A comparison of two different treatment approaches for adolescents with Osgood-Schlatter (the SOGOOD trial): Protocol of a randomized controlled superiority trial

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Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers.[1] The order of the items has been modified to group similar items, as recommended by the TRIALS journal.[2]

Version:{3} 1.4, 04-APR-2024. Revision history:

Version	Date	Amendment
1.0	30-MAR-2021	• First draft submitted to ethical review board (Regional Committees on Health Research Ethics for The Capitol Region).
1.1	30-NOV-2021	• Second draft (full protocol with embedded statistical analysis plan) with approval identifiers from the Capital Region Data Protection Agency, Denmark (P-2021-818) and the Regional Committees on Health Research Ethics for The Capitol Region, Denmark (H-21028912). • Registration submitted at ClinicalTrials.gov
1.2	30-DEC-2021	• Updated with ClinicalTrials.gov registration identifier (NCT05174182) and full protocol submitted as supplementary document.
1.3	01-MAR-2023	• Added pilot study results (n=15) and the consequential amendmends to trail procedures. • Added details on mediation analysis framework. • Added details on interventions (embargo lifted). • Added details on qualitative study. • Changed safety outcomes from “Serious adverse events” and “Adverse events” to “Any adverse events” in accordance with outline methods.
1.4	04-APR-2024	• Full protocol submitted as supplementary document to ClinicalTrials.gov registration (NCT05174182).
1.5	05-APR-2024	• Submitted (proofs) for peer-review publication in *BMC Sports Science, Medicine and Rehabilitation* in shorter journal format.

Appendices and supplementary:

Supplementary files doi.org/10.6084/m9.figshare.c.5730008.v1:

- REDCap instruments with all patient-reported outcomes and data-collection forms (Danish)
- Written participant information (Danish) {32}
- Informed consent forms (Danish) {24}
- Approval from Ethical review board (Danish) {24}
- Description and materials (Danish) for the interventions (previously under embargo)
- Full directed acyclic graph for proposed causal framework for mediation and moderation analysis

Abbreviations

AEs = Adverse events
AKPP-test = Anterior Knee Pain Provocation test
CONSORT = Consolidated Standards of Reporting Trials
EU = European Union
EQ-5D-Y = EuroQol, five domains, Youth
FINER = Feasible, Interesting, Novel, Ethical and Relevant
GROC = Global rating for Change
ICC = Intraclass Correlation Coefficient
KOOS = Knee Injury and Osteoarthritis Outcome Score
MCID = Minimially clinically important difference
MVPA = Moderate to Vigorous Physical Activity
NPRS = Numerical 0-10 pain rating scale
PA = Physical Activity
PASS = Patient Acceptable Symptom State
PHV = Peak Height Velocity
PICOT = Population, Intervention, Comparator, Outcome, Time frame
PRE-SPEC = PRE-SPECifying a statistical analysis strategy in clinical trials
PS-FS = Patient-Specific Functional Scale
QRPs = Questionable Research Practices
REDCap = Research Electronic Data Capture
SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials
TSK-17 = Tampa Scale of Kinesiophobia, 17 items
VAS = Visual Analogue Scale
WHO = World Health Organization
WIA = Working Alliance Inventory

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Abstract

Background

The most common growth-related injury is Osgood-Schlatter, which affects up to 1 in 5 physically active adolescents. It can cause long-term pain and potential discontinuation of sports and physical activity, with sequela well into adulthood. No effective treatments have been documented, and clinical practice is characterized by a wealth of conflicting advice and modalities. A novel treatment approach has shown promising results in a small single-cohort study. Therefore, we aim to compare this novel treatment with usual care in 10-16-year-old adolescents with Osgood-Schlatter.

Methods

This single-center pragmatic, double-blinded, randomized, controlled superiority trial, will have a two-group parallel arm design. Participants will undergo 3 months of treatment, followed by 2 months of self-management with self-reported knee function (KOOS-child 'Sport/play') at 5 months as the primary endpoint. In this protocol, we outline the planned methods and procedures, including the statistical analyses plan.

Discussion

This trial comparing a novel treatment with usual care for adolescents with Osgood-Schlatter could result in an evidence-based treatment that is ready for implementation in clinical practice, thereby improving patient outcomes and guide clinicians in the management of Osgood-Schlatter patients.

Trial registration and protocol repository: NCT05174182

Keywords: Osgood-Schlatter, Apophysitis, Adolescents, Sport, Physical activity, Knee, Load management, Strength training, Accelerometer, Ultrasound

Anticipated date of first recruitment: 03-JAN-2022

Target sample size: 130 participants

Introduction

Background and rationale {6a}

Being physically active during adult life is key for health and prevention of disease and carries additional benefits during adolescence, such as improved academic abilities and cognitive function.[3–6] Besides somatic advantages, participating in sports for adolescents fosters meaningful social networks, lowers the risk of criminal activity, drinking, and substance abuse.[7–9] The levels of physical activity declines during early adolescence, and less than 20% are currently meeting recommendations for moderate-vigorous physical activity or sports participation.[10]

As adolescence is a period of increased autonomy, behaviors established during this period could potentially last into adulthood.[11,12] Several barriers exist to physical activity and sports participation during adolescence, such as the risk of injury and pain during activity. In line with this, lower limb pain is the most frequent cause for seeking primary care during adolescence,[13] as 40% of active adolescents experience knee pain,[14] and up to half of sports active adolescents regularly take pain medication for injury-related pain.[15] In addition, almost a third of adolescents quitting their sport reports injuries or pain as the main reason.[16]

Osgood-Schlatter affects up to 1 in 5 physically active adolescents and is the most common growth-related injury.[17–21] The condition affects the knee, specifically the proximal tibial apophysis (the weakest part of the muscle-tendon-bone complex).[22,23] Osgood-Schlatter can lead to long-term pain, swelling, and most notably, potential discontinuation of sports and physical activity, with potential sequela into adulthood.[3,24–32] Osgood-Schlatter might also predispose to maladaptation in the maturing bone,[33,34] inhibition of muscle activation,[35] or more serious traumatic knee injuries, such as tendon-avulsion and ligament tear.[29,36,37] Increased loading from sports participation seems to be a trigger as adolescents who practice more have a higher rate of Osgood-Schlatter.[38] Data have also shown that adults who suffered sports-related injuries during youth are prone to musculoskeletal problems and poor health and having suffered knee pain before adulthood increase the risk of chronic pain later in life.[39,40,41] In addition, investigations into longstanding knee pain in adolescence have shown that suffering from knee pain is related to lower quality of life, general health, and sports participation.[31,42]

Research into Osgood-Schlatter and other lower limb apophysitis is only just emerging despite its first documentation in 1903.[43,44] Only trials on injection therapy exists, and the recommended types of modalities for conservative management of Osgood-Schlatter is abundant and conflicting in the literature, reflecting the lack of evidence in this area for first-line conservative treatments.[43,45–50]

The notion that adolescent knee pain is self-limiting with a favorable prognosis is widespread but recent data suggest this is not the case, as even when treated, it can be long-lasting.[42,45,47,51–54] This presumption might partly explain the state of the current management of Osgood-Schlatter, being characterized by a wealth of advice, from total cessation of sport, participation under the pain-limit, play-through-pain, wait-and-see, and cast-immobilization; to passive therapies such as shockwave therapy, ultrasound therapy, laser therapy, injections, surgery, vitamin-supplements, cryotherapy, dry-needling, massage, stretches, and manual manipulations.[31,43,45–47,49,55–58]

Need for a trial

This highlights the need for an effective conservative management approach. Our group recently published data from a cohort of adolescents with patellofemoral pain who received an intervention based on a self-management approach containing gradual exposure to sports and physical activity using a guidance tool based on pain response and progressive exercise therapy.[59] This was associated with a 86% rate of successful outcomes after 12 months, with 81% being back to sport and physical activity, and 67% being pain-free.[59] In line with this, our group explored a similar intervention in a smaller cohort of adolescents with Osgood-Schlatter and had comparable promising results.[60]

With our current knowledge, a robust comparison of our novel approach to a standardized usual care treatment package in a well-powered randomized setting is highly warranted. This would also require a mapping and synthesis of the current usual care practice as no standards exist.

Review of the current literature

We have performed a basic systematic literature review on trials in adolescents with Osgood-Schlatter to ensure that the trial is not redundant or wasteful.[61] We searched MEDLine, CENTRAL and EmBase using the search terms: (‘osgood’ OR ‘schlatter’) in June 2021. A systematic review that evaluated interventions for Osgood-Schlatter was found, concluding, “*Carefully controlled studies on well-described treatment approaches are needed to establish which conservative treatment options are most effective for patients with OSD*”.[62] In addition, four trials are registered on clinicaltrials.gov. One aims to evaluate cast immobilization with complete rest (completed 2016), another myofascial massage over usual care (currently recruiting), and a third comparing stretching with cryotherapy, NSAIDs, and relative rest (last updated 2013). One recent trial-registration from a member of our study group, compares some of the different components used in experimental intervention, in a 3-armed trial, thus comparing tailored progressive

loading and return to sport vs. pain guided activity vs. 4 week rest (recruitment started January 2023). Therefore, the rationale and scientific justification for this trial, remains.

Primary aim

The primary aim is to investigate the superiority of 3 months of a novel treatment approach compared to standardized usual care after 5 months, measured on the KOOS-child 'Sport/play' subscale, in adolescents with Osgood-Schlatter.

Research question

Therefore, we propose the following research question:
Is a novel 3 month treatment approach superior to standardized usual care for improving patient-reported knee function after 5 months in patients with Osgood-Schlatter?

Our research question fulfills the FINER-criteria, as it is considered both Feasible, Interesting, Novel, Ethical and Relevant.[63] These criteria are important when attempting to optimize features of trial design to maximize the usefulness of clinical trials.[64–66]

The research question is based on the PICOT model with the following denotations for each item:
Population: 10-16-year-old adolescents with Osgood-Schlatter
Intervention: 3 month of a novel treatment approach
Comparator: 3 month of standardized usual care
Outcome: Patient-reported knee function on KOOS-child 'Sport/play' subscale
Time frame: Primary endpoint after 5 months

Objectives

This trial has several objectives that have been outlined according to the SMART-model (Specific, Measurable, Achievable, Relevant, Time Bound)[67] in table 1.

Hypothesis

The hypothesis for the primary aim, is that the mean KOOS-child 'Sport/play' subscale change score at month 5 is larger for the novel treatment approach compared to standardized usual care in adolescents with Osgood-Schlatter.

Secondary aims

- Compare secondary and exploratory patient-reported, clinical and objective measures of improvement and adverse effect, also at secondary timepoints at 3 months, and at long-term follow-up after 8, 10, 12, 24, and 48 months (table 10 & 11).
- Supply detailed trajectories of treatment response by collecting weekly self-reported measures and data from activity sensors during the entire 5 month core study period using visualizations and mixed effect analysis models.
- Explore factors associated with effect moderation or mediation to determine who will potentially benefit more or less of treatment, and the pontential mechanisms responsible.
- Investigate the experience of undergoing the intervention and identify potential barriers or facilitators to treatment and adherence.
- Evaluate features and procedures of the trial in a pilot-setting to assess operational feasibility

Timepoints

The primary and secondary fixed endpoints are chosen based on the fact that our previous cohort had trajectories of pain, knee-function, and sports participation that were not fully recovered at 12 weeks,[60] and that some participants had not progressed fully through the exercise regime. Thus, we decided to add a period of complete self-management by adding 2 months to the timeline before the primary endpoint. We have found this alteration to be feasible in clinical practice.[68] This will also allow the novel treatment approach to work in a real self-management setting, rather than only during the course of the supervised treatment. To an overview of visits and timing of data collection, see figure 2 and table 11.

Table 1. Objectives {7}

Primary objective(s)	**Between-group compared endpoints related to primary objective(s) at month 5**
To assess the relative efficacy of the novel treatment approach on patient-reported knee function	Patient-reported knee-function evaluated with the KOOS-child 'Sport/play' subscale
Secondary objective(s)	**Between-group compared endpoints related to secondary objective(s) at month 5**
To assess the relative efficacy of the novel treatment approach on **patient-reported** outcomes	Patient-acceptable Symptom-state question (Y/N) KOOS-child 'Quality of Life' 0-100 subscale (5 items) KOOS-child 'Pain' 0-100 subscale (8 items) 4-week-average episodes of pain flares (≥4 on 0-10 NPRS) Worst pain past week (0-10 NPRS) Satisfaction with extent of sports participation Global rating of Change (7-point likert scale) Patient-specific function scale (NRS 0-10) Kinesiophobia (Tampa Scale of Kinesiophobia, 17 items) Self-rated health (EQ-D5-Y 0-100 VAS) Level of pain/discomfort (EQ-D5-Y 4) Pre knee pain level of sports participation Pre knee pain level of physical activity

	Time to return to sport (week no.) Satisfaction with treatment (Y/N) Problems with usual activities (EQ-D5-Y 3)
To assess the relative efficacy of the novel treatment approach on **objective** outcomes	Anterior Knee Pain Provocation test (0-10 NPRS) Pain during knee extension test (0-10 NPRS) Pressure-pain threshold at the tibial tubcle (kPa) Maximal isometric knee extenstion strength (Nm/kg) Countermovement jump height (cm) 4-week average hours of sports participation 4-week average hours of physical activity Known pain during manual palpation Pain during countermovement jump (0-10 NPRS) Countermovement power (W) Knee extensor flexibility change (°)
To assess the relative efficacy of the novel treatment approach on tissue **morphology** through ultrasound imaging	Tendinosis signs (thickening or hyperemia) Hyperemia of the tibial tubercle ad modum Öhberg Infrapatellar bursitis signs (thickening or hyperemia) Flaviis composite severity score
To assess the relative efficacy of the novel treatment approach on **safety**	Any adverse events
	Variables analyzed for moderating the effect on selected outcomes
To asses, if potential baseline variables **moderates** the effect of the intervention	Treatment expectations Peak height velocity offset Timing of maturation Flaviis composite severity score Maturation stage of the apophysis Pain frequency: KOOS-child child question P1 on 'Pain' subscale (1-5 likert scale) Symptom duration Kinesiophobia (Tampa Scale of Kinesiophobia, 17 items) Worst pain past week (0-10 NPRS)
	Variables analyzed for mediating the effect on the primary outcome
To asses, if potential intermediate variables **mediates** the effect of the intervention on the primary outcome	Change in worst pain past week (0-10 NPRS) at week 4 Change in pressure-pain threshold at the tibial tubcle (kPa) at week 4 Controlled return to sport (<2 hours/week) at week 5 Pain flare frequency (no.) at week 13 Therapeutic Alliance (WAI) at week 13 Change in kinesiophobia (Tampa Scale of Kinesiophobia, 17 items) at week 13 Change in pain during knee extension test (0-10 NPRS) at week 13 Change in maximal isometric knee extenstion strength (Nm/kg) at week 13 Change in distal patella tendon hyperemia (ad modum Öhberg 1-4) at week 13 Change in infrapatellar bursitis signs (thickening or hyperemia) at week 13
	Qualitative analysis
Investigate the **experience** of undergoing the intervention and identify potential barriers or facilitators to treatment and adherence (n=24)	Currently planned as analyses of experiences reported by participants in semi-structured interview group sessions stratified on group-allocation and age.
	Feasibility domains evaluated for first 15 participants until month 3
Evaluated features and procedures of the trial to assess **operational feasibility** (n=15)	Barriers to accepting enrollment or randomization Dropout rate and causes Incidents of staff og patient in-comprehension of procedures, measures or materials

	Capacity Safety concerns Any unforeseen challenges by staff
	Variables collected
Describe **features** of the included population sample	Previous treatment and use of painkillers Health-related behaviors Anthropometrics Pubertal and skeletal maturaity, and predicted adult height

Trial design, reporting, and conduct {8}

The trial is a single-center pragmatic, double-blinded randomized controlled superiority trial, with a two-group parallel arm design and 1:1 group allocation ratio.

The full clinical trial protocol is based on the PREPARE Trial Guide and follows the reporting items from the SPIRIT checklist in the order proposed by the Trials Protocol Template, and is supplemented by items from the WHO protocol recommendations; the Danish Committee on Health Research Ethics, and the Transparency Checklist.[1,2,69–72] The reporting of the results will adhere to the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting a) pragmatic trials, b) harms, and c) non-pharmacologic treatment interventions.[73,74] Description of interventions follows current best-practice guidelines for reporting exercise-based interventions.[75–77] The trial procedures will adhere to non-pharmaceutical standards of Good Clinical Practice E6(R2).[78] The embedded Statistical Analysis Plan will follow recommendations from the PRE-SPEC framework (PRE-SPECcification of statistical analysis strategies in clinical trials)[79] complemented with guidelines from the EMA (E9), JAMA, and field guidelines.[80–82] Analytical code for the primary outcomes will be shared along the primary publication.[83] Data will be reported in sufficient detail to allow inclusion in potential future meta-analyses.[84]

To increase the transparency, validity, and robustness of the trial, we have posted this protocol as a timestamped pre-print publication to the ClinicalTrials.gov repository before commencement of data collection as a supplementary to the registration (NCT05174182). Pre-registration and pre-print publication of protocols ensures greater adherence to a priori decisions regarding data collection and analyses and is thus associated with higher dissemination rate[85,86] and lower risk of bias.[87] In addition, it appears to address prevalent QRPs (Questionable Research Practices)[88,89] and produce more conservative estimates[90,91] and increased rate of null-findings.[92–94] However, sections describing the contents of the experimental intervention (and supplementary leaflets and precise descriptors) have been uploaded to the Figshare repository previously under embargo until final recruitment to prevent premature uptake of the

experimental intervention until data on its efficacy is established, and to prevent potential unblinding of group-content for potential future staff and participants (10.6084/m9.figshare.c.5730008.v1). However, as recruitment of personell is finalized and participant unblinding stemming from this version of the protocol is a minor concern at this stage is in the trial, the embargo has been lifted and intervention descriptions has been included in the protocol.

We chose features of trial design based on the following:
Superiority framework: As our preliminary study[60] has shown promising results for patients having tried other treatments and with a significant duration of symptoms, we hypothesize that the experimental intervention is superior, and the trial design and analyses-plan reflects this hypothesis, e.g. by utilizing one-sided hypothesis testing for statistical analysis.
Two-group parallel-arm design: This design was chosen as the design is simple and therefore easier to understand and implement for patients and clinicians, is simple to include in meta-analyses, has higher external validity than other designs, and incurs fewer statistical issues.[95]
Pragmatic framework: Using the PRECIS-2 tool (PRagmatic-Explanatory Continuum Indicator Summary) for categorizing our trial, we found our design to be mostly pragmatic (score 38 of 45) in terms of clinical domains (figure 11, table 18), making the potential results fit for real-world implementation with high ecological validity.[96] This is in line with our own successful implementation of the intervention in the clinic.[68] Some domains, in terms of follow-up and adherence measuring, are more explanatory in nature, making these features less fit for a clinical setting.[96,97]

Patient involvement

Osgood-Schlatter patients undergoing treatment in our department have been involved in discussions of the design of this trial in relation to their visits at the department, which have both informed and changed initial decisions regarding trial design. In an unstructured open manner, patients have been asked about their preference, acceptability, and other inputs, mainly regarding 1) number and duration of appointments during an intervention, 2) duration of the entire intervention, 3) type of outcomes relevant for them, 4) contents of the experimental intervention, and 5) relevance and importance of the research question and comparisons, and have thus provided a valuable basis for this protocol which could lead to increased enrollment and retention.[98] The nested qualitative study will incorporate the perspectives of trial-participants. In addition, following the analysis, new patients will be invited to discuss the interpretation of the results of the trial, as well as dissemination aspects, and receive compensation for their inputs. Relevant public and clinical stakeholders will be engaged in a possible implementation process once dissemination via

peer-reviewed journal publication is completed.

Embedded pilot study: results and ammendments

As outlined in previous protocol versions, the initial 15 participants acted as pilot-participants. This did not incur any additional burden to participants or change their experience or procedures compared to the intended setup for subsequent participants, but trial personnel recorded extra data during months 0-3 on specific pilot objectives (table 3). Pilot studies are the best way to assess the feasibility of a large, expensive full-scale study and avoid any adverse consequences or unforeseen pitfalls during the large-scale trial, and ensure that all the different components work together.[99–101] If the aim and features of the pilot trial is aligned with the main trial and participant data are deemed compatible such none or minimal amendments are needed for the main trial, their data be included in the analysis of the main trial.[100] The key difference from a pilot study and the main study are feasibility objectives and criteria for success that should reflect an operational perspective and aim but otherwise run as a miniature version of the main study.[99,101–103] We prespecified pilot objectives and criteria for either a success or failure of the pilot study (protocol version 1.2, table 2). The results and amendments are outlined in table 3, and the pilot-trial were deemed as successful, as only minor changes were needed to procedures, and participant-data was considered compatible with inclusion in the main trial dataset (outcome number 3 from table 2). Besides the amendments denoted in table 3, a few other minor changes to procedures was also implemented:

Table 2. Prespeficied criteria for successful/failed pilot study

	Success	Failure
1. Amendments to trial procedures that cause delay of the main study		X
2. Amendments to trial procedures that cause inability to include pilot-participant data in main study analyses		X
3. Amendments needed to trial procedure that does not postpone ongoing trial recruitment, and pilot-participant data can still be included in the in main study analyses	X	
4. No amendments needed to trial procedure and pilot-participant data can still be included in the in main study analyses	X	

- Changes to the REDCap-project, such as removing obsolete fields, fixed validation values, change wrong field values.
- Changed sequence of some clinical measures to increase time-efficiency
- As a few participants performed fewer than the planned 3 attempts of maximal knee extension strength test due to knee pain, the analysis of pain during testing will now consider the most painful attempt during these trials, rather a mean measure of pain across trials.

Table 3. Pilot objectives, criteria, results, and changes to trial conduct

Prespeficied Objectives	Prespeficied Criteria	Results	Changes

Potential participants refuse to enroll due to information about the study, other than randomization	≤50% (n=7/15)	33%, n=5/15	
Dropout rate	≤20% (n=3/15)	20%, n=3/15. 1 concussion 2 stopped responding/showing up	
Participants attending inclusion appointment was included in the trial	≥50% (n=8/15	87%, n=13/15	
Potential participants accepted to be randomized	≥50% (n=8/15)	100%, n=15/15	
Incidents of in-comprehension of intervention delivery or intervention materials	≤15% (n=2/15)	0%, n=15/15	
Incidents of in-comprehension of outcomes or testing procedures	≤15% (n=2/15)	0%, n=15/15	
Incidents of faulty data collection procedures (REDCap entry, sensors, scan, clinical tests)	≤5% (n=0/15)	33%, n=5/15 3 incidents of participants not fully using sensor-app 1 scanning error 1 REDcap error	• As sensor-app compliance is the responsibility of participants, full compliance likely cannot be achieved. Data-loss is accepted and expected to occur at same rate during the main trial • Index knee was not scanned, as patient recalled wrong symptomatic leg. Index knee from hereon are noted in the appointment-text for testing-staff • Wrong link to REDcap survey was used. Name and timepoint is hereon piped at the top of every survey
Safety incidents (major or minor)	0% (n=0/15)	33%, n=5/15 4 (minor) incidents of sensor-adhesive causing skin irritation 1 (minor) flare-up short-term during strength test	• New procedures for preventing and handling irritated skin • Added instructions to not push through pain during testing
Capacity: how many patients can we logistically handle per day/week?	≥5 enrollments weekly	2 baseline, or 3-4 follow-up appointments per day have been feasible	
Capacity: Are rooms and equipment available when needed?	Yes, or readily manageable	Yes, no issues	
Any unforeseen challenges by intervention- or outcome personnel	No, or readily manageable	Yes, no issues	
Inclusion criteria were deemed obvious and practical by inclusion staff	Yes, or readily manageable	Yes, no issues	

Embedded qualitative study

A qualitative study will be nested in the trial to understand barriers and facilitators to adhering to the interventions and describe the participant-perspective of undergoing the interventions as a whole.[104] The interviewguide and analysis is based the Theoretical Domains Framework and constructs pertaining to behavior change,[105] and the study conducted according to the COREQ checklist (consolidated criteria for reporting qualitative research.[106] Interviews will be performed in group sessions stratified by group-allocation. The planned sample size is 16 participants minimum, across 4-5 sessions with 4-5 participants in each sessions. The planned sample size is based on field-specific guidance from Malterud et. al regarding Information Power.[107,108] All interviews will be conducted by the PI under supervision of an experienced qualitative researcher. Participants from the main trial will be invited to group-sessions after undergoing their visit at 5 months (primary endpoint assessment). They will be provided with a leaflet detailing how the

session will take place and what themes questions are planned to revolve around. As compensation, participants will receive a voucher for movie theaters (280 dkr.) as well as generous refreshments during the session. The sessions will take place at Hvidovre Hospital in a standard meeting room. An adjacent room with refreshments will be made available for parents. The sessions are planned for 2 x 45 min. separated by a 45 min. break.

Methods: Participants, interventions, and outcomes

Study setting {9}

All trial-related procedures will take place at Hvidovre Hospital, Capital Region, Denmark. Participants will attend procedures related to enrollment, imaging, and end-of-study visits at the Department of Orthopedic Surgery, while visits pertaining to intervention delivery and clinical outcome assessments will be performed at the Department of Physiotherapy, located adjacent to the latter.

Key inclusion and exclusion criteria {10}

The diagnosis of Osgood-Schlatter will be made by a trained physiotherapist according to the following diagnostic criteria:[109]

- Pain or swelling of the tibial tuberosity for ≥6 weeks with a primary insidious onset, which is provoked by at least 2 of the following positions or activities; prolonged sitting or kneeling, squatting, running, hopping/jumping, stair walking, or during multidirectional sports
- Tenderness on palpation of the tibial tuberosity or pain during resisted isometric knee extensions

Adolescents aged 10-16 fulfilling these criteria at enrollment and report having either 1) markedly reduced sports participation, or 2) are severely affected by pain during participation during the past (representative) 6 weeks, will be eligible for inclusion. This will be assessed by having potential participants answering two pres-specified questions on these two domains.

Any other primary pathology or complaints from other structures of the knee will disqualify the participant from inclusion but will be allowed providing that primary complaints during the preceding ≥6 weeks are from the tibial tubercle. Previous fractures or avulsions of the tibial tubercle will disqualify patients. Any other injuries, complaints, or illnesses that may cause disability or specifically restricts levels of physical activity or sports participation will also be cause for exclusion. Previous surgery in the lower extremities or lumbar spine will be cause for exclusion. Congenital deformities, device implants, or cysts, or tumors of the knee will

also be cause for exclusion. If participants are currently being treated for Osgood-Schlatter and are not willing to cease this concomitant treatment, they will not be included. Participants and their parents should be able to understand and communicate in written and verbal Danish, and participants and at least one parent or guardian must be able to attend all visits together. The study director or their trained replacement will provide systematic verbal information to participants and their parents, answer any potential questions, and collect verbal and written informed consent from all participants and their parents/guardians at the enrollment visit (see the section 'Consent' for details).

Clinical examination during the enrollment process will consist of:

1. History taking:

    - Onset, nature, location of pain, mechanical symptoms (catching, locking, clicking, giving way), history of growth, history of patella luxations or apophysitis
    - Previous clinical and para-clinical examinations, treatment modalities, advice, or self-imposed management.
    - Painful situations, and current restrictions and level of participation in sports and physical activity

2. Physical examination:

    - Pain location in predefined anatomical sites (circum patella, quadriceps tendon, patella tendon, Hoffas fat pad, anterior joint-line, pes anserinus, tibial condyle, tibial tubercle, Gerdy's tubercle) identified by palpation.
    - Clinical testing of menisci (Meniscal stress test or Thessalys test), anterior cruciate ligament (Lachmanns test or anterior drawer test), medial and lateral collateral ligaments (varus- and valgus stress-test), Hoffas fat pad (Fat pad impingement test), knee joint edema (Ballottement Test) and isometric knee extension against manual resistance.

Written & verbal information

The study and enrollment process will be carried out in accordance with the principles of the Declaration of Helsinki. We supply verbal information in an undisturbed setting (similar to a regular medical consultation) for all participants and their parents/guardians, during which we go over the purpose, flow, tests, and self-reported measures, present the risk and benefits, and their rights as participants in a research project. The personnel giving verbal information and obtaining consent have extensive experience with treating and communicating with minors. Afterwards they can provide verbal and written consent if they wish to waive

their right to >24-hour extra consideration. If they wish to take their >24 hours consideration time or have an additional bystander present, they will reschedule for another similar appointment. In cases where only one parent/guardian can attend the enrollment visit, a written 'power of attorney' (Danish: fuldmagt) from the other parent/guardian will be required. All eligible participants will be provided with written information about the study >48 hours before a possible enrollment visit.

Consent {26a,26b}

We aim to observe the fullest possible degree of patient- and guardian consent.[110] The study director will obtain consent from parents/guardians to participate in the trials and to publish the results based on their pseudo-anonymous data. Participants over the age of 15 will also be asked to sign a written consent form themselves. Written and verbal information will be supplied to participants and their parents prior to consent. Verbal information will be delivered in an undisturbed setting, similar to a usual medical consultation. All participants will be informed of their additional rights as research participants, including that 1) they have the right to withdraw from the study at any time and does not have to provide a reason, and that this decision will not affect future care 2) that they can consider consenting to participate for at least 24 hours after having received written and in-person verbal information 3) they have the right to bring a by-stander/guardian before consenting 4) all information captured is confidential, and 5) that their data will be stored according to current laws and regulations, they can request access to all their documentation and data and request it deleted entirely, and 6) that they are eligible to potentially seek compensation in the event of unintended or unexpected injury or harm.

Interventions

The number and length of therapeutic visits will be equal across both groups and delivered in the same setting, to minimize performance bias and balance contextual factors that might add to the cumulative effect.[111,112]

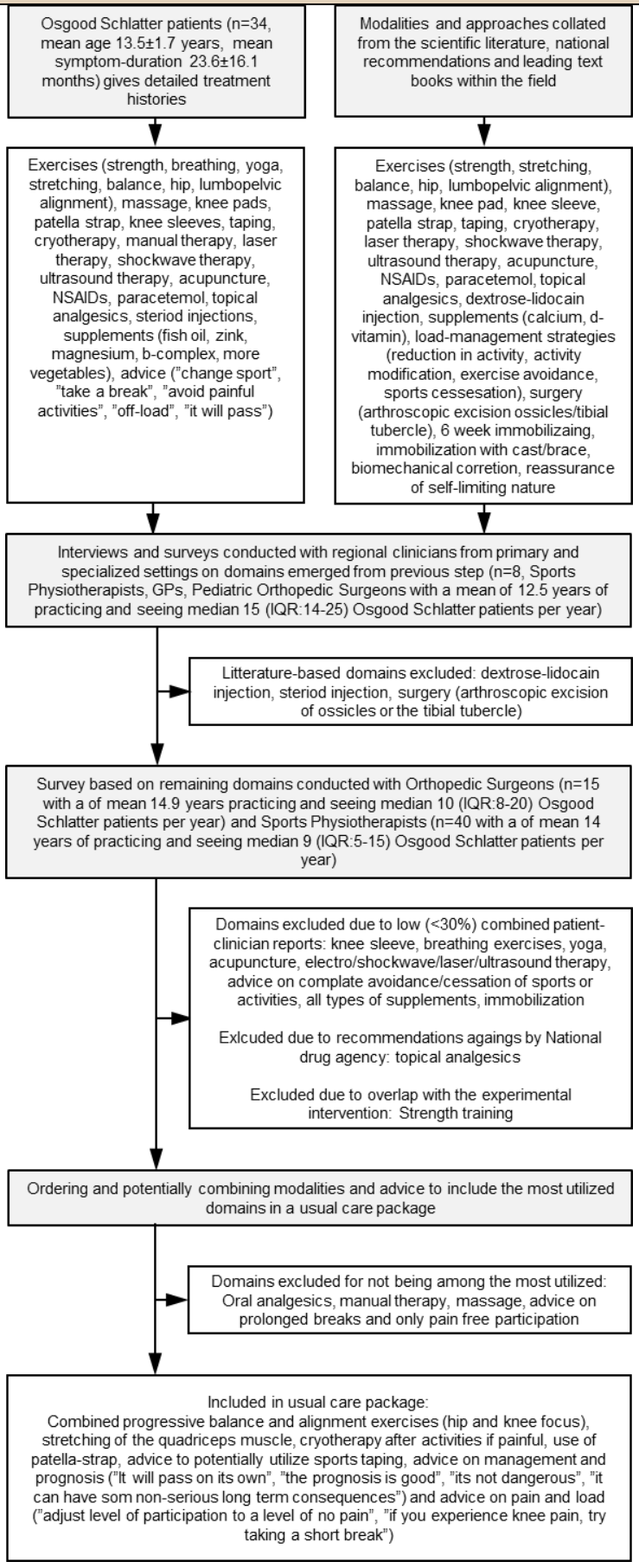
Comparator intervention: Usual Care (Arm 1) {6b}

The literature from Denmark and internationally is conflicting in recommendations for management of Osgood-Schlatter, and no specific guidelines exist.[113] Using a standardized usual care intervention as a comparator increase generalizability and have the potential to have clinical and policy impact.[114] An international study consisting of surveys and interviews with clinicians with a special interest in Osgood-Schlatter, found that 1 in 4 of these clinicians employed a wait-and-see approach, and the rest an active approach.[58] Most recommended advice on load management, exercises, compression strap, stretches, pain

medication, and cryotherapy. Other reports from patients or the literature suggest even more variation in approaches.[31,43,57] We have therefore performed a step-wise sub-study (figure 1) to investigate current standard of care in the most common settings in Denmark (Sports Physiotherapists mainly from private primary practice, and Orthopedic Surgeons caring for these patients invited from all public secondary care orthopedic departments in Denmark). Results were then combined with reports from patients seen in our clinic (n=34) who were questioned in detail on what modalities and advice they had previously received.[115] The results were mostly compatible with the recent international survey of clinicians treating Osgood-Schlatter.[58] With the findings from this process, we have developed a patient-aimed leaflet, which will contain vignettes and elaborations of the multimodal approaches included in the standardized usual care package (figure 1), which will be implemented through four visits (at months 0, 1, 2, 3) with a physiotherapist (mirroring the plan of care of the experimental group).

Figure 1. Flow of mixed-methods study

Flow of mixed-methods study with clinicians and patients using step-wise inclusion/exclusion of modalities and approaches to comprise a usual care treatment package



1) Progressive balance and alignment exercises

Participants will be performing one exercise incorporating balance and alignment every other day. The exercise can be one of 6 exercises on progressively more challenging levels. The exercise levels has been sourced or inspired by sections from a leading sports rehabilitation textbook[47] and subsequently adjusted and refined with an experienced clinician utilizing this type of modality with Osgood-Schlatter patients (23 years practiced, seeing appx. 40 Osgood-Schlatter patients/year).

If the participant continuously experience pain during any of the exercises, the participant is advised to stop performing the exercise regress to a previous pain-free level of exercise. If participants have bilateral Osgood-Schlatter, the exercises will be performed with double dosage, with each leg as the supporting leg interchangeably. For all the exercise levels, the participant must focus on stability/balance and hip-knee-foot alignment on the supporting/landing leg, defined as the symptomatic leg. When each exercise can be performed with a sufficient level of alignment and stability, the participant can progress to the next level. The participants will be instructed through their leaflet and visits with a physiotherapist on how to evaluated exercise qualities and when to progress exercises. During each visit, the physiotherapists will also evaluate the current exercise level. All exercises levels are depicted in table 4.

Alignment in this context is defined as the ability to

1) keep the pelvis horizontal in the coronal plane, neutral in the sagittal plane, and not twist around the center of mass in the axial plane
2) keep the knee from going into varus or valgus, and
3) keep the foot and midfoot arch from going into pronation or supination

Stability and balance in this context are defined as the ability to perform movement or holds without excessive perturbations, corrections, or otherwise inability to perform the movement with intended form or tempo.

Level 1 exercise "Standing on one leg": The exercise is performed by standing upright on one leg for 2 repetitions of 30 seconds.

Level 2 exercise "Side lifts": Standing upright on one leg, participants slowly and controlled lifts their contralateral straight sideways out in the coronal plane into hip abduction, and then back again, without the foot touching the ground. The exercise is performed for 2 sets of 10 repetitions in a slow controlled movement.

Level 3 exercise "Half moons": Standing upright on one leg, participants slowly and controlled tracks their contralateral foot just off the floor, drawing half-circles around themselves. The exercise is performed for 2

sets of 10 repetitions in a slow controlled movement.

Level 4 exercise "Side twists": Standing upright on one leg, the participant lifts the contralateral leg by grabbing their knee with one hand, tucks it toward their abdomen, and then rotates in the hip around their center of mass in the axial plane. Thereby the leg is slowly rotated to the side, all while keeping sufficient alignment on the supporting leg and sufficient stability and balance. The exercise is performed for 2 sets of 10 repetitions.

Level 5 exercise "Standing Superman": Standing upright on one leg with both arms flexed at the shoulder, and positioned straight in front them, they slowly and controlled lean forward with stretched arms while also lifting the other (asymptomatic) leg up behind themselves. The exercise is performed for 2 sets of 10 repetitions.

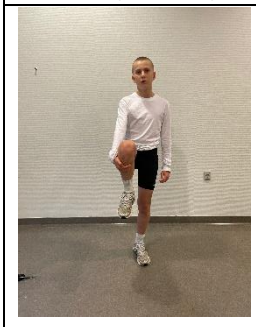
Level 6 exercise: Participants perform hops by setting off on the asymptomatic leg and landing on the symptomatic leg, and alignment and balance/stability are then evaluated during landing. The hop is performed in three different directions; straight forward, sideways, and diagonally. After each hop, participants takes a step back to the starting position. The exercise is performed for 3 repetitions of 8 hops to each direction, totaling 24 hops.

Table 4. Depiction of progressive balance and alignment exercise levels

Exercise level 1: "Standing on one leg"

Exercise level 2: "Side lifts"

Exercise level 3: "Half-moons"



Exercise level 4: "Side twists"

Exercise level 5: "Superman"

Exercise level 6: "One-legged hops"

2) Stretching of the quadriceps muscle

On the symptomatic leg(s), 2 sets of 30 seconds of the stretching for quadriceps muscle exercise are performed daily. The participants are instructed in standing stretches but can select a stretching exercise for the quadriceps muscle of their own choosing if desired.

3) Use of a patella strap

Each participant is given and instructed in the use of a patella strap according to manufacturer instructions (item 992, Mueller Sports Medicine Inc., Prairie du Sac, USA). The participants are instructed to use the patella strap if they are experiencing pain and find relief in using of the patella strap. They are also instructed to use the patella strap during sport or physical activity if they experience it as beneficial.

4) Advice on other modalities

Cryotherapy: ”Utilize after participating in sports or physical activity if you experience pain or swelling. Apply the icepack for 15-20 minutes, and repeat if necessary”. In addition, instructions on exactly what to use as an ice-pack and how to wrap it, and how to apply it safely.

Taping: “Specific taping of the knee can be useful for some if you have access to it. Maybe you have previous experience with applying sports-tape for your knee pain either on your own/with your parents, or by a coach, teammate, or health professional at your club.”

5) Advice on load, pain, and prognosis

Prognosis: “The prognosis is good. It will pass on its own, and the condition is not dangerous. It can, however, have some non-serious long-term consequences.”

Pain and sport: “We advise that you adjust your level of participation in sports and physical activity so that you participate with little pain or to your pain limit. If you experience pain, it can be helpful to take a short break (lasting from a few hours to a few days).”

Experimental intervention: A novel treatment approach (Arm A) {11a}

Rationale and scientific background

The experimental intervention was first comprised and tested in a large cohort of 10-14-year-old adolescents with a similar condition (patellofemoral pain) and was associated with a successful outcome after 12 weeks.[59] Afterwards, the intervention was changed slightly to target adolescents with Osgood-Schlatter and then pilot-tested in a cohort of 51 participants.[60] In this cohort, most participants needed more time to

progress through exercises and sport, and we have therefore piloted extending the intervention further in the clinic, with more success on these aspects.[68] We have also found that adolescents with Osgood-Schlatter had markedly decreased strength in knee extension and hip abduction compared to a control group or even to a group of adolescents with patellofemoral pain.[116]

Exercises with pain have been shown superior to pain-free exercises in short-term management of chronic pain,[117], and pain of up to 5 NPRS is usually tolerated in exercise programs for tendon-related conditions in adults.[117,118] Exercises with pain is a safe and effective way to increase gradual tolerance to loading activities and to decrease pain-response by inducing hypoalgesia and mitigating central and peripheral sensitization.[119,120] It has also been shown that exercise as a modality is effective for pain-related beliefs, such as kinesiophobia (fear of exercise), pain self-efficacy, and fear-avoidance behavior.[121,122] In adolescents with knee pain performing simple knee extension and flexion, increased kinesiophobia seems to necessitate additional neurological resources to compensate for pain-disrupted processing.[123]
Experimental studies have shown reductions in pain sensitivity after exercise,[124,125] including dynamic (concentric and eccentric contractions) and isometric resistance training.[125] Just a few weeks of resistance training can improve pain and function in musculoskeletal pain conditions,[126] and seems superior to other non-pharmacological modalities.[127] Patella tendon pain or damage can lead to quadriceps inhibition,[35] a disorder that responds well to resistance training.[128] In addition to being an appropriate and safe modality for Osgood-Schlatter, strength training also carries a wealth of other health and performance benefits,[129–137] especially for adolescents.[138]

In line with this, isometric exercises with a long time under tension (10-30 s) can be a good initial loading mode as it allows a high exercise volume with lower peak joint forces and has been shown to improve tissue quality in the patella tendon, induce strength and hypertrophy,[139,140] whilst allowing athletes to continue their sports participation.[139,141,142] Short rest periods (≤30 s) stimulates metabolic load and results in lower mechanical load and are, therefore, a safe and effective way to promote adaptations through anabolic/metabolic pathways.[143,144] Moreover, tendons have high collagen turnover during adolescence, with no turnover in the remaining lifespan;[145] and especially the distal part of the patella-tendon is susceptible to adaptations from exercise.[142] This highlights the need for a healthy stimulus during this phase of maturation.

Taking away the pain-evoking stimuli of loading from sports and vigorous physical activity while simultaneously introducing high volume exercise is therefore likely a key to allow subsequent gradual exposure to sports more successfully. The guidance through the return-to-sport process will be based on the

clinical exposure therapy, which is defined *"by repeatedly and systematically approaching stimuli that trigger pain-related distress or symptom preoccupation is counteracted, and the participant will gradually gain an increased tolerance to pain and pain-related distress"*[146] and aims to stop or slow the cycle of preoccupation with symptoms, avoidance behavior, and pain. Exposure-based interventions are particularly effective in reducing pain-related fear and the perceived harmfulness of physical activity, also by challenging catastrophic interpretations of movements or activities.[147–151]

Adolescents thus have to self-manage the dose of exercise and loading from sports and physical activity through the NPRS, putting decision-making on regression/progression in their hands. A self-management approach aimed at behavior-change has been identified as key for patients to adapt when facing social, emotional, and physical challenges when suffering from persistent musculoskeletal pain or pain disorders, and shifting the expectations of a cure to an active approach is central to continued management and is suggested to prevent long-term disability and pain.[152–156] In addition, Pain Self-efficacy, that is the belief in one's ability to manage and complete a task despite pain, seems to improve by employing self-management strategies.[122] The approach also supports participants in the step-wise path towards reaching self-management mindsets- and behavior change.[157]

Incorporating the parents is important during the intervention, as data have shown parents' protectiveness, catastrophizing, and mood is predictors of youth pain intensity, unpleasantness, and catastrophizing.[158] Further, parents play a critical role in managing pain in their children and improving function.[153] The intervention will be delivered with age-appropriate language and incorporate vignettes during adjunctive pain management education.[159,160]

Arm A will therefore contain an active approach with self-management of load and progressive exercise therapy, delivered through 4 one-on-one visits lasting approximately 20 minutes (at months 0, 1, 2, 3) over 3 months with a physiotherapist and an accompanying leaflet with written and illustrated exercise description, and advice and information.

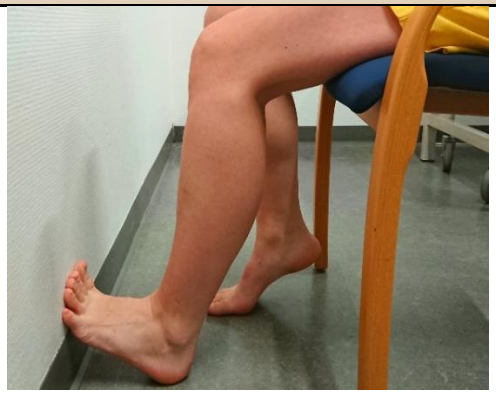
This intervention will also align with the high-value care recommendations for care in musculoskeletal pain and sports medicine.[161–163]

1) Exercises

For targeting the insertion site of the quadriceps femoris, the tibial tubercle, exercises at around 75° knee flexion will be performed, starting with the mild "knee-press" exercise during the first month, after which

participants will be instructed to proceed to the heavier weight-bearing wall-squats at appx 90° knee flexion, followed by unilateral lunges at approximately 125° knee flexion (table 5). The tensile force on the patella tendon is approximately half that during a bodyweight squat compared to a lunge with high range of motion.[164,165] The regression/progression of exercises will depend upon the pain experienced during and until the morning after performing the exercise – if pain has not exceeded NPRS 2, the standardized exercise-dose should be progressed. Alternatively, the exercise dose should be maintained or regressed until NPRS ≤2 is achieved. Besides knee-dominant exercises, the hip abductor bridge will be prescribed, with the same dose throughout months 0-3.

Table 5. Depiction of hip- and knee exercises



Knee press

Wall squats

Hip abductor bridge

Lunges

2) Loading from sport and physical activity

Participants will be asked to take a complete break from weight-bearing sports and rigorous physical activity during the first month. After month 1, gradual exposure to sport will begin, using the same pain-model to progress or regress loading, as well as sport-specific advice from a physiotherapist based on load-markers such as intensity, frequency, duration. Once full or maximum-possible sports participation has been

achieved, progression of load from rigorous physical activity will follow in the same manner.

3) Advice and education

The leaflet and conversations during visits will contain information and advice regarding the following domains: 1) Aetiology 2) Pain management 3) Effects of exercise and knee loading activities 4) Prognosis 5) Self-management decision-making tools and addressing real-world challenges for the participant. From month 3 to 5, the participants will completely self-manage their condition and is encouraged to maintain some level of self-chosen exercise dose (advice of 1-3 sets of lunges and hip abductor bridge, 2-3 times weekly)

Table 6. Short-form overview of the two treatments

	Experimental	**Comparator**
Month 0-1	Phase 1 ▪ Break from sports and moderate-to-vigirous physical activity ▪ Daily high-volume low load isometric training ▪ High-load hip-abductor training every other day ▪ Introduction to a pain-model for progression of exercises and exposure to sport/moderate-to-vigirous physical activity ▪ Education on pain science and management	▪ Introductionof progressive balance and alignment exercises every other day and continued ▪ Introduction of daily progressive quadriceps stretching ▪ Advice on approaches for preventing/treating pain flares: ▪ Cryotherapy after activity if painful ▪ Sports taping ▪ Handout and instructions in using a patella strap ▪ Advice on potential prognosis ▪ Advice participation in sports and physical activity when experiencing pain
Months 2-3	Phase 2 ▪ Self-managed introduction of gradual exposure to sport based on the pain-model ▪ Once acceptable sport-level achieved, self-managed gradual exposure to vigorous physical activity is introduced ▪ Introduction of progressively more loaded isometric and subsequent dynamic weight-bearing exercises for the knee extensors ▪ Continued high-load hip-abductor training every other day	
Months 4-5	Self-management phase ▪ Complete self-management of pain vs. loading from participation in sports and physical activity ▪ Potential self-management of self-chosen exercise dose	Self-management phase ▪ Complete self-management of pain vs. loading from participation in sports and physical activity ▪ Potential self-management of self-chosen exercise dose

Criteria for discontinuing or modifying allocated interventions {11b}

If scheduling or the availability of equipment (surface, chair) hinders the participant from following the exercise dosage, the treating physiotherapist will, together with the participant, try to amend the programme to better suit the preferences and context of the participant while still aiming for the correct dose and form in accordance with the original approach to the fullest extent possible.

Intervention adherence {11c}

Making exercises enjoyable, social, and convenient has been identified as the most likely barriers to exercise adherence in adolescents with musculoskeletal pain.[166] In line with this, the exercises prescribed in both groups are designed to be performed with only little if any exercise-equipment and are time-efficient (1- 20 minutes per day/every other day). We also encourage the participants to attend their regular sports team practices and perform the exercises in that environment, rather than potentially skipping practice altogether, and thereby gaining a social aspect of performing the exercises.[167] In both groups, the intervention personnel will remind participants to adhere to their respective interventions at visits at months 0, 1, 2, and 3. Reminders will firstly focus on the importance of adhering to dose and form of exercises and to the advice on loading by their own autonomy.[167] Secondly, the personnel will engage participants in potential context-based barriers to adherence and foster realistic expectations. Through weekly monitoring, participants are asked about their adherence to exercise and other group-specific modalities the past week (table 7-9 and figures 8-10). Also, we ask if they have currently returned to sports participation. In addition to weekly reports on adherence, participants will be asked at visits at months 1 and 3 about their current exercise dose and to demonstrate the exercises, which will then be rated by the observing therapist on a standardized form (table 7). To ensure honest answers regarding adherence, data from weekly monitoring will be unavailable to the treating physiotherapist, and the participant will be informed of this blinding at enrollment. Capturing detailed adherence of participants will allow post-hoc interpretation of the study results beyond the intention-to-treat approach.[168]

Table 7. Items for exercise evaluation forms as reported by the treating physiotherapist

	Balance/alignment exercises	Stretching	Hip abduction	Knee exercise
	Comparator group		Experimental group	
Sufficient focus on knee alignment	X			
Sufficient focus on hip alignment	X			
Sufficient attention to progression	X		X	X
Sufficient range of motion	X	X	X	X
Sufficient load (RM)			X	X
Accurate tempo and time under tension	X	X	X	X
Sufficient form to target to intended muscles or qualities	X	X	X	X
Intended pain level (<3 NPRS)			X	X

Compliance criteria

Adherence will be determined in 3 different epochs, which will vary between groups, as the experimental intervention is divided into two phases. In the experimental group, two epochs will be set from month 0-1 (phase 1) and month 1-5 (phase 2 and the self-management period). The comparator group will only have 1

epoch lasting the whole core study period (month 0-5). We have outlined criteria for weekly adherence criteria below (table 7-9 and figures 8-10). For phase 1 in the intervention group, 3 out of 4 weeks of full adherence is considered as compliant, and for phase 2 (week 4-13), 7 out of 9 weeks of full adherence is considered compliant. For the whole treatment period in the comparator group (week 0-13), 10 out of 13 weeks with full adherence is considered compliant, this mirroring the total count in the same period in the intervention group. For the self-management period (months 3-5), in both groups, the criteria for exercises are the same as during treatment, but the dose is self-chosen. For participants in either group, the compliance criteria must be achived in every epoch, the to be catogrized as compliant over the entire study periode (month 0-5)

Table 8. Adherence criteria for the intervention group

Epoch	Modality	Criteria for epoch	Measurement
Month 0-1 (phase 1)	Break from sports and MVPA	≤15 min of VPA and ≤30 min of MPA every day	Sensor-based
	Daily isometric knee-extensor exercise	4≥ full sessions per week	Weekly text: "How many sessions did you complete of your knee exercise this past week?"
Month 1-3 (phase 2):	Gradual exposure to sport with limitation of pain flares	Non-negative 4 week moving average of MVPA minutes (calculated from week 8)	Sensor-based
	Weightbearing knee-extensor exercise every other day	2≥ full sessions per week	Weekly text: "How many sessions did you complete of your knee exercise this past week?"
Month 0-3 (phase 1 & 2)	Hip-abductor exercise every other day	2≥ full sessions per week	Weekly text: "How many sessions did you complete of your hip exercise this past week?"
Month 3-5 (Self-management phase)	Self-chosen dose of knee-extensor exercise	2≥ sessions per week	Weekly text: "How many sessions did you complete of your knee exercise this past week?"
	Self-chosen dose of any hip-abductor exercise	2≥ sessions per week	Weekly text: "How many sessions did you complete of your hip exercise this past week?"
	No dramatic short-term changes in sports and physical activity	≤100% change in 4 week moving average of MVPA minutes	Sensor-based

Table 9. Adherence criteria for the comparator group

Epoch	Modality	Criteria	Measurement
Month 0-5	Balance and alignment exercises every other day	2≥ full sessions per week	Weekly text: "How many sessions did you complete of your balance exercise this past week?"
	Daily quadriceps stretching	4≥ full sessions per week	Weekly text: "How many sessions did you complete of your stretching exercise this past week?"
	Cryotherapy, sports taping, or patella strap	Utilized >1 times per week	Asked during visits: "How many times weekly have you used icepacks, taping, or straps?"

Criteria for discontinuing or modifying allocated interventions {11b}

If scheduling or the availability of equipment hinders the participant from following the exercise dosage, the treating physiotherapist will, together with the participant, try to amend the programme to better suit the preferences and context of the participant while still aiming for the correct dose and form in accordance with the original approach to the fullest extent possible.

Concomitant care during the trial {11d,30}

Participants will be encouraged only to receive treatment as outlined in their allocated group for the duration of the treatment (first 3 months) and the self-management period (month 3-5). Concomitant treatment will not be course for exclusion, but will be recorded at visits months 1, 3, and 5. We do not expect a high occurrence of concomitant treatment, but if this should occur, we will explore potential post-hoc moderation or subgroup analysis to better understand this aspect and its implications on the results of the trial. Participants will be instructed to not take any pain medication on the same day of testing to ensure that this does not affect any measurements. No post-trial treatment is planned.

Outcomes {12}

Besides long-term digital follow-up, patient-reported and clinical measures will be recorded at 5 possible time points; at baseline and months 1, 3, 5, and 8. Weekly monitoring will be done from baseline to month 5. Imaging will be performed at enrollment and at months 3, 5, and 8. Long-term patient-reported follow-up is planned for 1, 2, and 4 years after enrollment. All data, besides text-message, ultrasound images, and sensor-data, will be captured in REDCap (Research Electronic Data Capture, Vanderbilt Universit,y, USA),[169] a logged secure system designed to capture sensitive non-commercial clinical data hosted at Hvidovre Hospital. REDCap contains options for valid values, range checks, data validation, branching, scheduling, and stop-rules to increase data quality. Pain during all clinical tests will be recorded in addition to the primary measure. Ultrasound will be performed during the enrollment visits and again at months 3, 5, and 8. For a visual overview of data collection schedule, see table 11. We have reported our outcomes in a prioritized order in addition to designations as primary, secondary or exploratory, which also reflects the order of hypothesis-testing, analyses, and intentional order of reporting, with all primary and secondary outcomes intended for the primary report.[170] Note that for this reason, the order and count of outcomes below reflect the total number of variables of interest within each outcome. No core outcome set exists for this or similar populations, and the outcomes are chosen based on current literature and clinical experience.[171]

Table 10. Overview of outcome domains and prioritized hierarchy of outcomes

Outcome domain	Specific outcome variables

Primary outcome		
Sport function	1. KOOS-child 'Sport/play' 0-100 subscale (7 items)	
Secondary outcomes		
Patient-acceptable Symtom-state	2. PASS question (Y/N)	
Knee-related Quality of Life	3. KOOS-child 'Quality of Life' 0-100 subscale (5 items)	
Pain intensity and frequency (Pain flares)	4. 4-week-average episodes of pain flares (≥4 on 0-10 NPRS) 5. Worst pain past week (0-10 NPRS)	11. KOOS-child question P1 on 'Pain' subscale (1-5 Likert scale) 12. Level of pain/discomfort (EQ-D5-Y 4)
Participation in sports and physical activity	6. 4-week average hours of sports participation	13. 4-week average hours of MVPA 14. Satisfaction with extent of sports participation 15. Pre knee pain level of sports participation 16. Pre knee pain level of physical activity 17. Time to return to sport (week no.)
Osgood-Schlatter morphology (ultrasound imaging)	7. Flaviis composite severity score	18. Tendinosis signs (thickening or hyperemia) 19. Infrapatellar bursitis signs (effusion or hyperemia 20. Hyperemia of the tibial tubercle ad modum Öhberg
Pain during knee loading	8. Anterior Knee Pain Provocation test (0-10 NPRS)	21. Pain during knee extension test (0-10 NPRS) 22. Pressure-pain threshold at the tibial tubercle (kPa) 23. KOOS-child 'Pain' 0-100 subscale (8 items) 24. Known pain during manual palpation 25. Pain during countermovement jump (0-10 NPRS)
Objective knee function		26. Maximal isometric knee extension strength (Nm/kg) 27. Countermovement jump height (cm) 28. Countermovement power (W) 29. Knee extensor flexibility change (°)
Global rating of change	9. 7-point Likert scale	30. Satisfaction with treatment (Y/N)
Usual activities	10. Patient-specific function scale (NRS 0-10)	31. Problems with usual activities (EQ-D5-Y 3)
Pain beliefs		32. Kinesiophobia (Tampa Scale of Kinesiophobia, 17 items)
Health		33. Self-rated health (EQ-D5-Y 0-100 VAS)
Safety outcomes		
	1. Any adverse events	

Primary outcome

KOOS-child 'Sport/play' subscale

The primary between-group difference will be evaluated using the KOOS-child (Knee injury and Osteoarthritis Outcome Score – Child), designed specifically for adolescents and youths aged ≥10 years experiencing knee problems.[172] The KOOS-child contains 5 independent subscales with domains 'Pain' (11 items), 'Symptoms' (7 items), 'Activities of Daily Living' (11 items), 'Sport/play' (7 items), and 'Quality of Life' (6 items). The questions are answered on Likert scales from 0 to 4 points and pertains to the prior week. The scoring of each subscale is normalized to a 0-100 score, 0 being extreme symptoms and 100 being no symptoms. Four subscales (excluding 'Activities of Daily Living' due to low responsiveness[68,116]) will be recorded and presented, but the subscale 'Sport/play' will be prioritized based on study aims and feedback and preferences from patient representatives and will thus provide properties for sample size calculation. The four included subscales have low detectable change on the group level (1.86-2.66 points), acceptable standard error of measurement (5.69-8.14 points), and substantial/near-perfect test-retest reliability (ICC 0.78-91).

Secondary and exploratory outcomes

Patient Acceptable Symptom State

The question pertaining to Patient Acceptable Symptom State (PASS) is designed in collaboration with patient representatives. The recall period will be one week, and the outlook period a 'few months' as in previous applications in musculoskeletal conditions with fluctuating symptoms.[173] The phrasing of the PASS will be (approximate English translation): "If you consider your knee pain during the past week, and how it affects your ability to do activities of daily living (for example participating in school, in sports, and socially), would you consider your current symptom state acceptable for the next few months?". The proportions of yes/no in each group will be captured and compared at designated time points.

KOOS-child Quality of Life', 'Symptoms' and 'Pain' subscales

The above subscales will be collected and change scores compared in the same manner as the primary 'Sport/play' subscale.

Frequency and intensity of pain flares

A pain flare in this study is defined as any time a participant reports episodes of pain of NPRS ≥4 through weekly monitoring. As an outcome, a 4-week median of number of pain flares during week 19-22 (frequency of pain flares) and the worst pain the past week at week 22 (intensity of pain) will be calculated and

compared. In adult populations with knee pain, the 0-10 numerical pain rating scale has shown near-perfect test-retest reliability of ICC 0.95 and low detectable change of 1.33 points.[174] Frequency will also be captured using the P1 question from the KOOS-child 'Pain' subscale: "During the past month, how often have you experienced knee pain?" with potential responses "Never" (1), "Rarely" (2), "Sometimes" (3), "Often" (4), "All the time" (5). Finally, participants will rate their problems with Pain/Discomfort in the 3-point Likert EQ-D5-Y.

Participation in sports and physical activity

According to WHO recommendations, a daily minimum of 60 min of moderate to vigorous physical activity (MVPA, such as biking, running/exercising/high-intensity training) is needed to stay healthy for 5-17-year-olds.[175] Thus, being at either under or above this cutoff during a 4-week average from week 18-22 will be assessed, in addition to a continuous comparison between the two groups of minutes of MVPA during the same time period. Self-reported levels of physical activity are highly under-reported from trials-participants, and sensors increase the precision.[176] Minutes of MVPA will be captured using waterproof threeaaxis12 Hz accelerometers (SENS®, Copenhagen, Denmark) applied once to the participant's thigh during the enrollment visit using an adhesive patch (35 cm^2, 8 g). The sensors have shown 92±5% discriminate agreement when distinguishing between different activities (light sleep, deep sleep, lying/sitting, standing, sporadic walking/slow biking, walking, biking, running/exercising/high-intensity training).[177] Physical activity data will also allow posthoc analyses of exposure.

In addition to physical activity, the level of participation in sports will be captured through weekly monitoring. Participants will be asked how many hours they have been participating in sports in the preceding week. Return to sport time will be defined as the first week participating in sports, followed by one more week also with sports participation. Participants will also be asked during clinical visits if their return to sport was at their pre-injury level or less/more and if they are satisfied with the current extent of their sports participation.

Morphology

Involvement of the tendon is common in patients with Osgood-Schlatter,[178,179] and associated signs of bursitis and severity have shown to be prognostic of a worse outcome.[32] A series of Osgood-Schlatter patients has been described for whom less hyperemia on color doppler ultrasound was associated with milder symptoms.[109] Hyperemia on color doppler ultrasound (ad modum modified Öhberg 1-4) will therefore be assessed for the patella tendon and tibial tubercle (yes/no) at baseline, month 3, month 5, and month 8. High inter-rater reliability of color doppler evaluations in the patella tendon has been established,[180], and we

are currently investigating the reliability and clinical relevance of the full ultrasound protocol being employed in the study.[178]

Knee pain during loading

The pain evoked from loading the affected tissue will be measured in four different ways. Firstly, by rating the pain level after performing the Anterior Knee Pain Provocation test (we have recently shown this test to be associated with KOOS-child 'Sport/play' and NPRS, and response over time for adolescents with knee pain).[181] Secondly, by a NPRS 0-10 rating from performing the maximal isometric knee extension strength test and the countermovement jump (maximum pain during any of three trials). Thirdly, by manual palpation of the tibial tubercle for known pain (y/n). Finally, to evaluate local hyperalgesia, specifically at the tibial tubercle, we will use handheld algometry to detect the pressure (kPa) needed to evoke pain (going from no pain to the slightest sensation of pain) on the tibial tubercle on both knees. The intra-day and intra-tester reliability has been found to be >0.98 (ICC 3.1) for two similar sites; the center of the patella and the muscle belly of the tibialis anterior in young adults with longstanding knee pain.[182]

Knee function

Knee pain is known to reduce muscle function.[183] To evaluate the capacity of the quadriceps femoris muscle inserting at the site of pain, handheld dynamometry will be used to measure maximal isometric force generation, which will be normalized to body weight and lever-length (Nm/kg). This test has shown inter-tester reliability of ICC: 0.76-0.96[184,185] with a low standard error of measurement (5-11%)[185] and good validity compared to the gold standard of isokinetic strength assessment.[184,186,187] We have recently investigated the inter-tester reliability of this test in an Osgood-Schlatter cohort and found acceptable reliability.[188] As a measure of power and a sports-specific skill, a countermovement jump will be performed to record jump height (cm) and power-production (watts), using high-speed video analysis via a smartphone app (My Jump 2). The test has been found feasible in adolescents,[189] been validated against the gold standard of using a force-plate,[190–192] and is highly reliable.[190,192–195] Adolescents with Osgood-Schlatter have been reported to have tighter knee-extensor muscles, but it's unclear if this is thought to be a contributing cause or derived effect or if this is merely is a characteristic of increased musculoskeletal maturation.[38] We will compare the change in knee flexion angle, assessed by smartphone-inclinometry during a modified Thomas Test. Different apps based on the standard smartphone level-function have been investigated with near-perfect validity with other digital methods (video-analysis, digital inclinometers) and with good to excellent inter-and intra-tester reliability and low error of measurement and detectability.[196] However, we will utilize the built-in level app in iPhone 7 (Apple, USA) as the apps investigated in the literature are no longer available for download. We have recently investigated the inter-tester reliability of using the built-in

level app in the iPhone 7 to measure the knee flexion angle in an Osgood-Schlatter cohort and found acceptable reliability.[188]

Global rating of change

To assess patient-assessed improvement or worsening, we will ask participants to rate their perceived level of change from their first visit on a 7-point Likert scale ranging from 'Much worse' to 'Much better'. GROC-scales have been found to have sufficient reproducibility and responsiveness.[197]

Usual Activities

We will ask participants to rate their problems with an important activity using the Patient-Specific Functional Scale. They are asked to name a single important activity of their own choosing. Participants then rate their functional limitation with activity on a 0 to 10 scale, where 0 corresponds to being unable to perform activity and 10 is being able to perform activity at same level as before knee pain. At follow-up assessments, participants are asked to rate the previously nominated activity on the same scale.[198] For other conditions, the PS-FS has shown to be valid, reliable, and responsive.[199] In addition, the EQ-D5-Y question on problems with 'Usual Activities' will be collected.

Pain Beliefs

To capture the level of kinesiophobia, that is, the fear of pain due to movement or exercise, a type of fear-avoidance behavior, the patient-reported 17-item Tampa Scale of Kinesiophobia (TSK-17) will be used.[200] The instrument has good reliability and validity,[201,202] and has demonstrated good psychometric properties when used by adolescents.[203]

Self-rated Health

Recent studies have shown that self-rated adolescent health is associated with death, multimorbidity, primary care utilization, medicine use, social welfare benefits,[204–207] as well as persistent musculoskeletal pain.[208] Self-rated health will be collected through the 0-100 VAS for general health. The EQ-D5-Y questions pertaining to 'Self-care' and 'Mobility' will be omitted due to low responsivenes[68] and the question on 'Anxiety/depression' will only be used for mediation/moderator analysis and baseline descriptives. Our application of the questions on 'Usual Activities' and 'Pain/discomfort' is described early in this section. Test-retest reliability of the EQ-D5-Y has shown a percentual agreement of 70-99%.[209]

Adverse events

The potential occurrence of adverse events (AEs) in either treatment group will be reported as amount and

proportions, and described in prose regarding severity, timing, and duration.[210] If sufficient data is observed to complete contingency tables, the odds ratio will also be reported.[211] See the section "Adverse event reporting and harms" for a more detailed definition of AE. Adverse events will be collected in a systematically rather than spontaneous reporting by participants by utilizing a pre-specified instrument in REDCap for each clinical visit and the telephone consultation at month 2.[210]

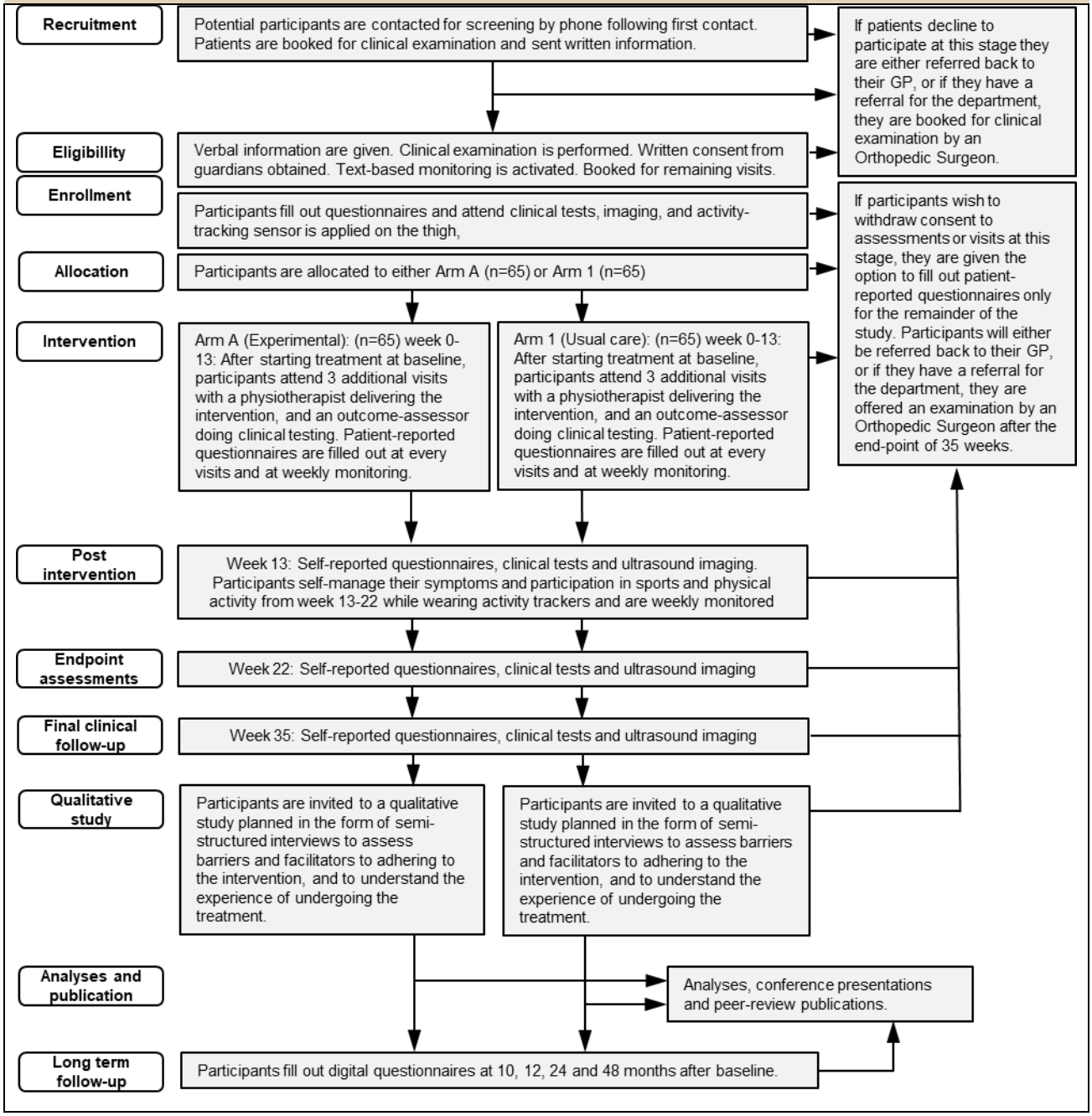
Participant demographics

The baseline survey will also include questions on age, body weight, stature, participation in sports and physical activity, previous care, bilateral pain, concomitant conditions (anterior knee pain conditions), symptom duration, health-related behaviors, anthropometrics, pubertal and skeletal maturity, and predicted adult height. Per CONSORT guidelines, we will not perform statistical comparisons of baseline charactistics.[73,212]

Study flow and participant timeline {13}

Patients will undergo pre-trial procedures (phone screening, examination, and history, oral and written information, signed consent) before enrollment and treatment start (baseline), which will then last 3 months (13 weeks). A telephone consultation with the treating physiotherapist is planned for month 2 (week 9), that can also result in a clinical visit if needed. Two months (9 weeks) after end-of-treatment, participants will attend the primary clinical follow-up visit at 5 months (22 weeks), followed by the final clinical visit at 8 months. Subsequently, long-term digital-only follow-up will be captured at months 10, 12, 24, and 48. See figure 2 for detailed study-flow, and table 11 for the study schedule.

Figure 2. Study flow



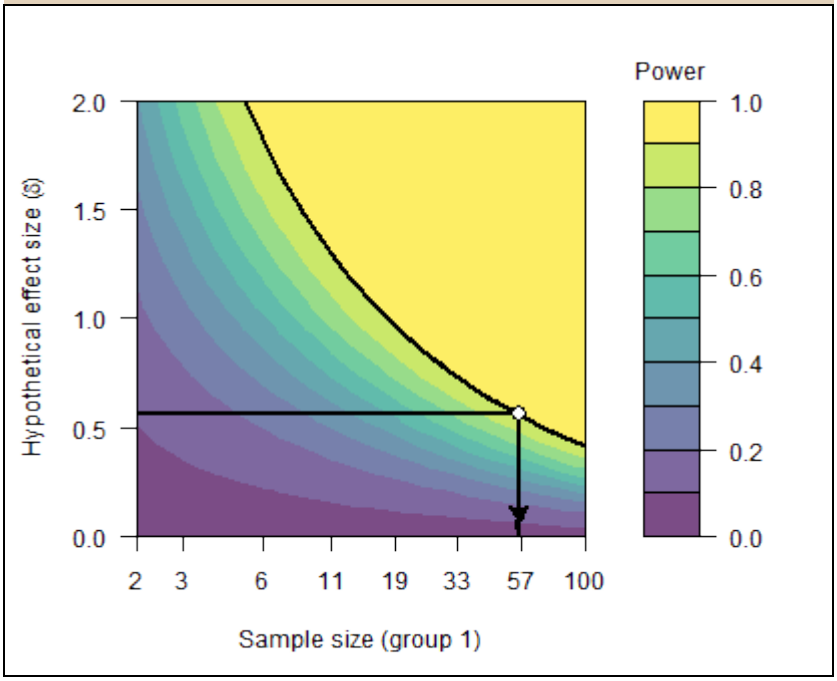
Sample size considerations {14}

The properties of the primary outcome measure KOOS-child and the "Sport/rec" subscale have been well investigated, with a validation study including adolescent participants with Osgood-Schlatter amongst other overuse- and acute knee disorders.[172] A small cohort of patients in our clinic (n=16) who 1) were eligible for inclusion in the trial at baseline, 2) received the intervention in question and 3) attended follow-up, reported their global rating of improvement on a 7 point Likert scale ranging from 'much worse (7)' to 'much better (1)'. Patients who reported 'much better (1)' or 'better (2)' had a mean improvement on KOOS-child

'Sport/play' subscale of 12.7±16 points, whereas patients reporting less improvement ('little' improvement or 'no change') only had a 3.57 point increase. In absence of more robust specific data in terms of severity, intervention, and length of follow-up,[213] we will utilize this 9 point difference as a threshold for determining superiority. We consider this to be a meaningful change and a relevant between-group difference, and is within the recommended range of 8-10 points (heartbeat-med.com/resources/knee-injury-and-osteoarthritis-outcome-score-koos). This change also exceeds the smallest detectable group-level change (2.66 points) and the standard error of measurement (8.02 points).[172]

In order to detect such a change with a standard deviation of 16 points an α level (type I/false positive error rate) of 5% and power (β-1, or probability of avoiding type II/false negative error rate) of 90%, 55 (54.8) participants per group would be needed based on an independent one-sided t-test (R 4.0.2, Foundation for Statistical Computing, Vienna, Austria; RStudio 1.0.153, power.t.test package). To account for a potential 15% dropout rate[59] a total of 130 participants will be included.

Figure 3. Effect size vs sample size plotted



This will correspond to a 0.56 Cohens d 'medium' effect size at 90% power (figure 3). The smallest effect size reliably detectable will thus be >0.482 (Cohens d 'small' effect size) at ≥80% power (Jamovi 1.2.25, jpower module), surpassing the trivial (<0.2) and small (>0.2) effect size thresholds. We also consider this sample size to be operationally feasible within the given timeframe and with the resources available to our group.

Recruitment {15}

Participants will be recruited through a combination of convenience and consecutive sampling from the uptake area of the Capital Region of Copenhagen, Denmark (1.8M inhabitants), through two different approaches; 1) patients referred to the secondary care specialized outpatient Orthopedic Department at Hvidovre Hospital, and 2) postings to our website encouraging parents of adolescents with anterior knee pain below the knee to contact the study director, which will be also be shared with sports clubs in the uptake area through our organizational network. Based on historical patient flow and past studies in this population, the planned recruitment rate is expected to be around 10-15 participants per month during non-holiday periods. Thus, inclusion is expected to last up to two years, from January 1st 2022 to December 31st 2023.

First contact

Accordingly, all 10-16-year-old patients referred for potential Osgood-Schlatter complaints to the department from other hospitals or general practice, or having contacted the study director themselves, will be screened for eligibility by telephone by the study director before potentially being invited to enrollment visit.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be allocated to either standardized usual care or the experimental intervention with a 1:1 allocation ratio. To perform adequate sequence generation, we will use The Robust Randomization App[214] (RRApp v3.0.1, https://clinicalresearch-apps.shinyapps.io/rrapp/) for a computer-generate sequence in random sized blocks with no stratifications, extracted by a person not otherwise involved in the trial.

Concealment mechanism {16b}

To conceal allocation and prevent selection bias, the sequence will be implemented using sequentially numbered in sealed opaque envelopes. A person not otherwise involved in the trial will be given the randomization sequence and 65 envelopes containing a paper reading ‘group 1’ and 65 envelopes containing a paper reading ‘group b’. The paper is sandwiched between two black pieces of cardboard, making it impossible to see through even with strong under-lighting. The envelopes have been sealed with glue. They will then order and number the envelopes according to the order from the randomization sequence.

Implementation of allocation {16c}

During the study period, staff involved in data collection and analysis will be blinded to randomization sequence and block size. Only the personnel responsible for including participants will have the ability to view group allocation, but only after the participant is irreversibly included in the study and have been allocated to their group.

Assignment of interventions: Blinding

Who will be blinded {17a}

Outcome assessors and the statistician performing analysis will be blinded in every way to group allocation. To yield valid results from the trial, we will blind intervention-receivers (participants) to treatment allocation and contents of the intervention they are not receiving. This will be done by providing minimal information to participants about the contents of either intervention until after group allocation, nor will they be informed if they are in the experimental (Group A) or usual care group (Group 1). The written and verbal information prior to inclusions will state that the two groups both contain first line treatment modalities such as different advice and exercises, offered as current practice based on the most recent literature.

One reason for not informing participants about the contents of the interventions is that knowledge about the actual content would increase the likelihood of contamination, as participants might want to implement parts of one intervention into the other or vice versa, for example, by doing stretches in addition to the exercises in the experimental group. This would contaminate the experimental intervention leading to a possible underestimation of the efficacy of the intervention in question. Secondly, by keeping participants blinded to treatment allocation, the adverse effects, such as disappointment of not receiving one or the other intervention, could be avoided. This is important because these effects could negatively affect the outcomes, with a risk of an overestimation of the relative efficacy of the intervention in question. This blinding aspect of participants with minimal information about treatment contents will increase the validity of the results. We consider this blinding aspect ethically warranted, as firstly, no current standardized recommendations or best practice of care for Osgood-Schlatter exists, and secondly, there is a considerable variation in the current type and extent of treatment modalities offered for Osgood-Schlatter patients.[58,115]

To minimize bias (performance- and verification bias), the intervention personnel will not be aware which, if any, of the two treatments is the experimental or the comparator, or if the trial is investigating superiority/non-inferiority/equivalence. Different personnel will deliver each intervention and will not be

aware of the contents of the intervention in the opposite arm. However, due to the nature of the interventions, it is required that they are aware of the group allocation of participants in order to deliver their assigned intervention, and they also need to engage participants in conversations about their current pain and symptoms, and their level of physical activity and sports, in order to guide participants through their respective treatments. Blinding intervention personnel to group allocation and some outcomes is therefore not feasible and is not performed, but they will not have access to any data collected by the outcome assessor during clinical testing and ultrasound scanning, nor the patient-reported instruments.

Procedure for unblinding if needed {17b}

As the study director and the Medical Advisor is unblinded to group allocation, unblinding is not expected to be necessary during the trial.

Study personnel

Intervention personnel will be 6-10 different trained physiotherapists, not be involved in other aspects of the trial. Personnel responsible for doing outcome collection will be 1-2 physiotherapists, not involved in other aspects of the trial and will be blinded to group allocation. Personnel responsible for diagnosis, inclusion, end-of-study visit will be one physiotherapist (KK) and a potential trained replacement, who will not be blinded to either group allocation or outcome measures. The Medical Advisor will be a Chief Orthopedic Surgeon (PH), who will examine participants in need of a second opinion regarding initial diagnosis, AEs, or other sudden health deterioration in participants. A biostatistician (TK) blinded to group allocation in the dataset will perform the analyses.

Study training

The PI has extensive experience delivering the experimental intervention, with all the chosen clinical outcome assessments from previous trials,[32,59,68,116,181,188,195] and clinical work in the target population. In addition, the PI have managed the process of constructing the usual care-intervention through investigation with clinical field experts.[115] Therefore, the PI will train the other physiotherapists in the respective interventions and clinical outcome assessments. All personnel will be trained in the nature of contamination effect and be trained in how to avoid unblinding when engaging participants.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Depending on the time point, participants will answer between 85 (baseline) and 38 questions (month 1) in their surveys. In table 11 we have described the schedule of data collection of all outcomes. All outcome data, both clinically obtained by an outcome assessor or patient-reported directly from the participants, will be entered into REDCap. Weekly monitoring will be performed using text-based service (SMS-track®, Esbjerg, Denmark) similarly starting the following Monday after the baseline visit and the following 22 weeks, totaling 23 weekly monitoring questionnaires containing 4-6 questions.

Table 11. Study schedule

Study phase	Pre-allocation	Baseline	Intervention period				Primary endpoint	Clinical follow-up	Long-term follow-up[d]
Timepoint		Mo 0	Weekly	Mo 1	Mo 2	Mo 3	Mo 5	Mo 8	Mo 10, 12, 24, 48
Enrollment procedures									
Clinical visit		X		X		X	X	X	
At home	X		X		X				X
Phone screening	X								
Written information	X	X							
Verbal information	X	X							
Written consent		X							
Allocation		X							
Clinical assessments									
Clinical examination		X					X		
Peak Height Velocity		X				X	X	X	
Adverse events		X		X	X	X	X	X	
Previous & concomitant treatments		X		X	X	X	X	X	
Clinical tests									
Pressure-Pain threshold		X		X		X	X	X	
Knee extension strength		X		X		X	X	X	
Countermovement jump		X		X		X	X	X	
Modified Thomas test		X		X		X	X	X	
Anterior knee pain provocation test		X		X		X	X	X	
Objective longitudinal measures									
Physical activity (sensors)		◆—	—	—	—	—	—◆		
Imaging									
Ultrasound scanning		X				X	X	X	
Patient-reported questionnaires									
KOOS-child 4 subscales		X		X	X	X	X	X	X
Acceptable Symptom State (PASS)		X		X	X	X	X	X	X
Global rating of change				X	X	X	X	X	X
Sport & Physical activity		X	X	X	X	X	X	X	X
Pain history		X	X	X	X	X	X	X	X
Self-rated health (EQ-5D-Y)		X				X	X	X	X
Kinesiophobia (Tampa)		X				X	X		
Therapeutic Alliance (WIA)						X			
Miscellaneous health[a]		X							
Pubertal stage (Tanner)		X				X	X		
Adherence to treatments			X	X		X	X	X	
Intervention									
Experimental or usual care treatment		◆—	—	—	—	—◆			
Complete self-management						◆—	—◆◆—	—	—◆

[a]Sleep duration and problems, vitamin and supplement consumption, PA = Physical activity, QoL = Quality of Life, [d] = digital

Plans to promote participant retention and complete follow-up {18b}

When capturing electronic questionnaire responses, participants will receive 2 reminders if having not responded and will subsequently be telephoned to ensure responses. We will continue data collection irrespective of adherence to interventions. Data collection will only discontinue if participants explicitly wish to withdraw from the study and not attend further visits. In such cases, we will offer participants the option to only complete electronic patient-reported forms or having treatments delivered by telephone or video chat, however, every reasonable effort will be made to retain all participants and collect all outcomes for every patient enrolled in the study.

Data management {19}

The study director will manage and curate data in collaboration with the blinded statistician (TK). Sonographs, videos (jump testing requires analyses of high-speed videos), or images (participants might occasionally be asked to send a picture of their knee with painful areas drawn up as part of inclusion or reporting of AEs) will be uploaded to a secure logged server with access restrictions. All other data will be entered directly into REDCap. REDCap users (study personnel) will only have access to their respective relevant instruments and data within the REDCap project to maintain blinding to group allocation, outcomes, and contents of interventions. Written consent forms and other hardcopy data will be stored in locked steel cabinets in a locked room and will be stored for 3 years after completion of the long-term follow-up of the study.

Data protection & Confidentiality {27,33}

In addition to data captured as outlined, we will keep standard confidential health records and store data in accordance with local laws and healthcare regulations: Our management and storing of data will comply with the articles of General Data Protection Regulation of May 20th 2018, under the EU, Regulation No 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, the Data Protection Act (in Danish: “databeskyttelsesloven”) and the Danish Health Care Act (in Danish: “sundhedsloven”). In addition, our plans (and sub-contractors) for use and handling of patient data have been reviewed and approved by the Capital Region Data Protection Agency, Denmark (P-2021-818) after the protocol was approved by the Capital Region Committee on Health Research Ethics, Denmark. Data will only be shared within the study group after unblinding at the pseudo-anonymized level and externally at the fully anonymized level. We plan for only the study director to hold access to the de-identifier key. We only expect to use this prematurely if participants wish to withdraw and have their data irrevocably deleted. As per usual

care, information regarding clinical findings, treatment plans, and delivery, will be noted in the participants regular electronic medical records to support possible post-trial care. No biological material will be obtained.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Analyses will be performed by a statistician blinded to group allocation and will be performed using (R Foundation for Statistical Computing, Vienna, Austria) in the Rstudio interface (RStudio Team, Boston, USA).

Change scores for KOOS-child 'sport/play' score (△KOOS) from baseline to month 5 will be calculated for all participants. We will fit a linear regression model using the 'lm' function for △KOOS-child as the dependent variable and including group allocation as an independent variable. Covariates are described with their measurement, timing and justification in table 12, and will potentially be added to the model.[82(p9),215] In order to not introduce unnecessary bias in the model, covariates will however only be included if doing so changes the primary estimate meaningfully, as we expect a equal distribution of these pre-specified covariates given the sample size. Significance level will not determine the inclusion of covariates. The linear model will be evaluated for linearity, multicollinearity, homogeneity of variance, distortion of outliers, homoskedasticity, correlation of variables, distribution of residuals using histograms. If these model assumptions are not met non parametric bootstrap estimation and tests will be used instead. Below we have outlined the intended steps with reproducible R code for Rstudio (version 3.6, 2021.09.0+351)

Statistical code example

Step 1: load necessary packages

```
#installs and loads all necessary packages

install.packages("stargazer")
library("stargazer")
install.packages("ggplot2")
library("ggplot2")
install.packages("performance")
library("performance")
install.packages("lindia")
library("lindia")
install.packages("see")
library("see")
install.packages("patchwork")
library("patchwork")
install.packages("readr")
```

```
library(readr)
```

Step 2: import data

```
#imports csv file into dataframe titled fu_data

fu_data <- read_delim("R/win-library/3.6/fu_data.csv", ";", escape_double = FALSE, trim_ws = TRUE)
```

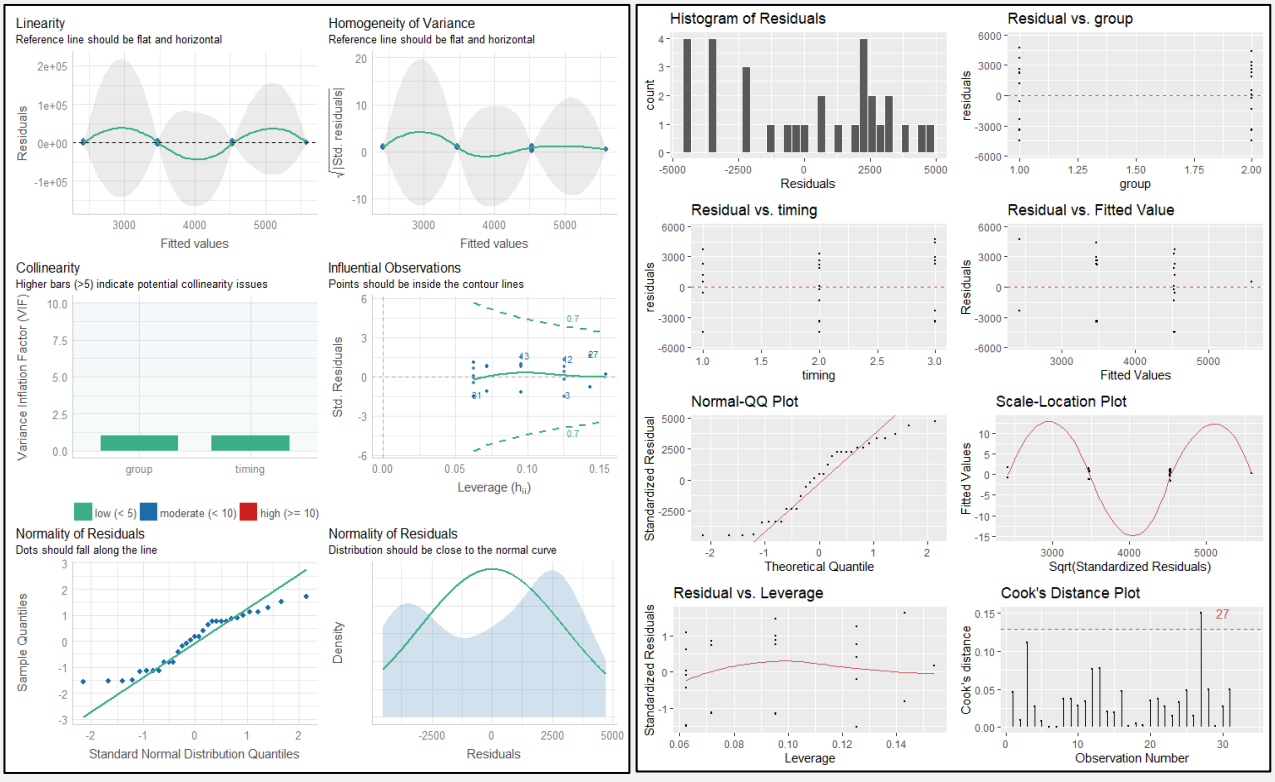
Step 3: run regression model

```
#runs linear regression model with 'koos_spor't as the dependent outcome variable
#and 'group' as the independent predictor variable. The model is named lm_koos_sp
#'timing' of maturation is included as a covariate.

lm_koos_sp <- lm(koos_sport~group + timing, data=fu_data)
```

Step 4: produce plots for model evaluation

```
#produce plots used for evaluation of model fit and assumptions

gg_diagnose(lm_koos_sp)
check_model(lm_koos_sp)
```

Step 5: evaluate model from plots



Step 6: print model output

```
#prints output from model from summary and stargazer function

summary(lm_koos_sp)
stargazer(lm_koos_sp, type = "text", style="all", title="Linear regression of KOOS-child
sport/rec")
```

Step 6: evaluate model output from console

```
Residuals:
    Min      1Q  Median      3Q     Max
-4504.4 -2863.1   485.1  2421.4  4720.6

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)   4541.2     2215.4   2.050   0.0498 *
group         1050.6     1145.6   0.917   0.3670
timing       -1056.5      776.5  -1.360   0.1845
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 3105 on 28 degrees of freedom
  (2 observations deleted due to missingness)
Multiple R-squared:  0.07503,           Adjusted R-squared:  0.008959
F-statistic: 1.136 on 2 and 28 DF,  p-value: 0.3356

Linear regression of KOOS-child sport/rec
================================================
                        Dependent variable:
                    ----------------------------
                              koos_sport
------------------------------------------------
group                          1,050.577
                              (1,145.632)
                               t = 0.917
                               p = 0.367
timing                         -1,056.458
                               (776.549)
                               t = -1.360
                               p = 0.185
Constant                      4,541.163**
                              (2,215.364)
                               t = 2.050
                               p = 0.050
------------------------------------------------
Observations                      31
R2                               0.075
Adjusted R2                      0.009
Residual Std. Error      3,104.971 (df = 28)
```

```
F Statistic         1.136 (df = 2; 28) (p = 0.336)
================================================
Note:                  *p<0.1; **p<0.05; ***p<0.01
```

We expect only to modify these procedures if more suitable methods, packages, or software is developed and will describe and justify these potential deviations from the pre-specified strategy in the final report. Intention-to-treat analyses, that is, analysis according to group allocation, will be performed as the standard analysis strategy unless otherwise denoted, to 1) investigate the relative effectiveness of being offered the experimental intervention over usual care, and 2) to maintain the balance of known and unknown confounders from randomization.

We will employ a similar analysis strategy for other numerical outcome variables. For non-numeric variables, differences between groups will be analyzed by logistic regression models, and non-normally distributed residuals for ratio-interval scale outcomes will be compared by non parametric boot strap tests. To supply detailed trajectories and inferences of treatment response over time, we will fit mixed-effects models for the imaging outcomes (months 0, 3, 5, 8); time-to-return to sport, weekly hours of sports participation, pain-flares, and sensor-based physical activity (weeks 0 to 22); clinical outcomes (months 0, 1, 3, 5, 8); and remaining patient-reported outcomes (months 0, 1, 3, 5, 8, 12, 24, 48).

Mean and SD values will be reported if data appear approximately normally distributed. If data are non-normally distributed, they will be presented as median and interquartile range (IQR). We will report 95% confidence intervals, exact p-values to the third decimal, and discussions of minimal detectable change (MDC) and minimal important change (MIC) when relevant/possible. Frequency data will be reported as "No. (%)".

Our standard option for all variables, is to be analyzed with the highest resolution possible, meaning no collapsing or dichotomization to retain as much information as possible in the dataset. However, some assessor-dependent scales, such as ultrasound scoring of the (non-normal maturation-related) fragmentation quality of the tibial tubercle bone, contains the potential values “none” (1), “unclear”, (2), “little”, or “apparent/extensive” (4). The same applies to some other ultrasound measures and clinical examination findings. Depending on the distribution of responses into these categories, we might choose to exclude data from the “unclear” category or collapse the “little” and “apparent/extensive” categories if we estimate the number of responses to be too low to make meaningful inferences.

Once the primary data have been analyzed, we will also compute and report the RCT-Fragility Index (how

many patients would need to change from success to non-success to render the potential experimental effect non-significant or equal) based on the PASS outcome for easier clinical interpretation of the robustness of results.[216]

Superiority framework and controlling error rates

The analysis will be evaluated based on a one-sided hypothesis as the trial employs a superiority design, meaning that if a one-sided test of significance fails in the direction of the experimental group, the null-hypothesis is rejected for our sample, and the level of significance in opposite direction is therefore not of interest.[217,218] To further safeguard this choice, we have made the decision to obtain 90% power (up to 94.6% if all participants retained), corresponding to a 10% false negative error rate). By default, we will not perform adjustments for multiple comparisons as we have arranged our hypotheses in a prioritized order, and we will also conduct and report hypotheses testing in this pre-specified order.[170,219] We will however adjust for multiple comparisons using Bonferroni corrections when multiple tests are performed for outcomes within the same construct or objective (e.g. the effect of group on acute pain response during loading, measured through 2 different outcomes: pain [0-10 NPRS] during maximal isometric knee extension test, and pain [0-10 NPRS] evoked from the Anterior Knee Pain Provocation test).

Interim analyses {21b}

No interim analyses or stopping rules are planned, due to very low safety concerns and to preserve statistical power. However, an evaluation of feasibility outcomes will be performed after including n=15 participants to decide if potential study amendments will result in these 15 participants being included in the primary dataset (see “Embedded pilot study” section).

Methods for additional analyses (e.g. subgroup analyses) {20b}

Besides the sensitivity analyses otherwise specified (covariate adjusted, mixed-effects, moderation, mediation), we will perform per-protocol analyses to test the robustness of the primary intention-to-treat analysis, by examining the effect of adherence according to the pre-specified compliance criteria.

Handling of non-adherence and any statistical methods to handle missing data {20c}

Assuming that data will be missing at random, multiple imputations using chain equations will be used to handle missing data. Imputation models for missing variables will be fitted using linear, logistic or polytomous regression models. All available variables will be included in the imputation models, unless a specific reason is given for exclusion. Imputation will only be performed for varialbes included in the

analysis. Multiple imputation will be done using R-package mice[].[220]

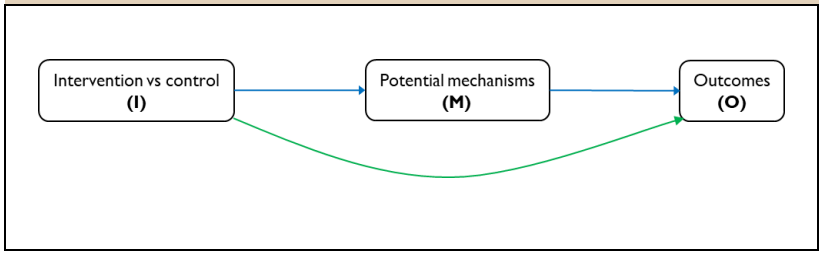
Plans to give access to the full protocol, participant level-data and statistical code {31c}

To increase transparency and dissemination, all statistical code and fully anonymized dataset will be shared to an open-access repository (such as YODA, Zenodo, or Figshare) with a digital objective identifier once all planned publications are accepted or published as pre-print.[221,222] Publication-specific datasets will potentially be posted along with published manuscripts in line with journal policies. If full anonymity cannot be achieved by removing unique data and identifies, a synthetic dataset will be created, which will mimic the original dataset by preserving the statistical properties and the relationships between variables.[223] Specific funding for Open-Access publication fees will be sought to allow dissemination to clinicians lacking institutional access or funding for journal access.

Effect moderation and mediation

As secondary analyses, we will perform moderation and mediation (if a superior treatment response in arm A is observed) analyses, which will be conducted and reported in accordance with the AGReMA Statement.[224] Through mediation analysis, the total effect of exposure to treatment groups 1 vs A (i.e. between-group difference) on the outcome, will be parsed into indirect effect pathways from exposure to mediator, and from mediator to the primary outcome (KOOS child 'Sport/play' subscale), which are the effects of interest in this mediation analysis (figure 4).[225,226] This will allow inference about the underlying responsible mechanisms for a potential effect. Such knowledge is key when optimizing or developing treatments, and for implementation efforts.[224,227] As the sample size is not planned specifically for mediation analysis, these analyses are considered secondary and should be interpreted with caution mainly based on its effect size and precision.[228] Although potential limitations of suboptimal power, this mediation analysis provides a novel preliminary step for potential identification of causal mechanisms for improvement in Osgood-Schlatter patients.

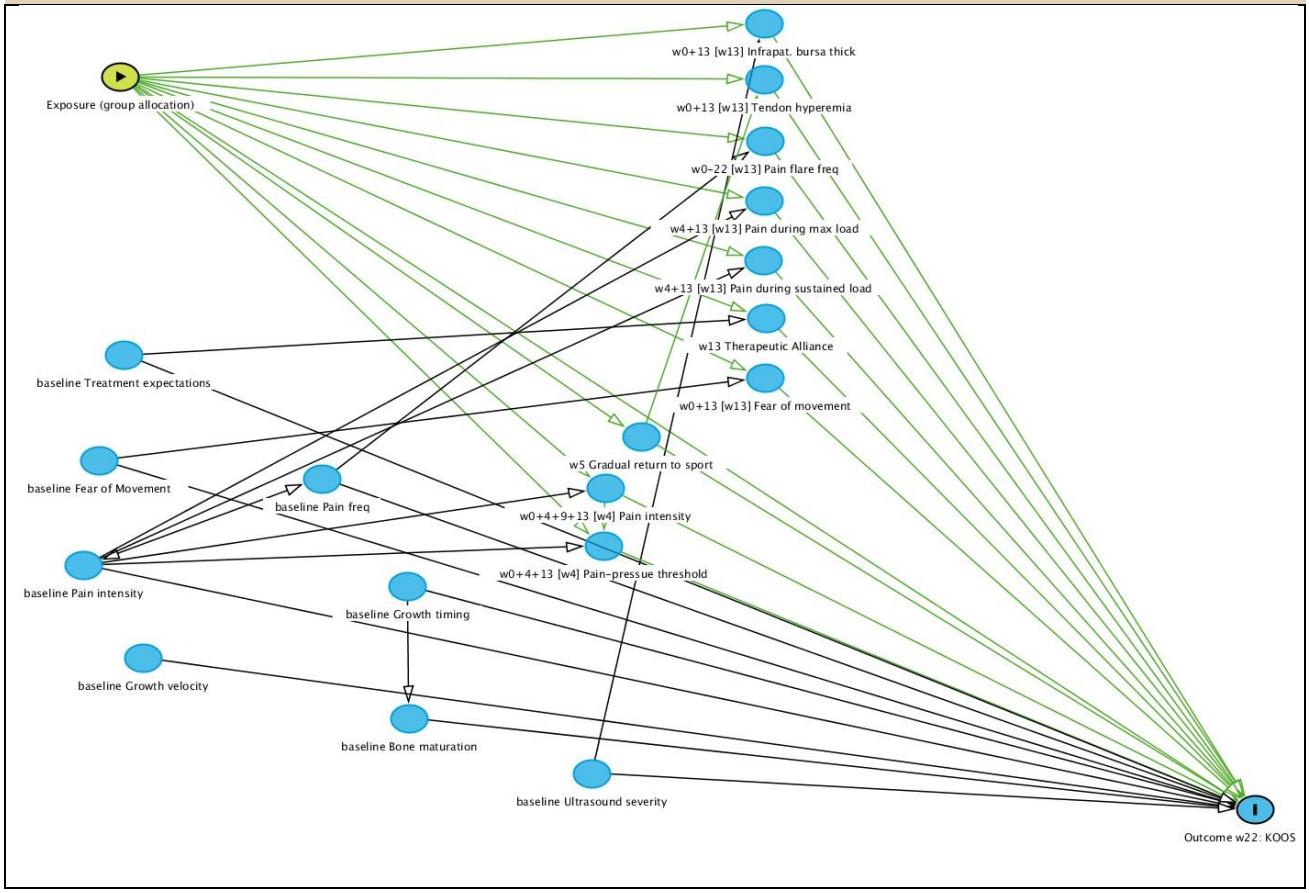
Figure 4. Visual example of mediator in the causal pathway



Mediators are represented by variables measured after randomization and before collection of outcome data, which are thought or known to be influenced by the treatment allocated to participants.[225,227] As large-scale randomization balances known and unknown confounders that can potentially influence the outcome as well as the exposure-mediator pathway, randomized trials are the optimal setting to perform causal mediation analysis.[225,226,229]

The assumed cauasal model we are investigating is illustrated as a directed acyclic graph below (figure 5) using the Dagitty software.[225,230]

Figure 5. Proposed directed acyclical graph for mediation analysis



Assumptions for causal mediation analysis

The four assumptions for unconfounded analysis of parsed mediation pathways require 1) no unmeasured exposure-outcome confounders, 2) no unmeasured mediator-outcome confounders, 3) no unmeasured exposure-mediator confounders, 4) no mediator-outcome confounder affected by exposure.[225,227,229] Assumption 1 and 3 should be mitigated by randomization and potential covariate adjustment. Because mediators are not randomized it is possible for the mediator-outcome pathway to be confounded

(assumption 2 and 4). To address assumption 2, we will include pre-treatment confounders based on available evidence and clinical expertise. This includes potential covariates/moderator variables outline (table 12) and baseline levels of the mediator-variables. Assumption 4 will be addressed by using interventional effects in the mediation analysis[231] along with inclusion of confounders. In addition, to address the assumption of no positivity, that is, a zero risk of any participant exhibiting a positive characteristic of a mediation variable at baseline,[227] all mediator variables with this potential issue, will be change-scores calculated from baseline.

Number of predictors for mediations analysis

Based on our sample size of n=130 and the use of multiple regression models, power of >80% and alpha level of 5% (t = 1.658, Df = 109), we calculated the potential number of predictors as 16 based on Fritz & MacKinnon sample size recommendations for mediation analysis (G*power 3.1.9.7, Düsseldorf University, Germany).[228,232,233] In our current model, we have included 15 predictors (8 mediators and 7 potential covariates/moderators).

Table 12. Proposed moderators and mediators

Variables	Measurement	Justification
Potential moderators/covariates		
Growth velocity$_{w0}$	Offset from predicted age at peak height velocity in years, calculated from clinically measured anthropometrics: sitting height, bodyweight, total stature, biological age.[234] Participants will be categorized into pre- (<-1.0 years offset), circa- (-1.0 to +0.5 years offset), and post-PHV (>+0.5 years offset), corrected for timing of the primary endpoint, resulting in a 5 month subtraction.	Overuse knee injuries, as well as injuries to the growth plate, in sports active adolescents are higher during peak height velocity and the year leading up to this point,[235–239] which is thought to be primarily due to vulnerable growth-related conditions, such as Osgood-Schlatter.[235] This has been supported by data showing higher growth velocity for Osgood-Schlatter patients than controls.[240]
Growth timing$_{w0}$	Based on algorithms for calculating anticipated age of peak height velocity which incorporates data on parents adult stature, we will classify participants as early maturers, average maturers, and late maturers (girls: <10.94, 10.94-12.94, and >12.94 years, respectively; boys: <12.64, 12.64-14.64, and >14.64 years, respectively).[241,242]	Reaching skeletal maturity either late or on average is a risk factor for developing Osgood-Schlatter compared to early maturation.[21,243]
Fear of movement$_{w13}$	Fear of movement will be captured by participants filling in the 17 items Tampa Scale of Kinesiophobia, each item scored on a 4-point likert scale with a score ranging from 0 to 68.[200,201]	Avoidance behavior might be related to a too apprehensive approach to gradual exposure and exercise therapy resulting in the patient not achieving a higher degree of participation in sports and physical activity. Osgood-Schlatter patients exhibits a high degree of kinesiophobia.[68]
Pain intensity$_{w0}$	Self-reported “worst pain past week” on the 0-10 NPRS.	Pain intensity has shown to be related to a worse prognosis for adolescents with anterior knee pain[54]
Pain frequency$_{w0}$	Self-reported on the P1 question of the KOOS-child Pain subscale on frequency of experience knee pain, answered on a 0-4 scale ranging from “Never” to “All the time”.[172]	Pain frequency have shown to be related to a worse prognosis for adolescents with anterior knee pain.[52,54]
Treatment expectations$_{w0}$	Self-reported through the question on change in “my ability to self-manage my knee pain” answered on a 1-4 likert scale from ‘worse’, ‘no difference’, ‘little improvement’, to ‘large improvement’.	Treatment expectations have been shown to moderate outcomes in trials of several different musculoskeletal conditions and chronic pain conditions.[244–248]

Tibial tubercle maturation$_{w0}$	Rated by sonographers ad modum Sailly[109,249] from on a 1-4 scale depending on features of cartilage, potential secondary ossification center, tendon, and the infrapatellar bursa.	The level of maturation of the apophysis has been shown to be related to the prevalence of Osgood-Schlatter symptoms with early (exhibiting no metaphysis-physis junction or apophyseal attachment of the patella tendon) and late stages (denoting full unification of metaphysis-physis junction and matured attached of the patella tendon) being low-risk stages, and the intermediate stages (exhibiting open metaphysis-physis junction, apophyseal attachment of the patella tendon, active ossification center) have a higher association to symptoms[109,250,251]
Severity$_{w0}$	Rated by sonographers ad modum Flaviis[251] from 'cartilage attachment' to 'mature attachment' on a nominal 1-4 scale.	Severity on the Flaviis scale has been associated with a worse prognosis.[32,251]
Potential mediators		
Pain intensity$_{w4}$	Self-reported "worst pain past week" change from baseline on the 0-10 NPRS.	The aim of the sports break (week 0-4) is to calm the sensitivity of the condition to achieve a more successful graded exposure to sports and physical activity.[59,60,68] One way to measure decreased sensitivity to load is by asking patients their worst level of pain during the past week.
Pressure sensitivity$_{w4}$	Through handheld algometry, the patient denotes when pressure applied to the symptomatic tibial tubercle goes from feeling as "pressure" to "pain", and the kPa at this threshold is recorded. Change score is calculated from baseline.	The aim of the sports break is to calm the sensitivity of the condition to achieve a more successful graded exposure to sports and physical activity.[59,60,68] Besides pain intensity, one way to measure decreased sensitivity of the condition is through pressure-pain detection threshold to evaluate local hyperalgesia specifically at the tibial tubercle.
Controlled return to sport$_{w5}$	Sports participation in the preceding week is self-reported through weekly text messages, ranging from 0 to >7 hours. <2 hours of sports participation in week 5 will be considered as a controlled return to sport.	Graded exposure requires a gradual introduction to sports, although this trajectory quickly can be accelerated if it appears to be tolerated. In the very first week of a gradual return to sports, modest sports participation should be a marker of adhering to the recommendation of gradual return.
Pain flare frequency during return to sport$_{w13}$	Number of pain flares (episodes of NRPS ≥4) in the preceding week is self-reported through weekly text messages.	Graded exposure according to the pain-model aims to both prevent pain flares, and to mitigate their intensity to NRPS ≤3.
Therapeutic Alliance$_{w13}$	Therapeutic Alliance will be captured by participants filling in the 12 item short-form Working Alliance Inventory, each item scored on a 7-point likert scale with a score ranging from 0 to 84 points.[252]	Achieving a strong therapeutic alliance has been shown to be related to improved outcomes in trials across several musculoskeletal conditions.[253,254]
Fear of movement$_{w13}$	Fear of movement will be captured by participants filling in the 17 items Tampa Scale of Kinesiophobia, each item scored on a 4-point likert scale with a score ranging from 17 to 68.[200,201]	Avoidance behavior might be related to a too apprehensive approach to gradual exposure and exercise therapy resulting in the patient not achieving a higher degree of participation in sports and physical activity. Osgood-Schlatter patients exhibits a high degree of kinesiophobia.[68]
Pain during maximal knee loading$_{w13}$	Participants will rate their pain using NRPS 0-10 during strength testing, that is, a 5 second maximal voluntary isometric contraction of the knee extensor muscles at 60˚ knee flexion.	Pain during loading is a key symptom of Osgood-Schlatter and is related to self-reported measures of quality of life, satisfaction with sports participation and hyperemia in the tendon.[68,109,116] The intervention aims to improve capacity to loading activities and should thus be better tolerated at this timepoint.
Knee extension strength$_{w13}$	Knee extension strength will be measured in newtons by handheld dynamometry during a 5 second maximal voluntary isometric contraction at 60˚ knee flexion. Newtons will be normalized to lever-length and bodyweight and expressed as Nm/kg.	Knee pain is known to reduce muscle function,[116,255] and strength training contribute to alleviate these deficits.[59,60]
Distal patella tendon hyperemia$_{w13}$	Rated by sonographers ad modum Öhberg from 'no neovessels' to '5 or more neovessels' on a 1-4 scale.[180,256–258]	A series of Osgood-Schlatter patients has been described for whom less hyperemia on color doppler ultrasound was associated with milder symptoms.[109] Neovessels can generate and diminish rather quickly and could therefore be highly responsive to change in condition.[259–261]
Infrapatellar bursitis sign$_{w13}$	Either denoted as thickened bursa (yes/no) or appearing with doppler as rated by sonographers (1-4 nominal scale).	In our previous cohort at 2-year follow-up, almost all participants still experiencing knee-pain also had Flaviis grade 4 (associated infrapatellar bursitis) at baseline, whilst participants classified as grade 1 (normal) were less likely to report pain at follow-up.[32] Thus, the sole finding of bursitis signs in the infrapatellar bursa will be tested as mediator.

Outcome		
Knee-related Function in Sport/Rec$_{w22}$	Self-reported on KOOS-child 'Sport/play' subscale, which measure how painful certain movements related to sports- and recreational activities are perceived on 7 items ranging from 'no pain' to 'extreme pain' on a 1-5 Likert scale, normalized to a 0-100 score.	Primary outcome outcome collected at 22 weeks.

Statistical approach to mediation analysis

Mediation analysis will be based on interventional effects, this will allow for the inclusion of multiple mediators and account for dependence between mediators.[231] With estimation done by Monte-Carlo based regressionmodels.Covariates will be included as moderators in the full model. For each mediator, we will calculate and report effect size as odds ratios and p-values, as well as 95% confidence intervals We will calculate and report estimated effect and percentage contribution to total effect for each mediator variable included in the final model, based of the mean indirect effect. The model will only include mediators that fulfill the temporal sequence of a causal relationship, that is exposure, mediator, outcome.

Oversight and monitoring

Composition and roles of the trial steering committee and data monitoring committee {5d, 21a}

The Sports Orthopedic Research Center – Copenhagen (SORC-C), specifically PhD-fellow Kasper Krommes (Study Director) and Professor Per Hölmich (Main Supervisor and Medical Advisor) and Professor Kristian Thorborg (Co-supervisor) at the Department of Orthopedic Surgery at Amager-Hvidovre Hospital has initiated and will manage the trial. Together, they also form the steering- and writing committee, which will oversee the trial and decide on authorships and assume stewardship of the data. No specific data monitoring committee is convened.

Adverse event reporting and harms {22}

In our published pilot-study[60] and during pilot-testing the intervention in the clinic,[68] we have not observed any adverse events suspected to be linked to undergoing the treatment, although this was not assessed systematically. Participants will be informed in writing and verbally about the blinding aspects and potential risks and discomforts of participating in the study prior to enrollment. As with usual activites, participants' symptoms may similarly temporarily flare up during testing. Especially the anterior knee provocation test is designed to provoke anterior knee pain symptoms, specifically. Also, the algometric pressure will inflict short-term low levels of pain when going from 0 to 1 on the numeral pain rating scale (0 being 'no pain' and 10 being 'worst pain imaginable'). The imaging used in the study is diagnostic ultrasound that uses high-

frequency soundwaves, with no ionizing radiation exposure and no discomfort during the scan. Usual care sometimes consists of invasive therapies such as injections and surgery, or other painful modalities, such as shockwave or dry-needling , however, the treatments and advice in the in the current study are solely based on straps, cryotherapy, exercises, and advice and education, and no adverse events are expected.[262] As such, the potential benefits (on the individual and public level) of the study far outweigh the potential risks.

To assess potential or any suspected harms and adverse events (AEs), participants will be asked during all clinical visits and the telephone consultation at month 2, through open-ended questioning about any new symptoms or illnesses, accidents, reasons for care-seeking, and knee-related questions on pain, locking, swelling, discoloration, or clicking experienced during exercises or other trial-related procedures, whether it can be attributed to the treatment or not. In addition, Serious (grade 3-5) unexpected side effects or AEs will be reported to the Capital Regional Ethics Committee in Denmark within 7 days after the study director has become aware of the incident. All AEs will be assessed by the study director and the Medical Advisor (PH) for possible relations with the assessments and/or intervention to consider whether there is a reasonable possibility that the AE can be caused by either. The study director will be notified of new AEs by personnel responsible for interventions or outcome assessments (at month 0, 1, 2, or 13) and will telephone the participant as soon as possible thereafter for further investigation; or when consulting the participants in person at month 0, 5 or 8. When needed, the participant will be seen by the Medical Advisor (PH). Adverse events will be categorized and graded by two independent reviewers according to the severity on from Grade 1-5 Using the Common Terminology Criteria for Adverse Events (CTCAE) grading:[263]

1. Mild: Asymptomatic or minor symptoms; clinical or diagnostic observations only; no intervention needed
2. Moderate: Minimal, local, or non-invasive intervention indicated
3. Severe: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling
4. Life-threatening consequences (i.e., immediate risk of death); urgent intervention indicated
5. Death related to adverse event

The occurrence will be reported according to the Council for International Organizations of Medical Sciences thresholds of occurrence,[264] however, the anticipated sample (n=130) will only allow to inferences regarding very common or common harms:

- Very common ≥ 1/10
- Common (frequent) < 1/10 AND ≥ 1/100
- Uncommon (infrequent) < 1/100 AND ≥ 1/1000

- Rare < 1/1000 AND ≥ 1/10000
- Very rare < 1/10000

Steps to minimize pain, risk, and inconveniences

To minimize pain during testing, the participants are told that they can always abort the test if the pain is felt as 'too much' or they start feeling fearful or uncertain of their symptoms during testing, but are ultimately told that potential pain felt during testing are not harmful and will subside within 24 hours, as is our experience from >1000 tests. During knee extension strength test, if the adolescent feels the metal of the gauge on their shinbone through the padding of the dynamometer, extra padding will be placed on the shin. During the algometric test, we will use an upper boundary of 1000 kPa not to cause any bruises if participants does not report pain at this level of pressure (corresponding to 1 newton/mm^2 or 10 kg/cm^2).

Justification of risks and drawbacks, and future therapeutic reward

There are no anticipated severe risks or drawbacks. All potential risks and drawbacks have been described and are considered minimal, with potential benefits far outweighing these both on the individual participant level and the public level. The choice to include 10-16-year-olds was made, as this is the age where Osgood-Schlatter occurs. The current sample of adolescents will receive a state-of-the-art examination, treatment, and follow-up care, superior to the current standard of care, which often is non-evidence based, sometimes invasive or painful, and with potential side-effects; or even minimal or no care at all. If the experimental intervention shows relative efficacy, it could easily be implemented in current practice, potentially benefiting the many adolescents suffering from Osgood-Schlatter in the future. In addition, this study will uncover the potential effect of the two different interventions on other central outcomes such as pain mechanisms, performance, tissue morphology, as well as potential moderating factors and potential mechanisms responsible for success through mediation analysis. Finally, the long-term follow-up assessments will help clarify if the effects are sustained with a potential for better quality of life, disease prevention, health, etc. through increased participation in sports and physical activity.

Compensation to patients

No participants will receive reimbursement for their travel expenses related to participation in the study, nor will participants be offered compensation of any kind. During treatment at Hvidovre Hospital, the participants will be covered under the Danish Patient Compensation Act (LBK no 995 of 14/06/2018, chapter 3 §19) (In Danish: Patienterstatningen), which is a scheme that deals with compensation claims of patients

treated in the public health system in Denmark who has sustained an unintended or unexpected injury or harm.

Frequency and plans for auditing trial conduct {23}

No trial audit is planned.

Plans for communicating important protocol amendments to relevant parties {25}

Amendments to the trial will be reported to the review board (Regional Committees on Health Research Ethics for The Capitol Region), and the amendments will be reported with justifications in the main report. If amendments affect trial participants during their participation, they will be informed by telephone or email.

Dissemination plans {31a}

All members of the study group will be invited as co-authors on the specific publications according to the International Committee of Medical Journal Editors (ICMJE) recommendations and The Danish Code of Conduct for Research Integrity codec.[265,266] All findings and results are planned to be published in international peer-reviewed scientific journals. Furthermore, the results will be presented at national and international conferences; as part of our collaborations with the Danish Society of Sports Physical Therapy, Danish Sports Medicine Association, Clinical-Academic Groups (CAGs) across Copenhagen University and University Hospitals; and as our capacity as IOC Research Center. The results will be posted to ClinicalTrials.gov once the primary results have been published. In addition, we will utilize appropriate social media channels to increase dissemination.[267] The results will be published regardless of positive, negative, or inconclusive findings. Kasper Krommes and Per Hölmich will enforce publications as first and senior authors respectively, unless other publication-specific contributions warrants or are otherwise agreed upon by the study group. We will frame the main conlusion based on the potentiel primary endpoint between-group difference, in line with the superiority framework, which will take into account the MCID (9 points), width of the confidence interval, the overlap of the confidence interval, and the statistical significance.

Acknowledgments

Patients and their parents attending meetings regarding objectives, design, and the practical implementation of the trial. Colleagues Mathias Fabricius Nielsen and Lasse Ishøi for ongoing valuable input. Pre-graduate students that have assisted in in performing studies and other preperational work for this protocol: Frederikke Villumsen, Amalie Bjerre Jørgensen, Oliver Olsen, Nickoline Andersen, Line Holm, Caroline Schad, Hjalte Nørremark. Ph.d. Candidate Marie Skov Breum and Professor Torben Martinussen for

valuable input and review of prespecified approach to mediation analysis. Senior Researcher Jeanetter Wassar Kirk for methodological guidance in designing and planning qualitative substudy.

Authors' contributions {31b}

All authors contributed to the protocol. Contributions are visualized in table 13.

Table 13. Author contributions *(CRediT Taxonomy)*

	KK	PH	KT	JL	MR	MC	TK
Conceptualization							
Funding acquisition							
Supervision							
Resources							
Draft of protocol							
Review and edit of protocol							
Methods: Trial design							
Methods: Analyses plan							
Methods: Imaging							
Methods: Interventions							
Methods: Outcomes							

Funding {4}

Sports Orthopedic Research Center – Copenhagen will provide, facilities, local operational support, some equipment, and 100% funding for statistical support. The following funders have provided grants to the project for other costs: Fysioterapipraksisfonden (dkr. 678.200), Østifterne (dkr. 599.958), Helsefonden (dkr. 350.000), Købmand Ferdinand Sallings Mindefond (dkr. 219.480), Hvidovre Hospitals Frie Forskningsmidler (dkr. 100.000), Beckett Fund (dkr. 70.000), FLSmidth Donation Fund (dkr. 50.000), Frimodt-Heineke Fonden (dkr. 50.000), Danish Association of Physiotherapists Research Fund (dkr. 36.600) and the Danish Society of Sports Physical Therapy (dkr. 6.000). Additional funding is being sought to secure the total operational costs of the trial, but the completion of the trial does not depend on additional funding. The local financial department will manage all funding. No funding body will have any control or involvement in data collection, analyses, interpretation, writing the report, or deciding whether to publish. The primary supervisor and responsible party, Per Hölmich, participates in the form of his affiliation with the University of Copenhagen as Professor and his role as Chief Surgeon at Arthroscopic Center at Hvidovre Hospital. Per Hölmich does not receive any financial support for his involvement in the project.

Trial status

We have piloted the intervention in three stages; in an original small published cohort[59] (n=51), in a case-series[68] (n=34) in our regular clinical setting, and for the initial 15 patients we have examined true operational feasibility of the trial. Patients and their parents attending our department have collaborated on key aspects of trial design. In addition, we have performed a stepwise mixed-methods study to determine the comparator usual care intervention with patients and clinicians (n=97). Inclusion for the trial is currently at 100% (n=130 of 130)

Availability of data and materials {29}

Materials are available at https://doi.org/10.6084/m9.figshare.c.5730008.v1. No additional data or materials is connected to conception of this protocol. For plans regarding data and materials for the trial, see section "Plans to give access to the full protocol, participant level-data and statistical code".

Competing interests {28}

Some of the authors have previously published in this area and have designed the experimental intervention being tested and are therefore prone to self-citation incentives and confirmation bias. Thomas Kallemose is paid dkr. 25.000 for statistical consultation and performing blinded analyses. There are no other conflicts of interest to declare.

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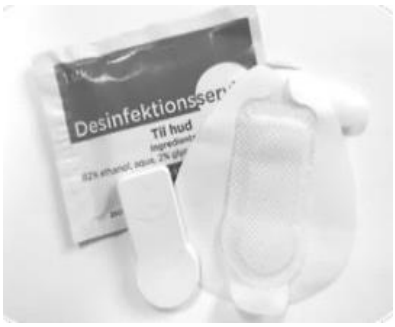
Appendix 1: Clinical test protocols{18a}

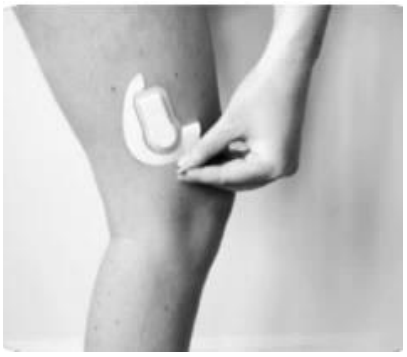
Objective tracking of physical activity: Activity motion sensors

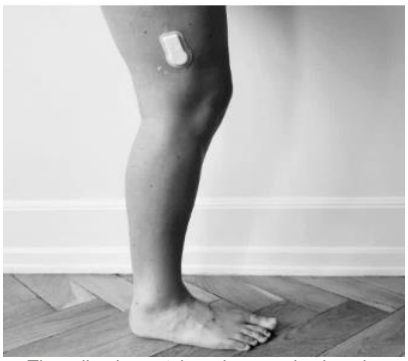
One waterproof SENS® motion sensor patch (35 cm2, 8 g) will be applied laterally on the preferred thigh, appx 10 cm from the knee joint during the inclusion visit.

The activity intensity is calculated as the average vector magnitude of the high-pass filtered 3 axis accelerometer measurements at 12 Hz sampling frequency, with subtracting the noise present on each measurement axis, and done on each 5-second epoch. Every epoch is categorized as a particular activity (light sleep, deep sleep, lying/sitting, standing, sporadic walking/slow biking, walking, biking, running/exercise/high-intensity training; 92±5% agreement).[177] Data is collected for up to 23 weeks after application through a blutooth connection to an app installed on the participant's or their parent's smartphone and onto a web-based secured private cloud. Sensor data will be analyzed at the 15-minute level and categorized into weekly and daily sedentary (lying, sitting, standing), light physical activity (sporadic walking, walking, light bicycling), and moderate/vigorous physical activity (cycling, running, high-intensity exercise), in addition to sleep activity. Participants will be instructed to wear the patch for the entire study period, change the adhesion patches when required weekly, and document physical activity at any periods where the sensor might have been taken off or lost.



SENS motion sensor and adhesive patch


Applying adhesive patch on the thigh


The adhesive patch and sensor is placed approximately 10 cm proximal to the knee

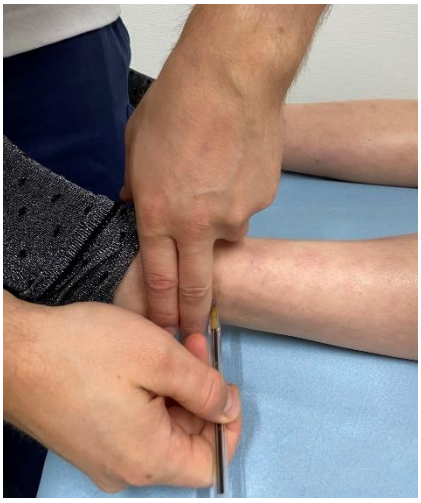
Knee extension strength: handheld dynamometry

With the participant sitting on the side of the examination bed, a handheld dynamometer is fixed anteriorly on the shin with a belt corresponding to app 4 cm proximal to the lateral malleolus. The participant is asked to hold on to the other side of the bed behind them with both hands and keep their upper body upright. Before testing, the following instructions a given:

"In this test, you must push a hard as you possible can without it being too painful, that is, 100% / maximum, from the moment I say "go" until I say "stop". So, I am going to say "3-1-2-go-press-press-press-press-stop." We are doing up to 3 trials on each leg after a familiarization trial at appx 50% of your maximum effort. There is going to be 30 seconds between trials, and let me know if you feel any pain during testing."

The assessor holds the leg in the starting position to allow full rest between trials. If the participant feels any pain during testing, they are asked to rate it on the NPRS. The position will be at 60° knee flexion and the angle of the belt on the dynamometer/shin will be 90º, both verified by handheld goniometry. This test has shown an inter-tester reliability of ICC: 0.76-0.96 with a low standard error of measurement (5-11%)[185] and good validity compared to the gold standard of isokinetic strength assessment.[186]

The dynamometer used is a MicroFet 2 (Hoggan, Scientific L.L.C., Salt Lake City, USA) with a sampling rate of 100hz. The force (newtons) obtained from the dynamometer will be normalized to lever length (knee joint line to the point of fixation in meters) and body weight (kg) to allow appropriate comparisons between participants (Nm/kg). The best of three trials will be analyzed, as well as the maximum pain rating.



Marking the probe placement 4cm proximal to the lateral malleolus

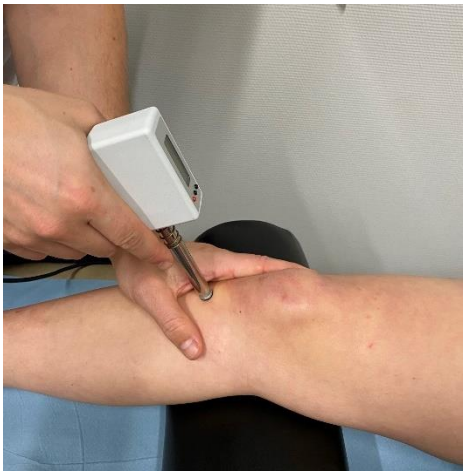
Measuring lever length from the knee joint line to the line of probe placement

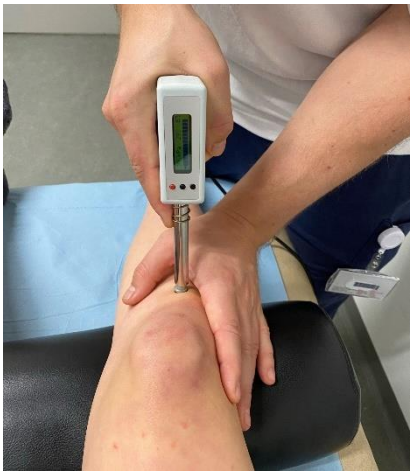
Knee extension strength test position

Pressure-pain threshold: handheld algometry

To assess the localized tissue hyperalgesia, e.g., sensitivity to pressure, a handheld pressure algometer (Algometer Type II; Somedic AB, Hörby, Sweden) will be used to measure the pain-pressure threshold, that is, the minimum pressure required to induce a painful sensation at the tibial tubercle. The probe measuring 1 cm^2 will be placed perpendicular on the pre-palpated tibial tubercle and pressure applied at appx 30 kPa/s. To minimize the risk of the probe sliding during testing, the skin is stretched to the side. To avoid excessive pressure applied, 1000 kPa will be used as a safety threshold.

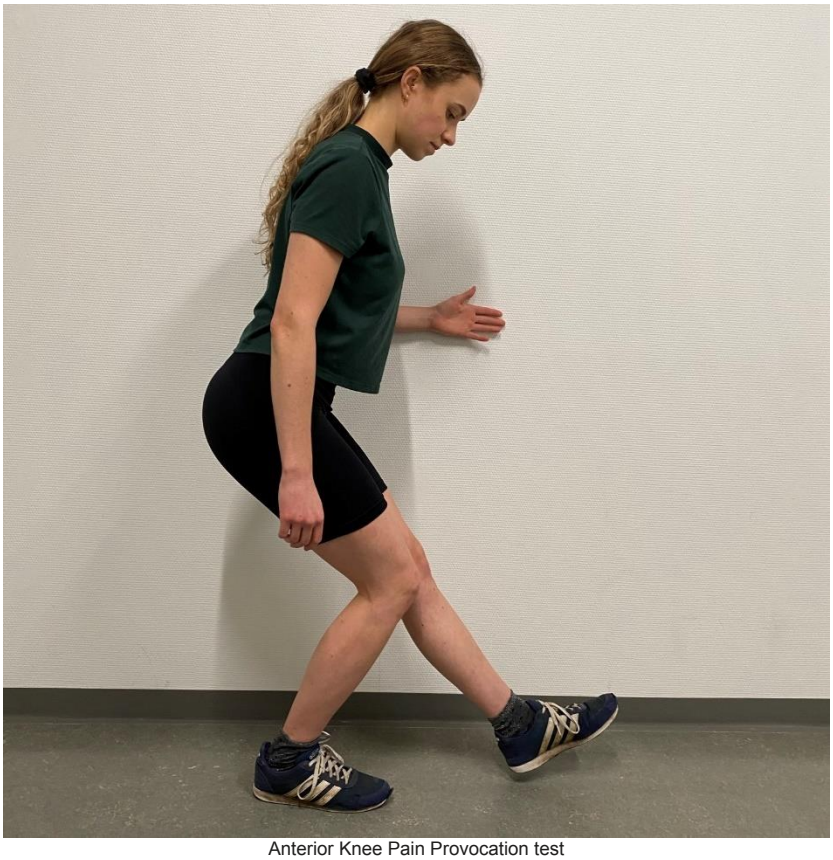
Participants will be lying supine with a solid tube under the knee during testing, while at appx 20˚ knee flexion. The participants will be instructed to press the button as soon as the pressure evokes pain, which will alarm the assessor to cease the application of pressure. Each knee will be measured twice with a minimum of 10 seconds between trials,[268] starting with the non-index. The mean of the two trials will be used in analyses.





Pain response to cumulative loading: The anterior knee pain provocation test

The AKPP-test is a 45-second unilateral test designed to provoke known anterior knee pain. The test is self-performed and self-rated. Prior to the test, participants are instructed in using the NPRS. The test is then performed in a static single-legged squat position with 60 degrees of knee flexion, which is held for 45 seconds. Participants provide their pain intensity immediately before and after completing the 45 s hold.[181] The test has been studied in a population of adolescents with longstanding knee pain and was associated with the current KOOS-child 'Sport/play' subscale and worst pain last 24 hours, as well as responsive to changes in these measures over time.[181]



Anterior Knee Pain Provocation test

Sports function and power-production: Countermovement jump

Increased countermovement jump height is associated with increased sprint performance, lower-body power, and enhanced force-velocity profile.[189,269,270] The test has also been found feasible in adolescents.[189] Calculating the power-output and jump height from anthropometric data and contact- and flight-time has been validated against the gold standard of using a force-plate,[190,191,195] and using a specific smartphone app providing the variable from a slow-motion video analysis is highly reliable.[190,193–195]

Thus, participants will perform 3 trials of the countermovement jump while being recorded on a smartphone camera (>240 frames per second) and subsequently analyzed for jump height and power using the MyJump 2 smartphone application.[190] Participants will perform a test trial, followed by 3 recorded trials. Participants will be asked to keep their hands on their hips and jump as high as possible.

Data will be normalized per Myjump 2 procedures to push-off distance (distance from the floor to trochanter major in a 90˚ squat position) combined with leg length (measured prone from the superior anterior iliac spine to the tip-toes in full plantar flexion). The mean of three trials will be used, and potential pain during testing will be recorded on the NPRS.

Countermovement jump test and video-recording (take-off position)

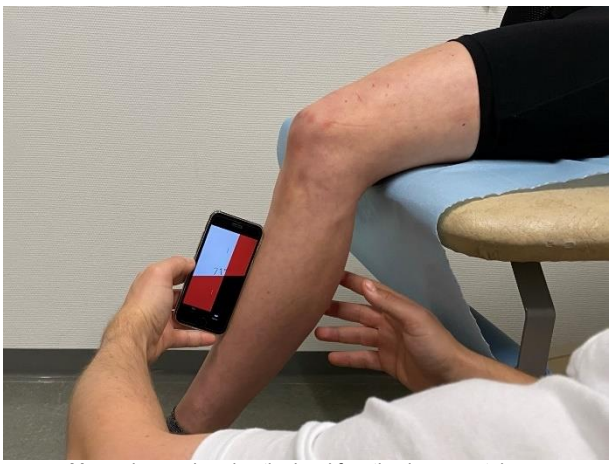
Countermovement jump test and video-recording (in the air)

Rectus femoris flexibility: The modified Thomas test

To assess the change in flexibility of the rectus femoris muscle between legs, participants will be asked to sit at the end of the examination bed with their thighs halfway off the bed. From here, participants will be instructed to lie back down and grab their index knee and hold it towards their chest, while the non-index leg is fully relaxed. In this position, the distal muscle belly of the quadriceps femoris is gently palpated and shaken to ensure there is no palpable tension. Then, by using a digital goniometer centered on the anterior tibial crest at the midpoint between the malleolus and the knee joint, the offset angle from horizontal is measured. The same assessment is the done for the index knee. The difference in degrees is then compared between the two knees, and for single knees over time.

The built-in 'Measure' app with a level function on the iPhone will be used (Apple Inc., San Jose, USA). Different apps based on the same level-function have been investigated with near-perfect validity with other digital methods (video-analysis, digital inclinometers) and good to excellent inter-and intra-tester reliability and low error of measurement and detectability.[196] Optimally, we would use an app that had specific evidence for its properties, but in a systematic review of studies of goniometer apps from May 2019, most of the included apps were at present (December 2020) not available for purchase/download. Therefore, the decision to use the underlying 'Measure' app was taken in light of the measure needed is also fairly simple and passive, and we found acceptable inter-tester reliability of this method in a recent study.[188]

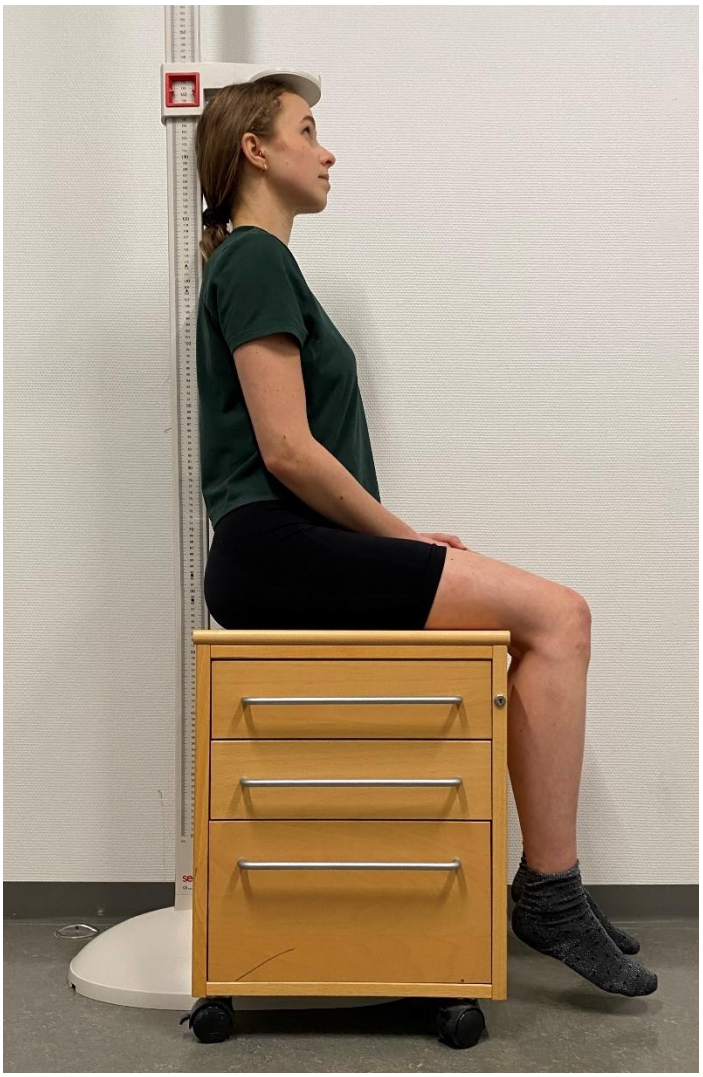
Modified Thomas test position



Measuring angle using the level function in a smartphone

Growth velocity offset: The anthropometrics-based Peak Height Velocity formula

To assess somatic maturation and growth velocity, participants offset from 'Peak Height Velocity' in years will be measured.[234] This method is non-invasive and uses only the following anthropometric variables: sex, chronological age, height, weight, and sitting height.[234] Height will be measured with a stadiometer with participants in their most upright positions with no shoes on and head placed in the Frankford plane. Similarly, sitting height will be measured from a flat box of 60 cm, also with a stadiometer.[271] Age is reported by the participants, and weight is measured with clothes (shirt, shorts, and no shoes) on a standard bathroom scale. The singular measures part of this composite measure has shown high reliability.[271]



Measuring sitting height with head in the Frankford Plane

Appendix 2: Ultrasound protocol

We have investigated the inter-tester reliability of novice operators performing the original outline of this protocol and found a moderate or substantial agreement for most measures (κ =0.41-0.79).[178] We have since improved or simplified the least reliable measures. The protocol is performed on each knee at baseline, starting with the right knee. All positive findings will be documented, and the sonographs and videos saved. The protocol consists of primarily longitudinal sonographs from the patella pole to the tibial tubercle. Although Osgood-Schlatter is a condition of the tibial tubercle or the adjacent tissue, our clinical experience is that a secondary proximal involvement of either the proximal patella tendon or the patella pole is not uncommon, and we have thus included measures within this region as well, to also assess these structures systematically at baseline. At follow-up, only the index-knee will be scanned.

Some of the singular measures collected are contained in the classification systems used. Thus, all singular measures collected will be (table 15):

- *Cartilage thickening* of patella pole and the tibial tubercle (Yes [1] or no [0]).[109,249,251,272]
- *Tendon thickening:* thickening of the proximal patella tendon or distal patella tendon: the subjective rating of the tendon appearing thickened (1) or not (0).[251,273]
- *Bursitis signs of the infrapatellar bursa:* If the infrapatellar fat pad appears either with fluid build up or with hyperemia, raters will denote signs of bursitis (1), and none if nothing abnormal is detected (0).[54,251]
- *Un-united ossicle*: If the secondary ossification center or an ossicle (deemed as cortical bone, rather than a more irregular calcified fragment) appears unattached superficial to site of fusion of the metaphysis and physis on the tibial tubercle (1) or not (0). [251,274]
- *Bone fragmentation* of the patella pole and the tibial tubercle: subjective rating of the fragmentation quality of the bone surface (excluding normal fragmented/fissuring maturation-related appearance of the metaphysis-physis junction) as either unclear (0), none (1), apparent (2).[251,272,274]

Classification systems (table 14):

- *Severity ad modum Flaviis*: We will use the Flaviis cumulative system to grade participants in severity-stages, as described in table 14, depending on swollen cartilage (1), swollen cartilage combined with a fragmented or hypoechoic outline of the ossification center, tendon thickening (3), and infrapatellar bursitis (4)).[32,251] If participants does not fall into any of these stages, they will be graded as 'normal' (0).

- *Maturation ad modum Sailly*: The maturation of the tibial tubercle will be graded based on the attachment of the patella tendon as either cartilage attachment without ossicle (1), cartilage attachment with ossicle (2), insertional cartilage (3), or mature (4).[109,249]
- *Hyperemia* of the patella, proximal patella tendon, distal patella tendon, infrapatellar bursa, tibial tubercle (excluding potential vessels located in the metaphysis-physis junction). Using color-doppler the level of hyperemia will be rated in the regions of interest according to the Öhberg score as used in previous studies in relevant tissues examining reliability in adults: None (1), 1-2 vessels or spots (2), 3 vessels, or spots (3), 4> vessels or spots (4).[180,256–258]

Table 14. Classification systems

Measure	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**
Sailly (Maturation)	Cartilage attachment without ossicle	Cartilage attachment with ossicle	Insertional cartilage	Mature
Öhberg (Doppler)	None	Mild / 1-2 vessels or spots	Moderate / 3 vessels or spots / <30% of ROI	Severe / 4≥ vessels or spots / >50% of ROI
	Flaviis severity classification			
	Swollen cartilage	Irregularity or fragmentation of the ossification center	Thickening of the tendon	Infrapatellar bursitis signs
1	X			
2	X	X		
3			X	
4				X

Table 15. Case Report form for ultrasound				
ROI	**Measure**	**Scale**	**Right knee**	**Left knee**
Proximal insertion (flexed knee)	Cartilage thickened	1/0		
	Severity of fragmentation	0-2		
	Tendon thickened	1/0		
Distal insertion (flexed knee)	Tendon thickened[F]	1/0		
	Infrapatellar bursa thickened[F]	1/0		
	Cartilage thickened[F]	1/0		
	Uninited ossicle[F]	1/0		
	Fragmentation[F]	0-2		
	Ducher/Sailly (Maturation)	1-4		
Proximal insertion (color doppler, extended knee)	Bone: Doppler Öhberg	1-4		
	Tendon: Doppler Öhberg	1-4		
Distal insertion (color doppler, extended knee)	Infrapatellar bursa: Doppler Öhberg[F]	1-4		
	Tendon: Doppler Öhberg	1-4		
	Bone: Doppler Öhberg	1-4		

Ultrasound operators

The ultrasound operator will be a post-graduate physiotherapist that is also doing a PhD-thesis related to musculoskeletal imaging. The physiotherapist is a certified sonographer from the Danish Association of Sports Physical Therapy and has 3 months of experience performing the protocol in adolescents with anterior knee pain, primarily in Osgood-Schlatter patients. He has been trained and supervised in performing the protocol and interpreting the sonographs by a professor (JLO) in rheumatology specialized within the field of using ultrasound as a diagnostic modality of overuse injuries in muscle-tendon tissue. If needed, a replacement will be trained.

Ultrasound equipment, settings, and position

Participants position: Participants will be seated in a resting position, halfway lying on their back with the headrest raised at approximately 70°, knees resting on a plint at about 30° knee flexion, and resting their feet on the heels. During color doppler assessment, participants will have their knees fully extended, and for evaluation of the infrapatellar bursa, the sonographer can choose to flex the knee to approximately 90° flexion at their discretion to acquire the best view and sonograph of a suspected positive finding. Participants will be able to co-view the sonographs during scanning.

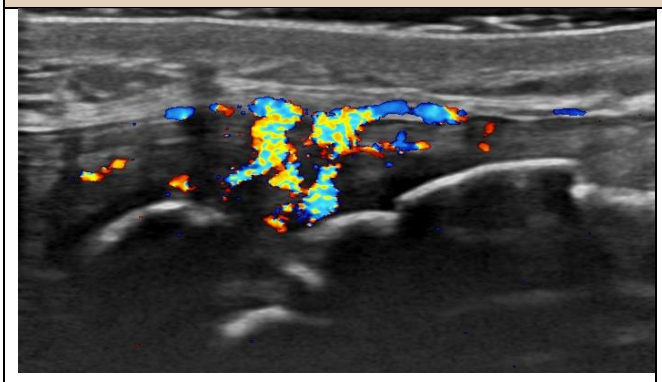
Rater position: During the scanning of both knees, the rater is seated next to the participant, operating the probe with their right dominant hand.

Probe placement: The probe is placed on the midportion of the patella tendon in the longitudinal/sagittal plane centered along with the continuity of the patella tendon. The probe is moved distally/proximally until the apex of the patella is in the proximal part of the sonograph. From here, the probe is moved distally until the tibial tubercle is in the middle/distal part of the sonograph, and measures are collected and rated along the way. All findings are confirmed by performing sweeps in medial-lateral plane and transerval sweeps, and the rater saves the best representation of the finding on the longitudinal plane, potentially supplemented by transveral sonographs. During doppler evaluation, minimal pressure is applied to the probe, and a thick visible layer of gel is applied to not constrict potential vessels.

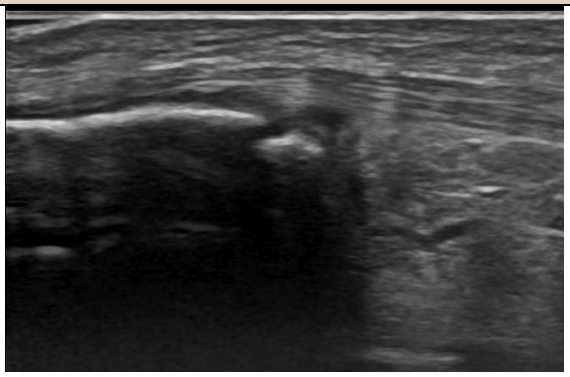
Equipment and settings: All ultrasound imaging will be captured using an Arrieta V70 (Hitachi, Japan) scanner and an L64 linear probe at 18–5 MHz (Hitachi, Japan). In collaboration with a consultant from the equipment supplier, an optimized preset was made for the study allowing only changes in depth, gain and focus. The settings for the preset are as follows:

- Depth: 2.0 cm (usually adjusted to 3.0 cm when assessing doppler)
- Gain: 80
- Focus: 1.1 cm
- Doppler speed: 2.03 cm/s
- Doppler frequency: 10.42 MHz
- CG: 140
- Placement of doppler ROI window: Anteriorly and maximized
- Frequency: High (approximately 18 MHz)

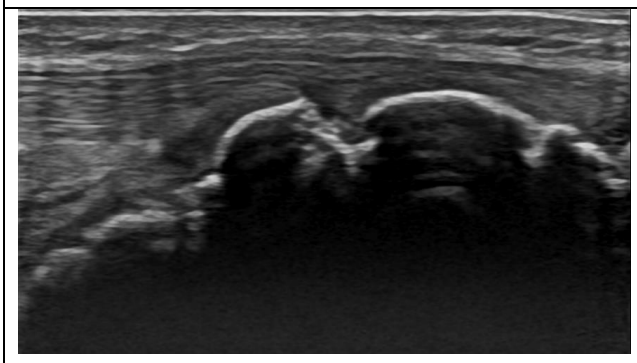
Figure 6. Examples of ultrasound assessments



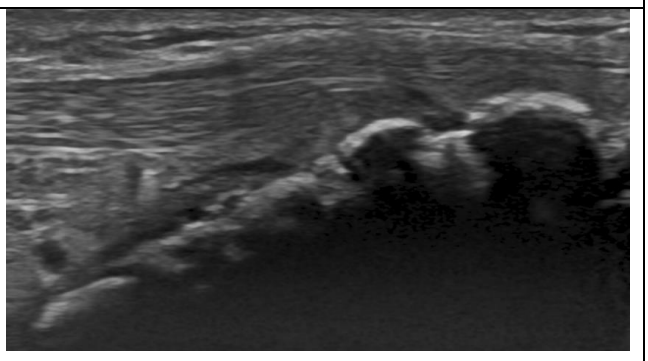
Color doppler: 3, swollen cartilage: 0, maturation: 2, unnited ossicle (1)



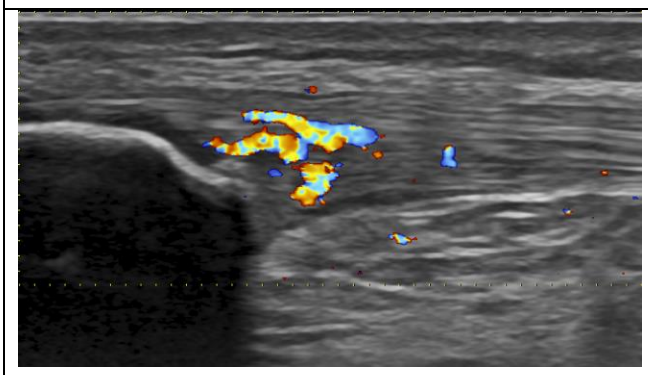
Fragementation: 2 (apex patella)



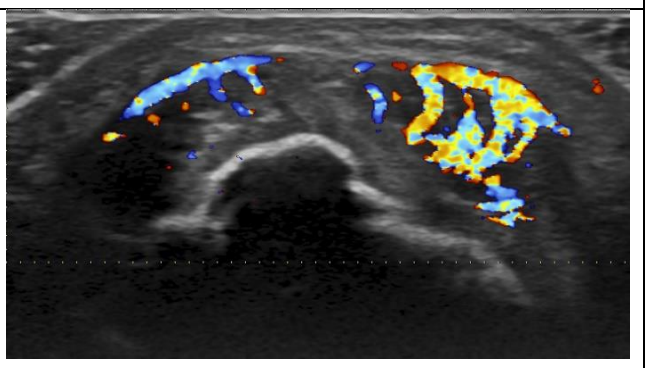
Fragmentation: 2. Maturation: 2



Fragmentation: 2. Maturation: 3

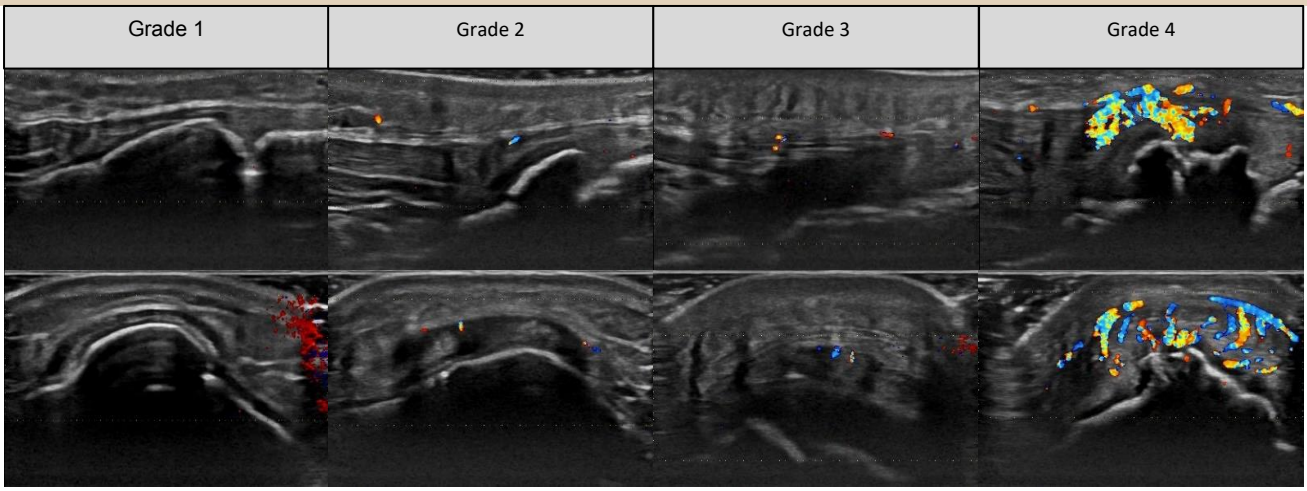


Tendon thickening (1), doppler (4) (apex patella)



Doppler (4), tendon thickening (1), tendon hypoechoic (1) at the tibial tubercle (transverse)

Figure 7. Examples of color doppler assessments at the tibial tubercle in the longitudinal and transversal plane



Appendix 3: Exercise descriptors and populated CERT/TIDierR checklists

Exercise in the experimental intervention described by parameters proposed by Toigo & Boutellier[75] (table 16) followed by a table of collated domains from CERT[77] (Checklist for Exercise Reporting Template) and TIDieR[76] (Template for Intervention Description and Replication) (table xx).

Table 16. Exercise descriptors for the experimental intervention

Exercise descriptors	**Knee-press** Continuous dose	**Hip abduction bridge** Continuous dose	**Wall-squat** Start dose	Target dose	**Lunges** Start dose	Target dose
Load magnitude	Unknown	≥12RM	1RM	5RM	1RM	12RM
Number of repetitions	10	12	1	5	1	12
Number of sets	10	2 (per leg)	1	1	1 (per leg)	3 (per leg)
Rest between sets	30 s	30 s	30 s	30 s	30 s	30 s
Sessions per week	7	3.5	3.5	3.5	3.5	3.5
Duration of the experimental period	1 month (phase 1)	3 months (phase 1 & 2)	0-2 months (phase 2)	0-2 months (phase 2)	0-2 months (phase 2)	0-2 months (phase 2)
Duration of contraction modes per repetition						
- Eccentric	None	2 s	2 s	2 s	2 s	2 s
- Isometric	30 s	4 s	2 s	30 s	2 s	2 s
- Concentric	None	2 s	2 s	2 s	2 s	2 s
Rest between repetitions	30 s	0 s	30 s	30 s	0 s	0 s
Time-under-tension (TUT) per repetition	30 s	8 s	8 s	34 s	6 s	6 s
Volitional muscular failure	No	Yes, or 12 reps	Yes, or stopping due to pain >2 NPRS	Yes, or stopping due to pain >2 NPRS	Yes, or stopping due to pain >2 NPRS	Yes, or stopping due to pain >2 NPRS
Range of motion	Fixed at 60° knee flexion	Appx 0-30° hip abduction	From 0-90° knee flexion, depending on pain >2NPRS	90° knee flexion	0-100° knee flexion	0-100° knee flexion
Recovery time between exercise sessions	1 day	2 days	2 days	2 days	2 days	2 days
Anatomical definition of the exercise (exercise form)	Sitting in a chair without shoes, and toes appx 15 cm from a wall, the participant puts their heel on the floor and toes on the wall and presses in the direction of the lower limb, and alternates between legs while resting one leg.	Lying on the side with legs together and knees flexing at appx 70-50°, the participant maintains their body in a straight line from head to knees while lifting their upper body on their elbow by having the lower arm in appx 90° shoulder abduction. From here, they simultaneously abduct both hips to appx. 30° hip abduction, thus lifting their lower body upwards.	While maintaining contact between the back and the buttocks onto the wall, the participant places their heels at 1½ foot length from the wall in shoulder-width, pointing straight ahead. The participant then lowers their upper body by sliding down the wall to appx 90° knee flexion, keeping the tension for x-seconds, and returns to the starting position.		Participants takes a long stride and stands with straight legs and appx 45° hip flexion for the front leg and 45° hip extension for the rear leg. Feet are pointing straight ahead and no more than shoulder-width apart. The participant maintains this position through the set. From here, the upper body is maintained in an upwards position is lowered directly downwards between the legs to appx 100° knee flexion of the front leg and without touching the ground.	

Red numbers and golden lines indicate the order and type of progression steps. NPRS = 0-10 numerical pain rating scale; RM = repetition maximum

Table 17. Collated populated TIDieR[76] and CERT[77] templates for the experimental treatment

Item no. TIDieR	Item no. CERT	Collated adapted item description
1	-	Provide the name or a phrase that describes the intervention. Self-management approach
2	-	Describe any rationale, theory, or goal of the elements essential to the intervention Page 20-27
3	1	Materials and equipment: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL). A leaflet detailing exercise form, dose and progression rules for both treatment-arms are supplied at baseline Folders and leaflets for the usual care intervention: doi.org/10.6084/m9.figshare.17099984 Folders and leaflets for the experimental intervention: doi.org/10.6084/m9.figshare.17099954
5	2	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given / *teaching/supervising expertise* See "study training" section page 43
6	3, 4	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group. Detail of supervised/unsupervised, and mode of delivery The intervention-instructions are delivered face-to-face at an individual level, and are done at home unsupervised by study personnel, however, parents are encouraged to supervise exercises when possible. By requests of participants, instructions by phone will be available. At each visit, participants are asked to perform their prior exercises, in order to rate if sufficient exercise-form was adhered to.
11	5	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them. Page 30-32
4	6	Detailed description of motivation strategies / Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities Page 30
-	7a	Detailed description of the decision rule(s) for determining exercise progression Page 23-29
-	7b	Detailed description of how the exercise program was progressed Page 23-29
-	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc) Page 27-28, 23-24
7	9	Where / Detailed description of any home program component (e.g. other exercises, stretching etc) All exercises are to be performed at home.
-	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc) Pages 25, 29
	11	Describe the type and number of adverse evens that occurred during exercise See a priori plans for collection and reporting of harms on page 57-58
7	12	Describe the setting in which the exercises are performed. Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features. All exercises are to be performed at home.
8, 4	13	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration. Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities + the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose See table 4,5,6. Exercise instructions are performed at the Department of Physiotherapy, and exercises are performed at home. Instructions are received a months 0, 1, 2, and 3.
9	14a, 14b	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual + Detailed description of how exercises are tailored to the individual

		If the intervention was planned to be personalized, titrated or adapted, then describe what, why, when, and how
		The exercise intervention is not personalized but are adapted to fit the individuals capacity for load, muscular endurance and pain in terms of starting point and progression. If, for some reason, a participant is not able to perform a specific exercise, alternatives will be provided by the treating physiotherapist.
-	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc.)
		All participants start with 1 month of de-loading, with only the knee-press exercise, and the hip abduction bridge with a set dose (see table 5). Participants are instructed to do 12 reps of the hip abduction bridge, or as many as they can, until they reach the 12-repetition level, which is then to be maintained throughout the intervention. After month 1, knee-press is substituted with a new knee exercise, the wall squat. During instructions, participants perform 1 repetition at (up to) 90º knee flexion, with a duration of up to 30 s hold, if they can, without NPRS >2. This determines their starting knee flexion angle and duration of the wall-squat exercise. After reaching the target dose for wall squats, they proceed to the start dose of lunges, which as many repetitions possible in one set with NPRS <3, or up 12 repetitions on each leg. See table 16 for further detailed descriptions and order of exercise progression parameters.
11	16	Describe how adherence or fidelity to the exercise intervention is assessed/measured
		Page 30-31

NPRS = 0-10 numerical pain rating scale; TIDieR = Template for Intervention Description and Replication; CERT = Checklist for Exercise Reporting Template. Omitted items due to being post hoc: TIDieR: 10, 12; CERT: 16b

Appendix 4: Weekly monitoring via text-messages (Danish)

Figure 8. Flow of text-based monitoring in the experimental group from week 4 to 22

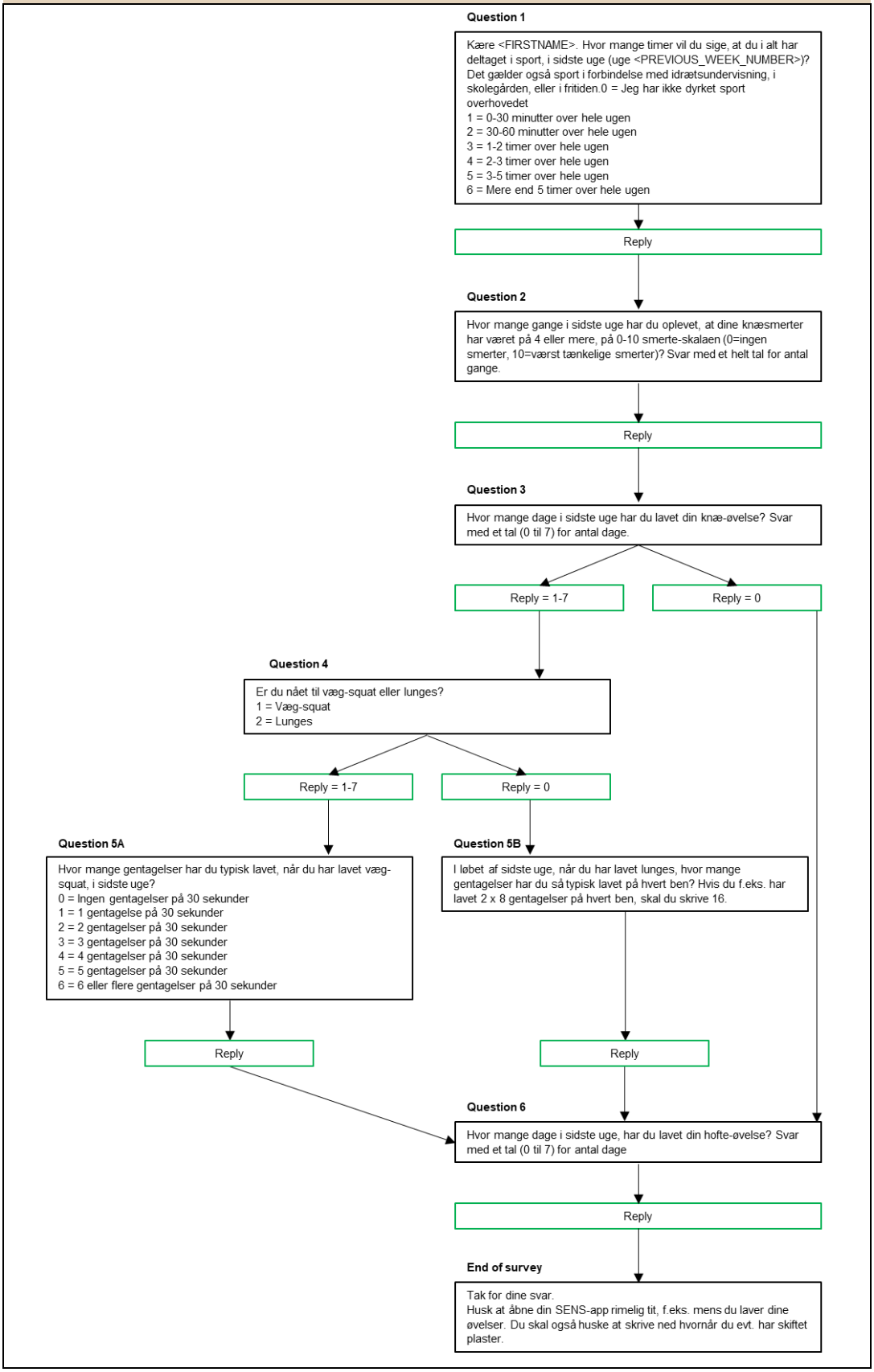


Figure 9. Flow of text-based monitoring in the experimental group from week 0 to 4

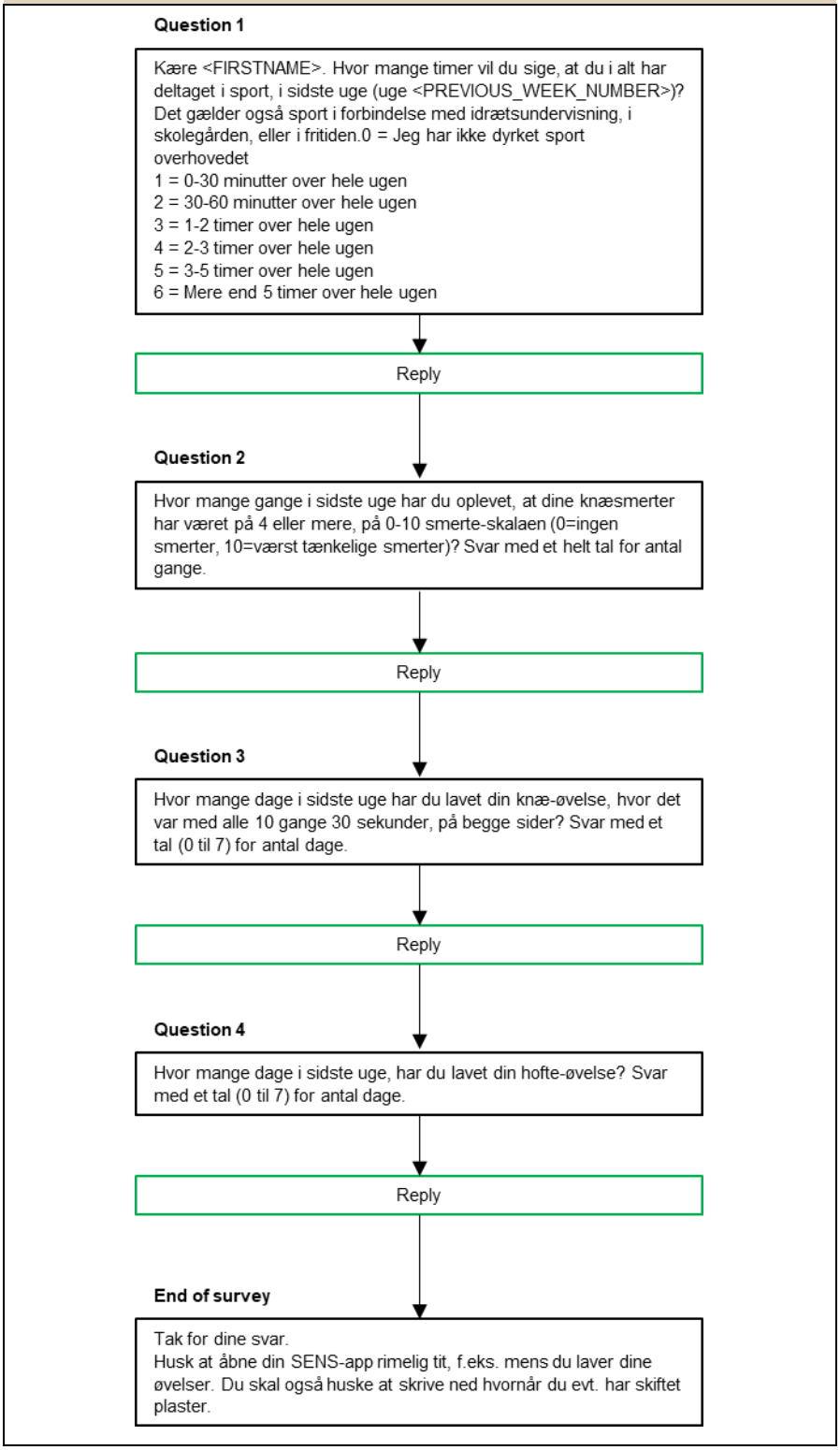
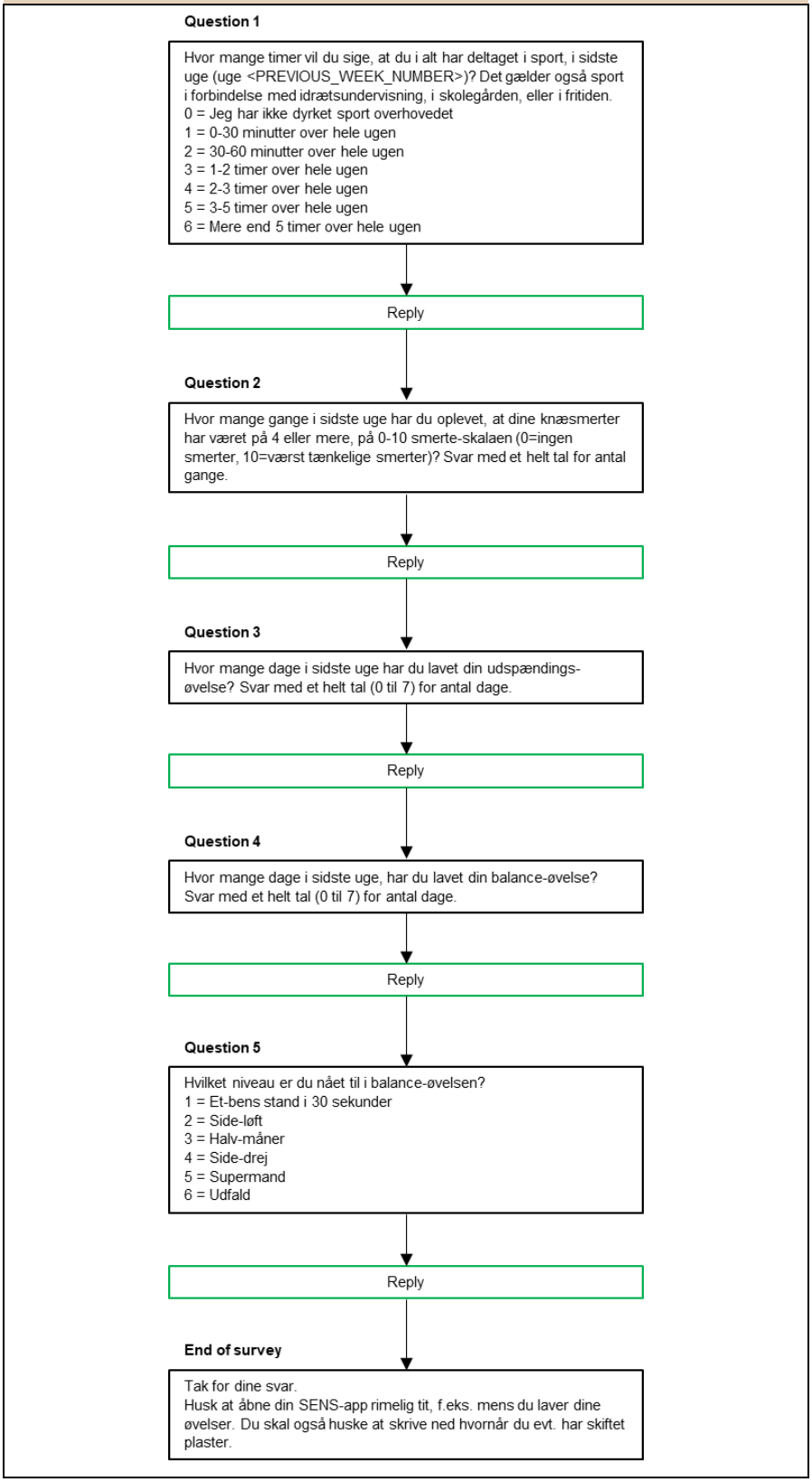


Figure 10. Flow of text-based monitoring in the usual care group from week 0 to 22



Appendix 5: Pragmatic-Explanatory indicators

Figure 11. PRagmatic-Explanatory Continuum Indicator Summary – PRECIS 'Wheel'

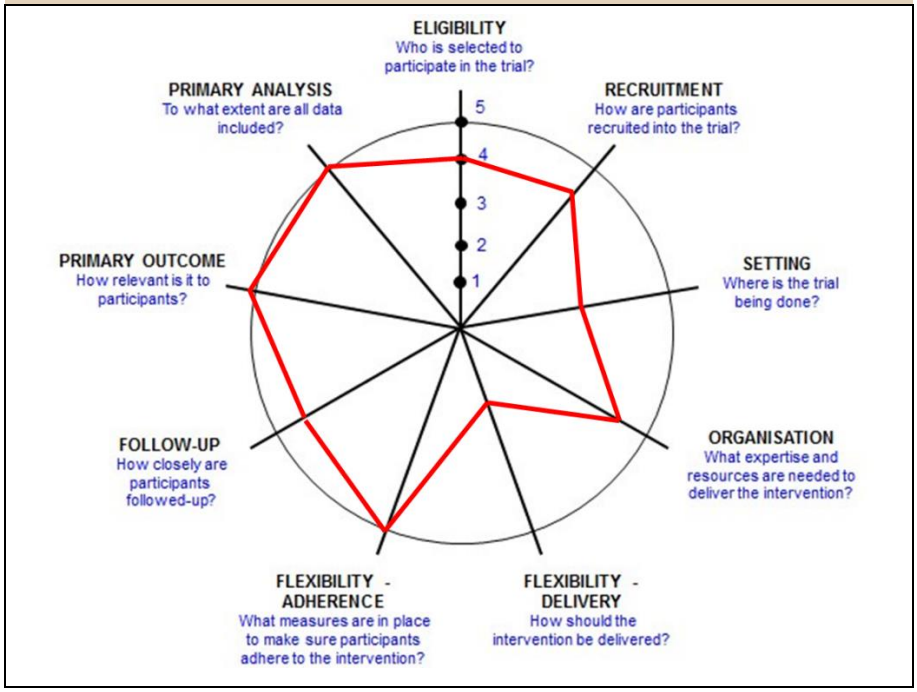


Table 18. PRECIS-2 scores for trial domains

	Domain	Score	Rationale
1	Eligibility Criteria	4	Participants included will resemble those that present in the clinic to a large degree, and concomitant complaints are also allowed to some degree.
2	Recruitment Path	4	As there are limited treatment options, participants are usually not contained in the health care system. For those that do seek treatment, we will supply nearby GP clinics and private physio clinics with contact information for potential participants. Similarly, nearby sports clubs will be provided the same material. Moreover, all patients who are referred for specialized care in the uptake area of our orthopedic department will be screened for eligibility. Finally, we will supplement the above recruitment channels with social media adverts for those that are not currently in the health care system, targeting 40-55-year-old (potential parents) in the uptake area. As such, we are attempting to potentially offer recruitment to the entirety of the local potential population.
3	Setting	3	The intervention and outcome assessments will take place at the physiotherapy department in the hospital.
4	Organization	4	The intervention is comprised by field experts, but the personnel trained to deliver the intervention will not have extensive experience with either the intervention or the target-population. Post-trial dissemination to other clinicians will consists of leaflets, intervention descriptions, and a clinician manuscript.
5	Flexibility of experimental intervention – Delivery	2	Only one mode of delivery will be used in the trial (in-person visits, combined with information leaflets), but the actual contents of the visits

			will vary based on the progress and context of the individual participant. The treatments are standardized.
6	Flexibility of experimental intervention – Adherence	5	All patients will be included in the final analyses, regardless of adherence levels.
7	Follow up	4	The number of clinical follow-up visits (4 visits) will likely be the same as in a physiotherapy clinic, however trial-related follow-up will exceed what could be expected in general settings.
8	Outcome	5	The primary outcome is self-reported validated measured of knee-function, supplemented by level and satisfaction with sport and physical activity participation levels.
9	Analysis	5	Intention-to-treat analysis is planned for all outcomes as the standard approach

Appendix 6: Directed acyclig graph