SUPER Knee

Study Protocol

The SUPER KNEE trial: comparing the effectiveness of a SUpervised exercise-therapy and Patient Education Rehabilitation (SUPER) program to minimal intervention (CONTROL) to improve symptoms and prevent osteoarthritis after anterior cruciate ligament reconstruction

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Table of Contents

1. Background

While osteoarthritis typically affects the elderly, 50% of the 100,000 Australians who incur a serious knee injury (anterior cruciate ligament rupture) and subsequent reconstruction (ACLR) annually will develop post-traumatic osteoarthritis and unacceptable persistent pain, functional loss and poor quality of life before the age of 40 years. These young adults usually have occupational and parental responsibilities and thus, the individual and societal burden is formidable.

There is an urgent need to prevent knee osteoarthritis, but primary prevention has thus far proved elusive. Therefore, secondary prevention strategies (targeting those with early manifestations of disease or at high risk of disease) are vital.

Of all young adults who undergo ACLR, the 50% who report inadequate recovery at approximately 1-2 year postoperatively (when full recovery is expected) are at significantly greater risk of poor long-term quality of life. Persistent symptoms, muscle weakness and functional impairments are also important risk factors for cartilage loss and radiographic knee osteoarthritis.

Exercise-therapy has compelling evidence to improve pain and function in older adults with knee osteoarthritis. However, international osteoarthritis guidelines identified an urgent need to determine whether the benefits of exercise-therapy are seen in younger people at risk of post-traumatic knee osteoarthritis. Exercise-therapy also has greater potential to slow disease worsening early in the osteoarthritis disease process, than in those with established osteoarthritis.

The SUPER KNEE trial is a randomised controlled trial aiming to evaluate the impact of physiotherapist-led exercise-therapy and education on optimising knee symptoms, function and quality of life, and preventing early osteoarthritis in young adults following ACLR. The trial will recruit 184 adults aged 18-40 years with persistent symptoms 9-36 months post-ACLR. The trial intervention will be run at multiple metropolitan and regional locations throughout Victoria, Australia.

2. Aims and Hypotheses

The aim of the SUPER KNEE trial is to determine the clinical effectiveness and cost-effectiveness of a SUpervised exercise-therapy and Patient Education Rehabilitation (SUPER) program compared to minimal intervention (CONTROL) in young adults at high risk of osteoarthritis following ACLR. To promote interpretation of the results and enable replication in the future, a process evaluation will be undertaken concurrently to capture patient attitudes, exposure, confidence and other factors affecting the implementation of the intervention components.

2.1 Primary hypothesis

That the SUPER program will result in greater improvements on the average score of four subscales (symptoms, pain, function and quality of life) of the Knee injury and Osteoarthritis Outcome Score ($KOOS_4$) compared to the CONTROL group at 4-months post-baseline [H_0: SUPER = CONTROL].

2.2 Secondary hypotheses

- That the SUPER program will result in greater improvements on $KOOS_4$ compared to the CONTROL group at 12- and 18-months post-baseline.

- That the SUPER program will result in reduced worsening of cartilage quality on magnetic resonance imaging (MRI) at 4- and 12-months post-baseline compared to the control group.
- That the SUPER program will be more cost-effective than the control over 18-months.

3. Research Plan

3.1 Experimental design

The SUPER KNEE trial is an assessor-blinded, superiority RCT with two parallel groups (SUPER vs CONTROL). Participants will be recruited from private surgeons and public hospital surgical lists. All aspects of the trial will be managed at La Trobe University. Randomisation will follow a 1:1 ratio and will be concealed using a secure randomisation service established independently. The primary end-point is knee symptoms, function and quality of life assessed with $KOOS_4$ after 4 months.

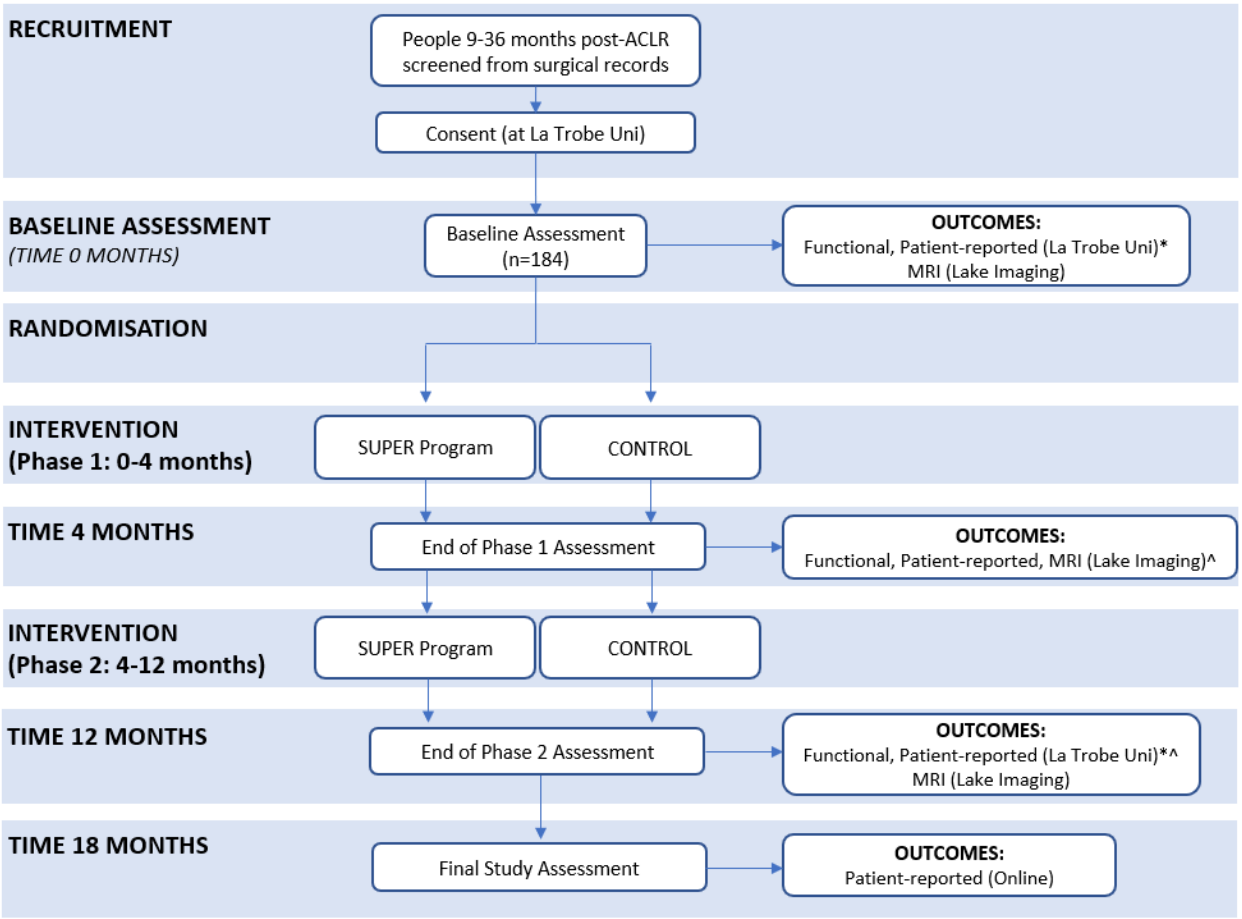

Figure 1. Trial process

* Optional biomechanical assessment at baseline and 12-months

^ Optional qualitative interview for process evaluation at 4-months and 12-months

3.2 Ethical Considerations

The SUPER KNEE trial will be conducted over five years and aligns with the SPIRIT guidelines and the Australian Good Clinical Practice guidelines adhering to the National Statement & Australian Code of

Responsible Research Conduct (trial is TGA exempt). This trial will be prospectively registered on the Australian & New Zealand Clinical Trial Registry (ANZCTR) and ethics clearance will be obtained prior to trial commencement. Additional Department of Health Services ethical approval will be obtained for data linkage of Medicare and Pharmaceutical Benefits Schemes as part of health economic analyses. The conduct of the trial will be overseen by an independent Data and Safety Monitoring Committee, which will assess the safety of the interventions during the trial.

Random sequence generation	☒	Independent computer randomisation (permuted blocks 4-8)
Allocation concealment	☒	Central independent randomisation service
Blinding of participants	☒	Participants blinded to hypotheses
Blinded outcome assessment	☒	Assessors blind to group allocation
Incomplete outcome data	☒	Online questionnaires available, reimbursed for follow-up
Selective reporting	☒	Plan to prospectively register trial and publish trial protocol
Other sources of bias	☒	Data analysed by statistician blind to group allocation

Figure 2. Rigour of proposed trial according to Cochrane Collaboration Risk of Bias tool

4. Participants

184 participants who have undergone ACLR will be recruited from greater Melbourne and Victoria.

4.1 Inclusion criteria

- aged 18-40 years at the time of ACLR
- 9-36 months following ACLR
- $KOOS_4$ score <80/100
- willing/able to complete exercise-therapy 2-3 times per week for at least 4 months

4.2 Exclusion criteria

- synthetic ACLR graft
- concomitant intra-articular knee fracture
- planning to relocate interstate/internationally in following 18 months or unable to commit to the various study assessments over the next 18 months
- knee re-injury/surgery in past 3 months (either knee)
- intra-articular knee injection in past 3 months (either knee)
- ACL graft rupture or cyclops lesion on baseline MRI
- participation in physiotherapy in past 6 weeks (for conditions affecting either knee)
- other health condition affecting physical function
- contraindications to MRI
- pregnancy
- inability to understand English

5. Research Procedure

5.1 Recruitment

Participants will be recruited from participating private orthopaedic surgeons and public hospital sites. Individuals who have undergone an ACLR 9-36 months previously by a participating private orthopaedic surgeon (and aged 18-40 years) will be identified from surgical lists (by the surgeon or practice manager) and mailed a study invitation letter (from the orthopaedic surgeon) together with the plain language statement and how they may participate if eligible. For participating public hospitals, individuals who had an ACLR 9-36 months previously (and aged 18-40 years) will be identified by a local site investigator screening surgical lists at each respective hospital site. Each site investigator will have access to the surgical list as part of their current clinical role. The site investigator will complete a written screening form including patient name, address, telephone number and e-mail address (if available). The site investigator and/or a member of the La Trobe University research team (assisting the site investigator) will send the introductory letter to potentially eligible patients (on behalf of the head of orthopaedics from the health service where the ACL reconstruction was performed) together with the participant information statement. The introductory letter will provide an opt out option, whereby potential participants who do not wish to be contacted further about the study may notify the research team to opt out from being contacted. The necessary agreements at each hospital site will be established to allow La Trobe researchers to assist in the administration tasks of mailing invitation letters and making follow-up phone calls (e.g., confidentiality agreement, student placement agreement, honorarium position). A member of the research team will follow-up individuals who have not contacted the research team by 2 weeks after the introductory letter being sent to provide more information and answer any questions. We have used this method successfully in previous pilot work[1].

5.2 Eligibility screening

Participants interested in participating will be screened using a short telephone screening survey to determine eligibility (including safety screening for MRI). The $KOOS_4$ screening questionnaire will be completed to confirm symptomatic eligibility. This can be completed over the phone, via an email link to a secure electronic data collection system (REDCap) or by hard copy via mail with a reply-paid envelope, with method of completion determined by individual preference.

5.3 Informed consent and baseline testing

Once eligibility has been confirmed, those meeting the criteria will be invited to participate. They will be asked to complete informed consent, demographic characteristics and patient-reported outcome measures using REDCap or paper forms as required. Participants will be assessed for baseline objective measures of physical function (e.g. hop, balance and strength tests) and gait biomechanics at La Trobe University, and undergo a knee MRI at Lake Imaging Specialist and Research Centre, North Melbourne (see Outcomes section for details).

5.4 Randomisation and blinding

Once baseline patient-reported and functional measures have been completed at La Trobe University, participants will be randomised to either the SUPER Intervention or CONTROL Intervention. Randomisation schedule will be developed by a secure randomisation service established independently to the research team (concealed allocation) and will include random permuted blocks of 4-8, so that an allocation ratio of 1:1 will be maintained at periodic intervals. The randomisation schedule for each participant will be revealed to an unblinded member of the research team who will communicate

treatment allocation to the participant. Research assistants who conduct the baseline and follow-up assessments will be masked to group allocation.

5.5 Fortnightly/Monthly questionnaires

All participants will receive either a fortnightly (during Phase 1) or monthly (during Phase 2) online questionnaire via the secure online platform (REDCap) (or hard copy mailed, or phone call depending on participant preference) to assess sports activity, adherence to exercise-therapy, and any adverse events/other treatment.

5.6 4-month follow-up assessment

All participants will be re-assessed for functional, patient-reported and MRI outcomes at the completion of Phase 1 of the trial (4-months post-baseline: primary outcome point for $KOOS_4$) at Lake Imaging Specialist and Research Centre, North Melbourne. Patient-reported outcomes will be completed via the secure online platform (REDCap) (or hard copy mailed if preferred), and all functional measures will be assessed by the blinded assessor.

5.7 12-month follow-up assessment

All participants will be reassessed at the completion of Phase 2 at 12-months post-baseline both at La Trobe University (functional, patient-reported outcomes) and Lake Imaging Specialist and Research Centre, North Melbourne for MRI.

5.8 18-month follow-up assessment

All participants will be reassessed for patient-reported outcomes at 18-months post-baseline via the secure online platform (REDCap) (or hard copy mailed if preferred). Participants do not need to attend the 18-month assessment in person as only patient-reported outcomes (online or post) will be assessed.

6. Interventions

6.1 Experimental Intervention

SUpervised exercise-therapy and Patient Education Rehabilitation (SUPER) Program

Lower-limb muscle weakness and under-loading of the knee are linked to the development of radiographic post-traumatic osteoarthritis and are some of the earliest findings in patients with post-traumatic osteoarthritis. Exercise-therapy to improve muscle strength and knee joint loading can address the risk factors for osteoarthritis and hence, are key components in the SUPER Program. The objectives of the SUPER intervention are to optimise lower-limb muscle strength, endurance and power, as well as functional performance and neuromuscular control, and facilitate return to desired sports activity and enhance physical activity.

The SUPER intervention has been designed with input from active clinicians and patients. Registered physiotherapists with ≥3 years of relevant experience will deliver the SUPER intervention in the community. To minimise participant burden, study physiotherapists will be located at multiple private physiotherapy clinics across our established clinical network in greater Melbourne and regional Victoria.

At the completion of baseline testing, participants who are randomised to the SUPER intervention will be provided with details of the SUPER intervention by a registered physiotherapist (not involved in baseline testing), which includes an intervention handbook detailing the types of exercises to be performed, demonstration of online educational resources, exercise log book, and "other treatments calendar" for healthcare resource utilisation information. The physiotherapy clinic most convenient for the participant will be notified of a new participant and will be provided with the participants baseline functional results to assist with initial set up of exercise choice and intensity. Participants will also be educated regarding the importance of supervised (and unsupervised) exercise-therapy adherence. Participants will be advised how to make an appointment with the relevant study physiotherapist to commence the SUPER program.

6.1.1 Exercise-therapy component

The SUPER intervention is split into two main phases. In Phase 1 (0-4 months), all participants randomised to the SUPER intervention, will receive the same duration and frequency of exercise-therapy and education (2 x weekly supervised sessions and 1 x weekly unsupervised session at gym/home, depending on individual preference) (Figure 3). Supervised physiotherapy-led sessions (either group or 1:1) will be 1-hour duration. The Phase 2 intervention will depend on whether predefined criteria are met at the 4-month follow-up assessment (Figure 3).

For participants meeting all criteria, Phase 2 will involve ongoing unsupervised exercise-therapy sessions (gym/home), with the option of booster physiotherapy sessions as required. If all criteria are not met, Phase 2 will involve ongoing once per week supervised exercise-therapy. Once all criteria are met, participants will continue exercise-therapy sessions at gym/home with booster sessions as required.

Participants will be contacted via phone at 2 monthly intervals to increase adherence, with the option of a second opinion by a member of our clinical expert physiotherapy team if the SUPER treatment is failing to facilitate improvement, or adherence is low (Figure 3). This approach of including second opinion reflects real-world clinical care. All participants in the SUPER intervention will be provided with a membership to a local gym to encourage unsupervised exercise-therapy adherence during Phase 2. Exercise options/progressions will be provided to the treating physiotherapists in a treatment manual at the initial physiotherapy training session. The specific exercises and education intervention will be tailored to each participant to match their individual preferences, goals and clinical presentation (e.g. strength, pain severity, personal, sporting, work and functional needs). The three key components (lower-limb and trunk muscle strength; movement quality; and sport- or activity-specific retraining) have phases of increasing difficulty. The physiotherapist will supervise and progress exercises based on defined criteria (perceived difficulty, minimal pain), and provide feedback during each visit. Equipment (e.g. TheraBand, weights) will be provided for participants to be able to complete exercises at home.

Treating physiotherapists will keep clinical records of exercises prescribed and dosage/intensity, and the completion of unsupervised exercises and dosage/intensity will be recorded via a phone application or paper-based log-books as preferred by the participant.

6.1.2 Health education component

Individualised health education regarding expectations and goals, improving adherence, long-term outcomes, weight control, and appropriate physical, occupational and sporting activity promotion, will be delivered during the physiotherapy treatment sessions. SUPER education is delivered face-to-face,

with supplementary web- and paper-based material (e.g. booklet, online videos). Education topics and guidelines will be provided to the physiotherapists at the training sessions and in the treatment manual. Treating physiotherapists will undertake motivational interviewing training with a qualified psychologist as part of the initial training session. Physiotherapists will use motivational interviewing techniques with participants to assist in behaviour change and optimise adherence to exercise-therapy. Participants will be counselled regarding physical activity levels with a targeted training program adhering to Australian Physical Activity Guidelines and an activity monitor (e.g. Garmin™) to promote physical activity goals.

At monthly intervals, physiotherapists will perform functional assessments in the clinic (hop tests, one leg rise) to provide feedback to participants, to help motivate participants and allow the physiotherapist to tailor and progress exercises. Participants will be able to have their travel costs to attend physiotherapy remunerated.

6.1.3 Standardisation

Treating physiotherapists will undergo a 4-hour training session, with treatment manuals, fidelity checks via auditing of treatment notes, and refresher training after 18 months.

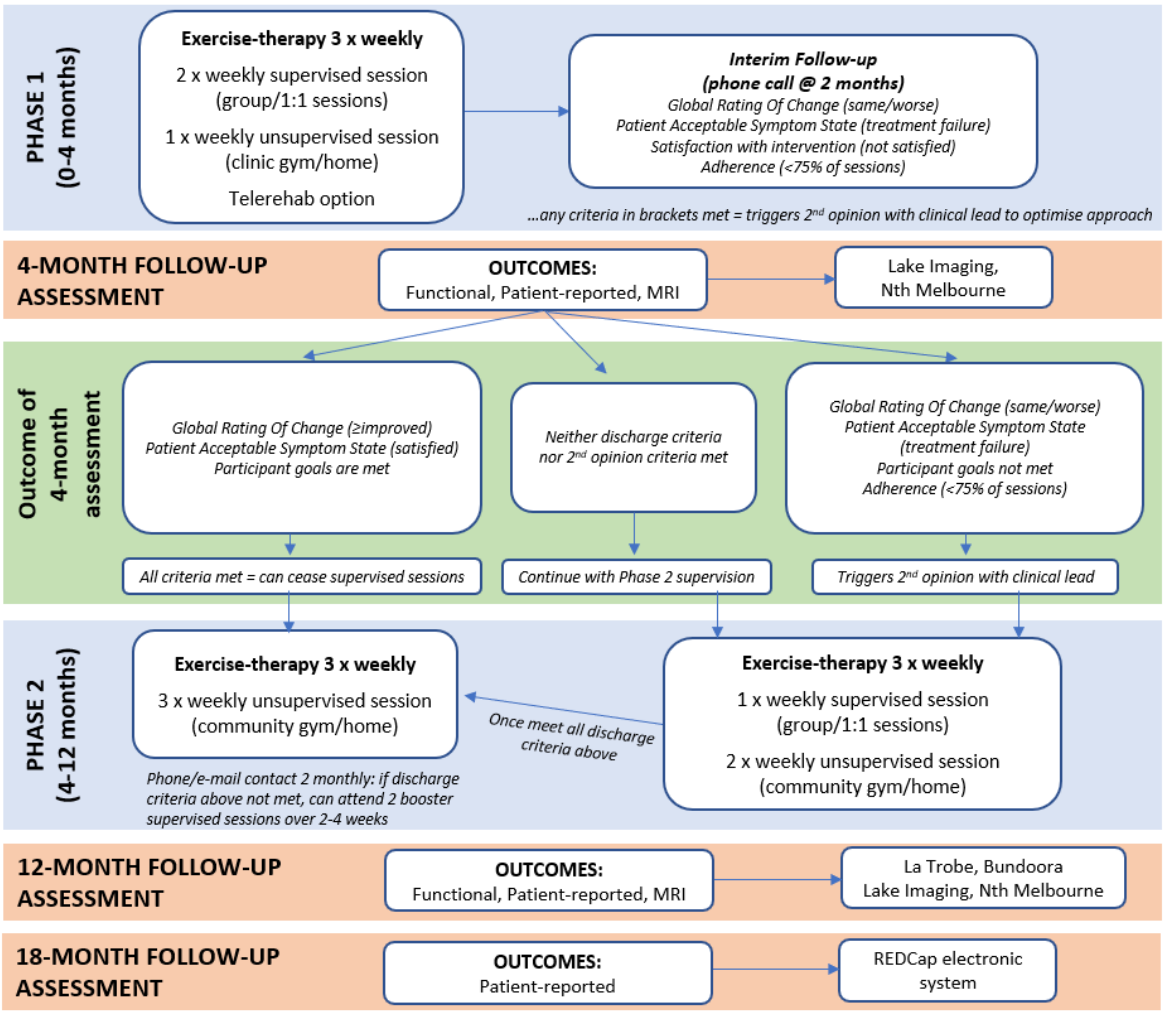

Figure 3. SUPER intervention flow chart

6.2 Control Intervention

Minimal Intervention CONTROL

Participants randomised to the CONTROL intervention (i.e. activity monitoring program) will receive a "best-practice guide" booklet and a face-to-face appointment (at baseline assessment) with a registered physiotherapist with ≥3 years clinical experience (not involved in treating SUPER participants). The physiotherapist will explain elements of the booklet and answer any questions. The booklet was produced based on the information to patients provided by orthopaedic surgeons participating in this trial, together with exercise prescription guidelines and best-available evidence for exercises and education following ACLR. Examples of exercises to strengthen specific lower-limb and trunk muscles, and methods to safely progress these are included, as well as education regarding monitoring and managing symptoms and safe return to sport.

Participants randomised to the CONTROL intervention may also contact the physiotherapist by phone to ask questions/get further clarification. The physiotherapist cannot volunteer information extending the scope of the booklet.

7. Study Outcomes

Blinded outcome assessment will occur at 4 months (primary outcome $KOOS_4$), 12 and 18 months. 12 and 18 months is the primary time-horizon for the knee structure (MRI) and economic evaluation, respectively. Fortnightly (Phase 1) and monthly (Phase 2) collection of co-interventions, adherence, adverse events, and physical activity will be completed via short questionnaires online or via paper log-books.

7.1 Baseline Descriptive Data

Baseline measures will include age, sex, occupational and sporting history, injury mechanism, time from injury to ACLR, rehabilitation, medication use, treatment expectations, family history of osteoarthritis and social determinants of health. Surgical details will be recorded from surgical files including date, graft type, and concomitant injuries/procedures.

7.2 Patient-reported Outcome Measures

- Knee injury and Osteoarthritis Outcome Score (KOOS): Average of four of the five KOOS subscales covering pain, symptoms, difficulty in sports and recreational activities and quality of life ($KOOS_4$). Scores range from 0 (worst) to 100 (best). $KOOS_4$ was validated and the primary outcome in the only high-quality RCT comparing rehabilitation with and without ACLR[2].
- The Tegner Activity Scale assesses knee-related sports activity. It is a numerical scale (0 to 10), with each value indicating the ability to perform specific activities (0=sick leave due to knee, 10=playing competitive sports such as soccer, football, and rugby at an elite level).
- Anterior cruciate ligament – return to sport index (ACL-RSI) assesses attitudes related to, and psychological readiness for, return to sport. Scores range from 0 (no confidence, very fearful) to 100 (full confidence, no fear)[3].
- Tampa Scale for Kinesiophobia assesses kinesiophobia related to the ACLR subjective experience of injury and physical activity[4].

- EQ5D-5L assesses health-related quality of life on five questions of health utility and a visual analogue scale of current overall health status[5].
- Knee self-efficacy scale (K-SES) assesses perceived knee-function self-efficacy capturing health locus of control and self-perceptions of knee function[6].
- Anterior knee pain scale assesses symptoms and levels of current knee function in relation to anterior knee pain.
- Global rating of change (GROC) for pain and function will be assessed on a 7-point Likert scale (much worse, worse, a little worse, no change, a little better, better, much better). Success will be defined as a response of either better or much better.
- Patient acceptable symptom state (PASS) assesses satisfaction with current state of function and to what degree treatment may have failed.
- Health and Labour Questionnaire is a standardised instrument for measuring and valuing health-related productivity losses[7].
- Work Limitations Questionnaire estimates economic influence of presentism at work[8].
- International Physical Activity Questionnaire (IPAQ) to assess self-reported physical activity.
- ACL knowledge and beliefs questionnaire assesses knowledge around key domains of exercise-therapy, psychological impact of injury and long-term joint health.
- ACL-Quality of Life questionnaire (ACL-QOL) assesses knee-related quality of life.

7.3 Objective Clinical Outcomes

- Height, weight, and waist girth will be assessed with standardised wall-mounted stadiometer, scales and tape measure, respectively.
- A common post-injury battery of hop tests including hop for distance, triple crossover hop for distance, side hop and Y-balance test will assess lower-limb function on the index knee compared to the contralateral knee.
- The one-leg rise (maximum sit to stands on one leg from a standardised height chair) will assess lower-limb strength and endurance.
- Quadriceps and hamstring isometric muscle strength will be assessed using an isokinetic dynamometer (Biodex) and rate of force development and steadiness captured.
- Knee effusion (swelling assessed with the sweep test), joint line tenderness and crepitus will be assessed with usual clinical tests.
- Movement quality will be assessed by videotaping knee motion during a single leg squat, single-leg hopping and drop-jump task (drop down off a small step and then jump as high as possible). Degree of knee flexion and frontal plane movement will be assessed from the videos. These videos will not include participant faces so will be unidentifiable.

7.4 Biomechanics

At the baseline and 12-month follow-up visits, we will assess 3D lower-limb biomechanics (VICON) during walking and running, single and double leg drop-jump and single leg hopping. Reflective markers will be placed on the lower-limbs and trunk and participants will be asked to walk and run across force plates in the La Trobe University Gait Laboratory to assess lower-limb kinematics and kinetics. Participants will also drop off a 30cm high step and land on: i) one-leg and ii) two legs.

7.5 Structural Outcomes on MRI

MRIs will be obtained using a 3T scanner (GE) and 16-channel knee coil, on the ACLR knee of all participants at baseline, 4 and 12-month follow-up. Positioning aids will immobilise and support patients laying supine, ensuring consistent, reproducible images. A contralateral knee MRI will also be acquired in a subset of participants without contralateral knee injury/surgery history. Sequences acquired will include proton density weighted fat suppressed sagittal, axial and coronal sequences, and a T2 mapping multi-echo spin-echo sequence. Lake Imaging will provide a radiology report written by a licensed and registered Radiologist with The Royal Australian and New Zealand College of Radiologist

Structural outcomes will be: i) cartilage quality using T2 relaxation time; ii) whole joint morphology using MRI osteoarthritis knee score (MOAKS); and iii) cartilage thickness

Degeneration in cartilage collagen content and orientation in extracellular matrices will be defined by quantitative changes in T2 relaxation times[9]. Post-processing software incorporating automated registration in 3D developed at University of San Francisco, California will be used.

Knee osteoarthritis features (e.g. cartilage, meniscal and bone marrow lesions and osteophytes) will be scored with MOAKS [10] by a trained reader blinded to clinical outcomes. Individual osteoarthritis feature worsening will be defined as increase in the size or depth of lesions as previously established [11].

Cartilage thickness will be assessed by segmentation of knee cartilage plates and reported as the mean cartilage thickness over the total area of the subchondral bone.

7.6 Process evaluation

Semi-structured interviews will be conducted on a subset of participants at 4-months and 12-months post commencement of intervention. Interviews will explore beliefs/experiences; knowledge and understanding of interventions received including potential benefits; acceptability and perceived effectiveness of the intervention; and reasons for adhering (or not) to exercise-therapy and education provided. Purposive sampling will be used to recruit interview participants from different sites (including public and private), and participants will be stratified based upon characteristics and outcomes of trial (good outcome; poor outcome). Approximately 30 interviews (15 SUPER; 15 CONTROL) will be conducted for each time-point (or until saturation is reached). Interviews will be audio recorded, transcribed and analysed using Framework Analysis,[12] supported by NVivo software. Re-identifiable (i.e. coded) audio recording transcriptions will be completed by 'Transcription Australia' on their secure, encrypted Australian-based software. Participants will have the opportunity to review the transcripts and edit their responses as appropriate prior to analysis. Following the completion of analysis of this transcription, the audio file associated with the interview will be deleted.

The qualitative coding process will start with a research team member checked transcripts being read for overall understanding, and to identify emergent themes and concepts. An integrated approach will follow two lines of reasoning. First, the data will be coded deductively according to the code structure generated by the interview topic guide. Second, an inductive thematic analysis following a grounded approach will be applied until no new themes emerge. To enhance reliability, the final code structure will then be re-applied to the data independently by a second member of the research team. Any discrepancies will be discussed between the two researchers until a consensus is reached. NVivo computer software will be used to assist the coding process.

Table 1. Overview of outcomes

	Baseline	2 months	4 months	12 months	18 months
Baseline characteristics					
Age	X				
Sex	X				
Education level, health literacy	X				
Employment status	X				
Prior knee injury/treatment	X				
Injury and rehabilitation details	X				
Medication	X				
Family history of osteoarthritis	X				
Patient-reported Outcomes					
Knee injury Osteoarthritis Outcome Score	X	X	X	X	X
EQ-5D	X	X	X	X	X
ACL – return to sport index	X		X	X	X
Tegner Activity Scale	X	X	X	X	X
Tampa Scale of Kinesiophobia	X		X	X	X
Knee self-efficacy scale	X		X	X	X
Global rating of change		X	X	X	X
Anterior knee pain scale	X		X	X	X
Patient acceptable symptoms state	X	X	X	X	X
Health and Labour Questionnaire	X		X	X	X
ACL-QOL	X		X	X	X
Work Limitations Questionnaire	X		X	X	X
Objective Clinical Outcomes					
Height, weight, waist girth	X		X	X	
Hop tests	X		X	X	
One-leg rise	X		X	X	
Knee effusion	X		X	X	
Muscle strength	X			X	
Movement quality	X			X	
MRI Outcomes	X		X	X	
Biomechanics	X			X	
Semi-structured interviews			X	X	

All participants will receive either a fortnightly (during Phase 1) or monthly (during Phase 2) online questionnaire via the secure online platform (REDCap) (or hard copy mailed, or phone call depending on participant preference) to assess sports activity, adherence to exercise-therapy, and any adverse events/other treatment.

8. Data Management

Data will be generated directly from participants. Participants will complete patient reported outcome measures, physical measures, MRI and qualitative interviews. This information collected from each participant will form the basis of the data generated from this project. Participant questionnaires will be stored electronically on a secure electronic data collection server hosted by La Trobe University

(REDCap) or completed on hard copy and uploaded to REDCap/Excel. Physical measures will be recorded on hard copy data collection sheets and uploaded to REDCap/Excel.

All study related documentation will be stored securely in a locked filing cabinet in a locked office at La Trobe University and in electronic files password protected and stored on the La Trobe University research drive (P:) only accessible to the research team. All data will be deidentified with the use of a participant code.

Identifying documents (e.g. consent forms, screening sheets, data linkage files, intervention clinical notes (by treating physiotherapists)) will be securely stored separately from re-identifiable (i.e. coded) data.

At the completion of the study when the specified period of retention has finished, identifiable data will be disposed in a secure and safe manner in accordance with the Australian Code for the Responsible Conduct of Research, the University Records and Archives Management Policy, and the Victorian Public Records Act 1973.

As recommended by the NHMRC Open Access Policy, non-identifiable data will be made available to be used in future related research upon reasonable request to the research team. CI Crossley will have ongoing custody of data and research outputs, including any intellectual property ownership. Participant privacy will be protected when data are made available by making the data entirely non-identifiable. It will not be possible to identify individual participants from this data.

9. Data Analysis

For the primary hypothesis, generalised linear models (with baseline value as a covariate and treatment condition and referral source [public vs private] as fixed factors) will be used to evaluate the treatment effect on $KOOS_4$ at 4 months ($p<0.05$). A generalised linear model utilising repeated measures at all time-points (for 12 and 18-month secondary hypotheses) will allow non-biased estimates of treatment effect in the presence of any potential missing cases, providing data are missing at random. However, a sensitivity analysis to missing data will also be carried out using multiple imputation to ensure there are no unexpected biases. This approach also permits adjustment for differences between groups in potential confounders at baseline (age, sex, BMI, duration between injury and surgery). A confidence interval excluding 10 points or more on the $KOOS_4$ will be interpreted as a lack of a clinically meaningful difference.

For secondary binomial outcomes (e.g. cartilage defect worsening assessed with the MOAKS), mixed-effect logistic regression models will be used to assess the effect of treatment. Treatment will be included as a fixed factor and covariates will also be included to adjust for potential confounding factors. Estimates of association will be presented as unstandardized regression coefficients and risk ratios, together with 95% CIs.

All randomised participants will be included in the intention to treat analysis and in the safety analysis. Per protocol and as treated analyses will be performed for primary and secondary outcomes by a statistician blinded to group allocation.

10. Economic evaluation

The primary measure for the economic evaluation for each trial arm will be the cost (healthcare system perspective) per Quality Adjusted Life Year (QALY) derived from EQ-5D assessments. Program costs of delivering each intervention will be summarised and included in estimating average costs per patients treated in each arm of the study. Cost estimates will be calculated from treatment resource use, healthcare resource utilisation including co-interventions for knee symptoms (e.g. medicines, complementary treatments, and hospital presentations). These costs will be collected from several sources for corroboration and analysis up to the 18-month primary time horizon. Participant log-books and monthly questionnaires will be used, alongside data from the Medicare and Pharmaceutical Benefits Scheme databases (rebated and out-of-pocket costs).

The EQ-5D is a reliable and valid measure of health-related QoL recommended for economic evaluations[5], and suitable for use in people following ACLR. It will be administered at baseline, 4, 12, and 18 months to permit calculation of QALYs using an area under the curve approach. A utility score will be generated from the EQ-5D questionnaire, which ranges from 1 (perfect health) to -0.59 (severe problems on all 5 domains).

Indirect costs (e.g. lost work days) that are not accruable to healthcare costs will be reported, but not included in the primary economic evaluation from the healthcare system perspective. Healthcare utilisation data will be costed at market rates (e.g. using Medicare and PBS costing). A trial-based incremental cost-effectiveness ratio (ICER) will estimate the incremental cost-effectiveness of the treatment approaches consistent with the trial arm comparisons outlined in the data analysis.

11. Fidelity Assessment

Fidelity assessment will be undertaken annually at each physiotherapy site where at least 5 participants have been treated to ensure key components of the intervention are delivered, adherence to the protocol throughout the trial. Files will be audited, and routine interventions will be observed at least annually.

12. Intervention adherence, adverse effects and co-intervention

In both SUPER and CONTROL groups, adherence will be collected in a number of ways: i) via a secure online app (e.g. Physitrack™) and/or self-reported paper log-books as preferred; and ii) via a monthly physical activity/exercise-therapy questionnaire completed via a secure online platform (REDCap). For participants randomised to the SUPER group, adherence will also be collected via attendance at physiotherapy supervised group/1:1 sessions.

To increase adherence, we will provide opportunity for participants to attend physiotherapy clinics at various locations, to minimise transport burden, and telerehabilitation (via Zoom) is available if needed. We will also train treating physiotherapists in the use of motivational interviewing techniques to assist adherence and retention. Participants from both SUPER and CONTROL groups will have their travel costs to attend baseline and follow-up assessments remunerated.

Any adverse events and serious adverse events will be recorded via a fortnightly (during Phase 1) and monthly (during Phase 2) questionnaire by asking participants if they have experienced any illness or injury that has affected their ability to function normally, and whether they have seen any health care professional (apart from physiotherapy as part of the SUPER intervention). Furthermore, open probe questioning will enquire about possible adverse events at each of the follow-ups. The MBS data obtained as part of cost-effectiveness analysis at final follow-up will also be checked for any possible adverse events.

An adverse event is defined as any undesirable experience during follow-up causing participants to seek medical treatment (e.g. general practitioner). A serious adverse event is defined as any undesirable event/illness/injury classified as having the potential to significantly compromise clinical outcome or result in significant disability or incapacity, those requiring inpatient or outpatient hospital care, to be life-threatening, or to result in death. Adverse events will be categorised into index knee or other sites and will be provided to the data safety monitoring committee for assessment.

In both randomised groups, co-interventions will be monitored with a "other treatment log-book" and via a fortnightly (during Phase 1) and monthly (during Phase 2) questionnaire regarding other treatments.

13. Sample Size

A total of 184 participants (equally allocated) will enter this two-armed parallel-design trial. For the primary outcome of $KOOS_4$, the overall effect size for exercise-therapy on self-reported pain and disability is moderate (0.50) [13]. With this effect size, to achieve 85% power at a two-sided 0.05 significance level on the $KOOS_4$, 146 participants are required. To account for an estimated 20% drop-out, we will recruit 184 participants. This sample size will be sufficient to detect a minimal important change (MIC) in $KOOS_4$ of 9-points (with standard deviation of 15)[14 15]. If the intended sample size is not reached at 30 months after recruitment commencement, the inclusion of participants will stop at 160, which will ensure a power of 80%, anticipating 20% loss to follow-up.

Including a minimum of 160 participants will also provide ≥90% power to detect a statistically significant difference (α=0.05) on the secondary outcome of cartilage quality on MRI (change in cartilage T2 relaxation time) between SUPER and CONTROL groups (anticipated effect size of 0.59)[16].

14. Privacy and Confidentiality

Participants will be made aware that re-identifiable (i.e. coded) data will be used for this study. All data will be reported in a re-identifiable and aggregated format so that individuals will not be able to be identified. All records will have an identifying number only and will not include the names or contact details of participants. The code linking participant names and contact details will be kept separately in a locked filing system. All data will be stored according to La Trobe University and hospital policies; these comply with NHMRC guidelines for conduct of research (http://www.nhmrc.gov.au/publications/synopses/e72syn.htm). Participants will be informed that if they choose to withdraw from the trial that personal health information already collected will be

retained, unless an explicit request to the contrary, to ensure that the results of the research project can be measures properly.

Data obtained at hospital sites during the screening process on the participant screening sheet will be scanned and transferred to the Trial Coordination Site (La Trobe University) by e-mail. Data will be electronically shared using organisational email addresses only. Electronically shared data will be stored in electronic password protected folders on the La Trobe University research drive (P:) only accessible to the research team. Electronic data transfer will allow for timely data collection.

Re-identifiable (i.e. coded) linked data provided by the Medicare and Pharmaceutical Benefits Scheme databases will be submitted into, and maintained within, a secure data research storage system. Only approved members of the research team will have access to these data and it will be used solely for the purposes of this project.

15. Reporting Project Results

Reports containing the results of the project will be provided to the NHMRC who provided funding, and a lay summary report will be available for study participants on request. The results will be reported in peer-reviewed publications and presented at scientific conferences. Only aggregate data will be reported. Individuals named as site investigators on the Clinical Trial Research Agreements (CTRAs) and/or *Health Service* Research Governance authorisations will be recognised in the acknowledgments section of all publications arising from the study that include participants recruited from *Study staff, Health Service or Institution* unless they elect not to be acknowledged. Private orthopaedic surgeons who have at least one of their patients included in the study will also be recognised in the acknowledgments sections of all publications arising from the study unless they elect not be acknowledged.

16. Funding

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17. Potential Significance

Despite the best efforts of primary prevention strategies, ACL injuries and subsequent reconstructions in young Australians have increased ~200% over the past 20 years (Medicare Data 1994-2016). These young adults are at high risk for persistent pain and symptoms, impaired QoL and early-onset knee OA. This underscores an urgent need for secondary prevention strategies to prevent post-traumatic knee osteoarthritis - an epidemic of young people with old knees.

This study will evaluate the world's most comprehensive education and exercise-therapy intervention for people with post-traumatic knee osteoarthritis, which is: (i) developed on the foundation of our substantial prior work in this field; (ii) informed by patients and clinicians; (iii) feasible to implement; and (iv) underpinned by a strong scientific rationale to reduce the burden for those at risk of post-traumatic osteoarthritis. The SUPER intervention has the potential to reduce the symptomatic burden, be cost-

effective, and slow the structural disease trajectory. Our trial fills an urgent need for clinical trials evaluating musculoskeletal conditions in Australia.

By improving patient outcomes beyond the unacceptable levels currently experienced, we will enable greater participation in work, physical, family and social activities. These improvements in outcomes are integral to a productive and available Australian workforce and facilitating healthy ageing.

By establishing the cost-effectiveness, we will demonstrate the benefits of our best-practice intervention to inform future models of osteoarthritis care. Changing healthcare funding models is beyond the scope of this proposal, but cost-effectiveness data will contribute to evidence-informed resource allocation.

If we succeed in reducing the rates of osteoarthritis worsening, we will be the first in the world to modify the trajectory of post-traumatic structural osteoarthritis disease with an exercise-therapy intervention. Our results will have potential for longer term outcomes, including reducing the risk of early joint replacement. We will help to keep these young adults, who are typically active and healthy prior to injury, from becoming major participants in our future health care system.

This project has the potential to transform the research and practice landscape of knee injury, ACLR and osteoarthritis rehabilitation. Optimising management to achieve better outcomes and curtail the rapid trajectory of post-traumatic knee osteoarthritis will reduce the formidable personal and health care expenditure burden currently associated with this common condition.

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