the two supplementary files (CERT table and intervention handbook).

5. DESIGN/COMPARATOR: The 'minimal intervention control' group receives a 'best practice' intervention that is likely better than the care most patients in the real world (outside of a clinical trial) would receive, at least in the United States where many patients would have to pay out-of-pocket for these services and many generic clinics may not have the resources or expertise to provide the quality of evaluation and education. Therefore, there is a strong possibility that the minimal intervention control group may (also) improve. Please discuss more thoroughly why the present design was selected and why a wait-list control group was not also included.

Author Response: We agree that there is a possibility that the minimal intervention control group will also improve. That gets to the overarching aim of our clinical trial, to determine if improvements from the SUPER intervention exceed those of the minimal intervention group. Similar minimal intervention control groups have been used in previous clinical trials in musculoskeletal pain (e.g., Stevens et al., 2016; doi:10.1136/bmjopen-2016-011492). We did not include a wait-list control group as this would reduce equipoise and likely lead to decreased engagement and higher drop out rates (if used instead of our minimal intervention control) and considerably increased the required sample size (if used as a third comparator group).

Author Action: We have added text to the discussion further explaining our choice of comparator group (page 23, line 520-2):
We did not include a wait-list control group as this would have reduced equipoise and increased the risk of resentful demoralisation (if used instead of our minimal intervention control) and considerably increased the required sample size (if used as a third comparator group).

6. OUTCOMES: Please explain a bit more thoroughly why the timepoints are selected and why only patient reported outcomes (i.e., no physical performance tests) are analyzed at 2 months.

Author Response: As per our response to reviewer #1, the primary endpoint will be at 4 months following baseline as this aligns with the end of the intensive supervised exercise-therapy intervention period (i.e., Phase 1 of SUPER programme). Based on preliminary data in people with, or at risk of, osteoarthritis (Munukka et al., Osteoarthritis Cartilage 2016;24:1708; PubMed Roos et al., Arthritis Rheum 2005;52:3507), 4 PubMed months is also sufficient time for exercise-therapy to demonstrate a significant effect on joint structure (i.e., knee cartilage composition), which is an important secondary outcome. We will continue to follow-up participants at 12 months post-baseline to enable the longer-term effect of the interventions to be evaluated. Additionally, longer-term follow-ups beyond 12 months will hopefully be possible (dependent on funding). We only collect patient-reported outcomes at 2-month follow-up to minimise participant burden, as we expect that many participants in our trial will be located >1-2 hours away from our research lab (i.e., in regional Victoria, Australia).

Author Action: We have clarified in the paper that the primary endpoint of 4 months aligns with the end of the intensive supervised rehabilitation (page 6, line 142-3):
The primary endpoint will be at 4 months (immediately following the intensive supervised exercise-therapy phase), with additional follow-up at a minimum of 12 months (further longer-term follow-up dependent on funding).

We have added content to the discussion to clarify why only patient-reported outcomes are collected at 2 months (page 23, line 523-4):

Furthermore, only patient-reported outcomes are collected at 2-month follow-up to minimise participant burden.

7. OUTCOMES: Lines 363-365 state: 'Objective physical activity will be captured using a Garmin vívofit® 4 actvity tracker (Garmin® International Inc., KS, USA) or participant's own device, if appropriate.' This non-research grade, wrist-mounted activity monitor may not be the most accurate method at capturing activity (e.g., step counts), and comparing to other devices has limitations. Please comment.

Author Response: We agree that this commercial wrist-worn activity tracker may not be as accurate as research-grade activity monitors (i.e., Actigraph accelerometers). However, the Garmin vivofit 4 device we use in our trial is one of the most accurate on the market, reported to only underestimate step counts by 1% (i.e., 10 steps for every 1,000 steps) (Modave et al., JMIR Mhealth Uhealth 2017; doi:10.2196/mhealth.7870). Other varieties of activity trackers from a number of different companies also only under-/over-estimate step counts by <4% (Modave et al., JMIR Mhealth Uhealth 2017; doi:10.2196/mhealth.7870). However, we acknowledge that this is a limitation compared to giving every participant an identical research-grade accelerometer).

Author Action: We have added content to the discussion section acknowledging this limitation (page 23, line 524-6):
We also acknowledge that the wrist-worn activity tracker (Garmin vívofit® 4) or other commercial devices that participants wear may under-/over-estimate daily step counts, however the differences with research-grade accelerometers appear minimal[69].

8. There is also a typographical error on line 364 (actvity should be activity).

Author Response: We have now corrected this error.

Thank you for including the detailed study description including many supplemental files that thoroughly describe the study and will be immensely helpful for readers/clinicians. I commend the authors for designing and conducting this study and look forward to reading the results in a few years.

Author Response: We thank the reviewer for the positive comments regarding our paper.

1

VERSION 2 – REVIEW

REVIEWER	Rhim, Hye Chang Harvard Medical School, Physical Medicine and Rehabilitation
REVIEW RETURNED	13-Dec-2022

GENERAL COMMENTS	The authors addressed the comments/concerns well.