

# Evaluation of a 12-week app-guided exercise intervention in patients with knee osteoarthritis (re.flex): a study protocol for a randomized controlled trial.

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## Study protocol

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# Abstract

## Background

The current health care demonstrates an insufficient provision and utilization of physical exercises that are recommended as first-line treatment in clinical guidelines for patients with knee osteoarthritis. Mobile health (m-health) technologies offer new opportunities to guide and monitor home-based exercise programs by using mobile devices and inertial sensors in combination with a digital application (app). This study evaluates patients benefit using the specific digital health application re.flex for patients with knee osteoarthritis (OA).

## Methods

This monocentric, two-arm, randomized controlled parallel-group trial evaluates the effectiveness of the app- and sensor-guided exercise program re.flex for patients with moderate to severe knee OA. We aim to recruit 200 participants via newspaper, newsletter and information events. Participants will be randomly allocated to the intervention group (IG) and the control group (C) in a 1:1 ratio. Participants of C do not receive any study intervention or instruction for any change to their previous health care utilization. IG comprises a 12-week home training program with three sessions per week in addition to regular care. Exercises are guided and monitored by use of the training app (re.flex) and two accelerometers that are attached proximally and distally to the affected knee joint. Pre- and post-measurements will take place at baseline (t0) and after 12 weeks (t1). Primary outcomes will be osteoarthritis-specific pain and physical function measured with the Knee Osteoarthritis Outcome Score (KOOS) subscales Pain and Function in daily living (ADL). Secondary, further self-reported health outcomes, a performance measurement, app logfiles and safety will be assessed.

## Discussion

M-health interventions can be used independently from time and location and allow most patients to get access to this kind of exercise guidance. As such, re.flex can bridge part of the gap between recommendations for strengthening exercises in patients with knee OA and the insufficient actual care situation. This randomized controlled trial is designed to provide conclusions on the effectiveness of the health application re.flex for the population under study and will give further insight into adherence rates and the safety of its use.

## Trial registration

The trial was registered on 20/01/2023 at [www.drks.de](http://www.drks.de) (ID: DRKS00030932).

## Background

Osteoarthritis (OA) is the most common degenerative joint disorder in Germany and worldwide. According to the GEDA 2014/2015-EH Interview Survey of the Robert Koch Institute, the 12-months prevalence for OA in adults in Germany is assessed at 17.9% (1). It is estimated that more than half of those affected suffer from knee OA (2). Higher age, female gender and biomechanical stress induced by overuse or malalignment as well as previous injuries or overweight are potential risk factors for OA (1).

Disease progression is frequently associated with increasing pain and growing limitations in physical functioning and health related quality of life. Due to its progressive degenerative character, interventions primarily aim for a reduction of disease symptoms and improvements in physical functioning. They further intend to foster disease self-management and patient education. Medical guidelines worldwide recommend physical exercises and patient education as non-pharmacological core treatments for patients with knee OA (3, 4). However, there is an insufficient provision and utilization of these first-line treatment in current health care: A recent meta-analysis on 15 studies evaluating the quality of OA care in the community concluded that less than 40% of eligible OA patients received recommendations to exercise (5). Furthermore, only 35% of the German people with OA state doing strengthening exercise at least twice a week (6). Data of a German health insurance company show that more than 60% of the insurance holders aged 60 years and above and diagnosed with OA received medication in comparison to only 41% receiving a prescription for physiotherapy (7). The latter does not necessarily include exercise instructions (8).

From a mechanical perspective, strengthening exercises aim for stabilizing the affected joint and decreasing abnormal joint loads by improving muscle strength and neuro-muscular control (9, 10). Up to now, many studies on exercise therapy in knee OA have shown to increase strength in the short- and mid-term (11, 12). However, evidence on the long-term effectiveness of exercise interventions in OA is still lacking. In this regard, adherence to exercise seems to be crucial as exercise interventions belong to the so-called life-style interventions. Initial instructions are recommended after which exercises should then be continued in a self-dependently manner (13). An ongoing need for the development of exercise programs with a high stimulating character for longtime adherence can therefore be postulated (12). In this regard, home-based exercise programs seem to be of particular relevance as they can be conducted independently (9). Digital health applications have a great potential to support patients in performing exercises correctly and safely. Outstanding advantages of digital health applications are related to their extensive availability, allowing users to be instructed in exercises independently of time and location. They further appeal to a wide range of possible users (14–16) and have the possibility of closer monitoring, such as an objective method of measuring adherence to exercise by use of additional motion sensors (17).

The digital transformation in health care is advancing rapidly. One example for this ongoing process is the Digital-Care-Law in Germany which came into force in 2019 (18). This law aims for a better care using digitalization and innovation. Among others, it allows patients to get access to specific health apps that are listed in a register for disease-specific digital health applications (DiGA). Costs for DiGAs are reimbursed from the statutory health insurance companies. However, evidence of a positive care effect such as patient benefit is a prerequisite for final inclusion of a DiGA into the reimbursable DiGA-register (19).

This randomized controlled trial investigates patient benefit of the preliminary listed DiGA re.flex that is used to instruct and guide exercises for patients with knee OA.

## Objectives

The main objective of this study is to investigate the effectiveness of the 12-week sensor-assisted and app-supported exercise intervention in addition to regular care (IG) in comparison to a control group with regular care only (C).

The two primary endpoints are the comparison of baseline-adjusted scores between IG and C regarding osteoarthritis-specific pain (subscale Pain of the Knee Osteoarthritis Outcome Score, KOOS) and physical function (subscale Function in daily living (ADL) of the Knee Osteoarthritis Outcome Score, KOOS) directly after the 12-week intervention phase. Other study endpoints include further self-reported health outcomes, a performance measurement, app logfiles and safety aspects (Table 2).

## Methods

### Study Design

The study is designed as a monocentric pragmatic two-armed randomized controlled superiority trial and will be conducted in an academic hospital with an outpatient clinic for Sports Medicine located in Tuebingen, Germany. Subjects are randomly allocated to IG and C in a 1:1 ratio with n = 100 in each group.

Pre- and post-measurements will take place at baseline (t0) and after 12 weeks (t1). The study was prospectively registered in the German Clinical Trial Register (DRKS00030932) on 20/01/2023 and is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (20) (Supplement 1).

### Eligibility criteria

Eligible are patients of any gender at full age suffering from knee OA (International Classification of Disease, ICD-Codes M17.0-17.5 and 17.9). Knee OA must be the primary location of symptoms. Knee osteoarthritis is first diagnosed via self-reported previous OA diagnosis by a physician according to the wording of the GEDA questionnaire (1). Patients are further asked for OA severity via the Subscale Pain of the KOOS (21, 22). Only patients with at least moderate self-reported symptoms at the time of screening are eligible for the study (KOOS pain  $\leq$  60 points where 100 points indicate no complaints at all). OA diagnosis is verified in the context of the physical examination at t0 by a physician (orthopedist). Further in- and exclusion criteria are outlined in Table 1.

Table 1  
In- and Exclusion Criteria

Inclusion criteria	Exclusion criteria
- $\geq 18$ years	
- Mobile electronic device with an iOS or Android operating system	- No mobile electronic device or device with an operating system other than iOS or Android
<ul style="list-style-type: none"> <li>- Willingness to participate in the study</li> <li>- Willingness to use the app to exercise</li> <li>- Informed consent of the participant</li> </ul>	
<ul style="list-style-type: none"> <li>- Self-reported previous knee OA diagnosis by a physician according to the wording of the GEDA questionnaire (1)</li> <li>- Verification of knee OA diagnosis in the context of the physical examination at t0 by a physician (orthopedist)</li> <li>- Self-reported KOOS Subscale Pain Score <math>\leq 60</math> during the screening process</li> <li>- The knee joint is the index joint<sup>1</sup></li> </ul>	<ul style="list-style-type: none"> <li>- OA primarily located in the hip joint or others than the knee (the knee joint is not the index joint<sup>1</sup>)</li> <li>- Diffuse knee pain or retro-patellar pain only</li> <li>- History of knee joint replacement or osteotomy on the index joint</li> </ul>
	<ul style="list-style-type: none"> <li>- Any medical or physical impairment precluding safe participation in exercise, measured by use of the Physical Activity Readiness Questionnaire (PAR-Q) (23, 24) and verified by the physician at t0</li> <li>- Any complaints of the lower extremity or lower back other than knee OA that are currently treated by a physician and/or physiotherapist</li> <li>- Any previous surgeries, injuries or complaints that are a contraindication to exercise without supervision</li> <li>- Any scheduled elective orthopedic surgery in the lower limb or lower back in the next 4 months</li> <li>- Inability to walk unaided</li> <li>- (Digital) exercise interventions that are similar to the intervention under study, i.e. other physiotherapy applications for OA or regular structured strengthening exercise for the lower extremities more than once a week during the past 6 months</li> <li>- Insufficient German language skills to understand the study documents and the instructions of the app</li> </ul>

Inclusion criteria	Exclusion criteria
<sup>1</sup> The index joint is the joint that is most affected by self-reported symptoms of OA in case of multi-site OA.	

## Intervention

### Control group

Participants of the control group do not receive any study intervention or instruction for any change to their previous health care utilization. They are allowed to make use of usual health care provided by the treating physician, if applicable.

Usual care is defined as any kind of prescribed pharmacological or physical interventions a patient with knee OA usually receives when consulting a medical doctor because of knee OA. These may include physical therapies such as regular physiotherapy, manual therapy, electrotherapy as well as orthotic devices, and medical prescriptions for pharmacological agents such as nonsteroidal anti-inflammatory drugs (NSAID) (25). These reflect the relevant treatment options according to the current national guidelines in Germany (3).

### **App-guided exercise intervention for knee osteoarthritis (IG)**

The exercise intervention comprises a 12-week app-guided home training program that was specifically designed for patients with knee osteoarthritis. Exercises are guided by use of the training app and two accelerometers (re.flex, © 2019, KINETO TECH REHAB SRL) that are attached proximally and distally to the affected knee joint (Fig. 1).

The use of the app and sensors is introduced in the context of the baseline examination and patients further receive a manual for using the soft- and hardware.

The app acts as a virtual training partner, providing exercise descriptions and videos (Fig. 1), setting the number of repetitions and sets, pre-defining joint angles and the related range of motion for the exercises as well as defining the movement velocity of the exercises.

Each of the 12 weeks foresees 3 exercise sessions with a respective duration of 25–30 minutes each. Different types and variations of exercise (i.e., the use of long or short lever arms or different starting positions: supine, seated, stance) as well as elastic exercise bands are used to allow progression of training loads. All one-sided exercises are conducted alternately with the leg equipped with sensors as well as with the other one to avoid muscular imbalances.

The primary focus of the intervention is to strengthen knee extensors, knee flexors as well as hip abductors. Further exercises aim for joint mobilization, muscle stretching and balance training.

The first two weeks focuses on familiarization with different kinds of exercises and exercise loads. In this regard, patients should be enabled to adapt exercise intensity self-determinately according to perceived

strain and pain. Therefore, patients can choose between two different intensity grades. They further must comment about their strain and pain levels after each set of exercise (see outcome measures). The following four weeks are designed to increase strength endurance, enhance the range of motion of the lower extremities and improve balance ability. In this phase, strengthening exercises should be performed with 2 x 25 repetitions (Fig. 2).

The last six weeks of the intervention mainly focuses on muscle building with higher intensities and lower repetition numbers. Strengthening should be performed with 3 x 15 repetitions in this phase. Moreover, balance and range of motion should be further improved (Fig. 2). From week 5 onwards the training program can partly be modified by the users by choosing their preferred exercises for some of the strengthening, mobility, stretch or balance tasks out of the exercise pool that they became familiar within previous sessions. Alternative exercises relate to the same musculature and task, yet they may differ regarding the exercise pose or an open versus closed kinetic chain mode.

The app further reminds the user to conduct upcoming training sessions via push notifications. Throughout the intervention phase, users can contact the provider via the app messenger. The provider is responsible for clarification of technical issues. Participants are instructed to interrupt the training program in case of any suspicious symptoms, fatigue or excessive pain during the exercise intervention with the re.flex system. They are asked to inform the study personal about any adverse event to allow judgement on how to proceed. This decision is up to the study physician as well as the study personal (sports scientist/physiotherapist) and will refer to the options of modification of the training regime, or its temporary or complete discontinuation.

In correspondence to the control group, participants of the intervention group are allowed to make use of usual health care provided by the treating physician, if applicable.

## Outcome measures

The following Table 2 gives an overview of all outcome measures, their study instruments with references and their time-points of assessment. Details on each measure are provided in the subsequent sections. Patient-reported outcome measures (PROMs) are assessed using an online-questionnaire (Questback GmbH, Köln, Germany) during the examinations at the study site (t0, t1) and at home (only applicable for concomitant care at 4 and 8 weeks). The physical performance measure will be assessed on-site at t0 and t1. Socio-demographic data, clinical status (e. g. relevant previous injuries or surgeries, comorbid conditions) (26), outcome expectations (27), previous experiences with strengthening exercises and physical activity as well as technical affinity (28) and fear of movement (29) are assessed additionally to the primary and secondary outcomes. The participants will receive an e-mail prior to the data collection, reminding them of the upcoming data collection.

The selection of outcome measures aligns with the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) core domain set for trials of people with hip and knee osteoarthritis (30). The selection also aligns to the Consensus of the International Consortium for Health Outcomes Measurement Hip and Knee Osteoarthritis Working Group (ICHOM) on Standard Outcome

Measures for hip and knee OA released in 2016 (26). The mandatory set of outcome measures is supplemented by further relevant outcomes measures in the context of exercise therapy and m-Health.

Table 2

Outcome measures and study instruments.

Outcome Description	Instrument [ref]	Sample	Collection points
<b>Patient characteristics</b>			
Socio-demographic data, anthropometric data, other baseline data	Variables and definitions according to the International Standard Set of Outcome measures for patients with hip or knee OA (26)	IG, C	t0
Technical affinity towards electronic devices	Self-reported questionnaire on subjective technical affinity (Technical Affinity - Electronic Devices (TA-EG)) (28)	IG, C	t0
Outcome expectations	Expectation for Treatment Scale (ETS, German version) (27)	IG, C	t0
Fear of Movement	Tampa Scale for Kinesiophobia (German Version, TSK-GV) (29)	IG, C	t0
<b>Health outcome measures</b>			
<b><i>Patient reported outcome measures (PROMS)</i></b>			
Subscale knee pain (Co-1° outcome)	Knee Osteoarthritis Outcome Score KOOS (21, 22): A disease related questionnaire asking for patient's opinion about their complaints.	IG, C	t0, t1
Subscale function in daily living (ADL) (Co-1° outcome)	Knee Osteoarthritis Outcome Score KOOS (21, 22): A disease related questionnaire asking for patient's opinion about their complaints.	IG, C	t0, t1
Subscales symptoms, function in sport and recreation (Sport/Rec), knee-related quality of life (QoL)	Knee Osteoarthritis Outcome Score KOOS (21, 22): A disease related questionnaire asking for patient's opinion about their complaints.	IG, C	t0, t1
Patient's global assessment	Patient Global Assessment of osteoarthritis – Knee (31)	IG, C	t0, t1
Health related quality of life	VR-12 Questionnaire (32)	IG, C	t0, t1
Subjective assessment of overall change, change in pain and function	Transition question according to Angst, Benz (33)	IG, C	t1



Outcome Description	Instrument [ref]	Sample	Collection points
<b>Objective outcome measures</b>			
Functional strength measure for the lower extremities	30-sec Chair Stand Test (34)	IG, C	t0, t1
<b>Concomitant care</b>			
Treatment progression	Variables and definitions according to the International Standard Set of Outcome measures for patients with hip or knee OA (26).	IG, C	t0, t1
Care utilization		IG, C	t0, t1 + after 4 and 8 weeks
<b>Perceived human-digital interaction, patient satisfaction</b>			
Usability of the app	- mHealth App Usability Questionnaire (MAUQ) (35) - 1 item from Harder, Holroyd (36) (Item B1)	IG	t1
Patient satisfaction with the app	Patient satisfaction questionnaire (ZUF-8) (37)	IG	t1
Patient satisfaction with the results of the treatment	Satisfaction with the results (26)	IG, C	t1
<b>Logfiles</b>			
Adherence to exercise	Logfiles relate to adherence to overall training sessions and each exercise.	IG	continuously during intervention phase
Rating of perceived exertion (RPE) during exercising	Entry into the app after each exercise and after the training using an adapted RPE-Scale (NRS 0-10).	IG	continuously during intervention phase
Rating of perceived pain before, during and after exercising	Entry into the app before/after the training and after each exercise using a faces pain scale referring to the numbers 0, 2, 4, 6, 8, 10).	IG	continuously during intervention phase
<b>Safety aspects</b>			
Exercise related pain	Frequency, duration, intensity	IG, C	t1
Adverse event report	Direct contact to study personal	IG, C	if reported
t0 Baseline, t1 directly after the 12- week intervention phase, IG Intervention group, C Control group			

# Primary outcomes

The KOOS is a widely accepted and comprehensive outcome measure for several domains including pain and physical function. It was developed as a nonproprietary comprehensive extension to the Western Ontario and McMaster Universities Arthritis Index (WOMAC) that has proven valid, reliable, and responsive to OA outcomes (26). The Knee injury and Osteoarthritis Outcome Score (KOOS) (21, 22) was developed to assess the patient's opinion about their knee and associated problems. The KOOS evaluates both short-term and long-term consequences of knee injury and also consequences of primary OA. It holds 42 items in five separately scored subscales: KOOS Pain, KOOS Symptoms, Function in daily living (KOOS ADL), Function in Sport and Recreation (KOOS Sport/Rec), and knee-related Quality of Life (KOOS QoL). All scores will be included, however the KOOS Pain score and the KOOS ADL score are the primary outcomes of the study.

## Secondary and other outcomes

### Patient reported outcome measures (PROMs)

#### (1) Further OA-specific complaints

Further subscales from the KOOS such as the subscales Symptoms, Function in Sport and Recreation (Sport/Rec) and knee-related Quality of Life (QoL) will be analyzed for considering a wide range of OA-specific complaints.

#### (2) Patient's global assessment

Patient's global assessment of knee osteoarthritis will be used as a one-item scale "Considering all the ways your osteoarthritis in your knee affects you, how are you doing today?" using a 5-point Likert scale (1-very good: asymptomatic and no limitation of normal activities; 2-good: mild symptoms and no limitation of normal activities; 3-fair: moderate symptoms and limitation of some normal activities; 4-poor: severe symptoms and inability to carry out most normal activities; 5-very poor: very severe symptoms which are intolerable and inability to carry out all normal activities). The description for each answer category refers to Schnitzer and Colleagues and will be translated into German language (31).

#### (3) Health related quality of life

The Veterans RAND 12-Item Health Survey (VR-12) (32) is a generic questionnaire to assess the patient's opinion about their health-related quality of life. The VR-12 allows the calculation of a mental as well as a physical component scale and also includes a 1-item scale for general health.

#### (4) Subjective assessment of overall change, change in pain and function

The following transition questions are used to assess the subjective change in health status at t1: "Please imagine how your health status was 3 months ago. How do you feel about your osteoarthritis in the index knee joint today compared to 3 months ago? Please mark the answers that are applicable: (1) in general; (2) in the area of pain; (3) in the area of walking." The questions are each answered with a 5-point Likert scale

with the response options “much better”, “somewhat better”, “unchanged”, “somewhat worse” and “much worse”. The questions and answers refers to Angst and colleagues and were translated into German language by the author (33).

## **Objective measures**

The 30 Second Chair Stand Test (34) aims for testing leg strength as well as leg strength endurance. The participant is seated in the middle of a chair with the hands and arms crossed in front of the upper body. Feet are completely positioned on the floor and the back is straight. Out of this initial position the participant is asked to stand up until an upright position and to seat again as often as possible within a 30 second time window. Results can be related to gender and age-matched norm values.

## **Concomitant care**

Utilization of previous care and treatment will be assessed at t0 with a retrospective time-window of 12 months. Utilization of concomitant care during the study period will be assessed 4 and 8 weeks after baseline and at t1 (twelve weeks after baseline) with a retrospective time window of 4 weeks. Assessments will include the type of care utilization (i. e. physical therapist, general practitioner, dietician etc.) and the type of received treatment referring to different kinds of information/advice, self-managed care, nonsurgical, clinical care and surgery, respectively (26). Within the categories self-managed care / clinical care, medication intake (regularly, sporadic, no), the type of medication taken, as well as its dose and frequency of intake will explicitly be asked for.

## **Perceived human-digital interaction, patient satisfaction**

The perceived usability of the digital health application will be assessed with the m-Health App Usability Questionnaire (MAUQ) (35) in addition with 1 item from Harder, Holroyd (36) (Item B1). The MAUQ is not available in a validated German language version and is used in a self-translated version. The assessment of these questionnaire takes place after the exercise intervention period.

The modified version of the 8-items scale ZUF-8 will be used to assess patient’s satisfaction with the received care (37). The modifications relate to changes according to the kind of care (stand-alone app here versus hospital setting in the original version).

Patient perspective on the satisfaction with the results of their treatment in general will be asked with the one-item question “How satisfied are you with the results of your treatment?” using a 5-point Likert scale (very satisfied; satisfied; neither satisfied nor dissatisfied; unsatisfied; very unsatisfied) (26).

## **Logfiles**

Logfiles of the re.flex digital application for the evaluation of adherence to exercise, rating of perceived exertion during exercising and perceived pain before, during and after exercising will be read out for each training session separately.

(1) Adherence to exercise

Overall adherence will be quantified using the percentage of conducted exercise sessions relative to the overall number of prescribed exercise sessions, irrespective of the compliance to the prescribed exercise dosage. In addition, logfiles of the app provide detailed information on the number of valid repetitions and sets of each exercise within a given training session as well as overall data for each training session along the 12-week intervention phase for the sensor-equipped leg. Training adherence is therefore further quantified by calculating the percentage of all valid repetitions conducted with the affected leg during the training related to the number of requested repetitions. The overall exercise repetition adherence is the mean value of the adherence of all training sessions of the 12-week program considering the calculating procedure as mentioned before. Further data include the time in action as well as the total training time (including calibration, instruction, training of the other leg etc.).

## (2) Rating of perceived exertion (RPE) during exercising

Participants are asked to rate their exertion using the entry field of the app after each set of exercise as well as overall exertion at the end of the training session. RPE is measured using a numerical rating scale (NRS) with 0 indicating no exertion at all and 10 indicating the maximal conceivable exertion. Values are read out for each set of an exercise separately. Average values are calculated.

## (3) Perceived pain before, during and after exercising

Pain ratings are requested before and after each training as well as after each exercise set. Values are read out for each exercise separately. Patients are asked to rate their pain using the entry field of the app. Perceived pain is measured in the style of the Faces Pain Scale (FPS-R) (38). Face emojis are scored 0 (no pain), 2 (little pain), 4 (moderate pain), 6 (much pain), 8 (very much pain) or 10 (highest imaginable pain). In case of an entry with a pain index of more than 8, the user gets a recommendation to pause training and to contact the physician in charge.

The in-app pain report does not aim to replace the comprehensive KOOS. It rather intends to monitor pain levels throughout the course of the exercise intervention.

# Safety aspects

Exercise related pain and adverse events are questioned retrospectively at t1 including frequency, duration, intensity, and potential reasons. Exercise related pain will only be assessed in participants of IG, adverse events (AE) will be assessed in both study arms.

Participants are informed at t0 to contact the study personal in case of AEs during the study period. Minor adverse events (AE) have to be reported to the responsible study personal within one week (postal letter, email, telephone, in-app support chat). Adverse events causing the need for referral to a physician or hospital have to be reported to the responsible study personal immediately. Judgement on whether the AE is related to the intervention is carried out by an orthopedist or physician for internal medicine of the Dept. of Sports Medicine. In case of an unclear connection between AE and intervention or in case of a serious AE, representatives of the study sponsor Sporlastic and other study independent physicians of the University

Hospital are announced to a safety board. This safety board then has to decide on the continuation or premature termination of the trial for safety reasons.

## Participant timeline and recruitment

First patient in was in January 2023. Continued inclusion of patients is planned until the end of April 2023. Assessments at baseline (t0) and immediately after the 12-week intervention/control phase (t1) will be conducted on-site at the University Hospital, Tuebingen, Germany and data will be collected as outlined in Fig. 3 and Table 2. Assessors for the performance outcome measure are thoroughly instructed into the use of the measurement instrument prior to the start of the study. Additionally, an online-questionnaire asking for concomitant care will be sent at week 4 and 8. All participants are expected to have completed the study by the end of July 2023.

A detailed timeline for the individual patient can be seen in the study flow chart in Fig. 3.

Potential study participants are recruited via newspaper, newsletter for employees of the University Hospital and the University and people who were interested in participating in a previous study (DRKS00023269), but could not be included because of bicondylar symptoms (eligibility criteria have been changed for this trial).

Recruiting takes place in a two-step procedure. The first contact will be held by telephone or email. It aims for informing the interested person about the content and aims of the study as well as its timeline. The first screening for eligibility by querying the inclusion- and exclusion criteria is also part of this contact. In this regard the Physical Activity Readiness-Questionnaire PAR-Q is used to screen for exercise suitability. If one or more questions related to restrictions other than musculoskeletal are answered with „yes“, the interested person must provide a confirmation for cardio-pulmonary exercise suitability from his personal doctor in case of further interest in study participation. This step takes place before study inclusion and must be done on patient's initiative.

In the context of the second step, the eligible patient is invited to a face-to-face meeting. This meeting includes comprehensive oral and written study information and the option for the patient to ask and get response to open study-related questions. After providing written consent, the patient is included on a provisional base and referred to the study physician (orthopedist) for medical examination (anamnesis and physical examination). The patient is finally included in case of alignment to inclusion criteria and absence of exclusion criteria. Otherwise, the subject is definitely excluded before randomization takes place.

The examination is followed by the outcome assessments. Finally, patients are randomized to IG or C. This first baseline examination will take approximately two hours. The first examination (t0) is followed by the 12-week intervention or control phase. Follow-up measures (t1) are conducted directly after the 12-week intervention or control phase. The complete study duration for each participant lasts about 14 weeks including two assessments as well as the 12-week intervention or control phase.

## Sample Size

The two primary endpoints of the study are the KOOS Subscales Pain and ADL. Results of a pilot study comparing the KOOS Subscale Pain and KOOS Subscale ADL of 29 patients of the control group (usual care) with 15 patients of the intervention group (re.flex) using baseline adjusted analysis of covariance revealed an effect size of 1.16 (Subscale Pain) and 1.03 (Subscale ADL). A recent meta-analysis on exercise interventions in patients with knee OA reported a standardized mean difference of 0.5 (95% CI 0.37 to 0.63) for pain reduction immediately post treatment in comparison to usual care or minimal treatment (39). Additionally, minimal clinically important differences (MCIDs) were reported between 5.5 to 8.7 points of the WOMAC pain subscale (Score 0-100) for non-surgical treatment strategies in patients with knee OA (33, 40). These correspond to standardized mean difference between 0.59 and 0.94. Based on the preceding, rather heterogeneous results with effect sizes between 0.5 and 1.2 from the results of the pilot study and findings and recommendations of other sources, the planned study is powered to demonstrate a MCID of 5 points (0-100) on the KOOS Subscale Pain between the intervention and control group with a standard deviation of 10. This leads to an effect size of 0.5 and to a sample size of evaluable participants of  $2 \times 78 = 156$ . For adjustment of baseline, etiology, medication and laterality 4 additional degrees of freedom are spent and the sample size is increased to 160. Considering a drop-out rate of ~ 20%, 200 patients will be recruited to achieve a power of 80% with a type 1 error of 0.025 (two-sided, Bonferroni correction for two confirmatory outcomes) by baseline adjusted comparison of outcome values at t1 between study arms (analysis of covariance, ANCOVA).

## Randomization

Before study start, randomization lists will be created for each of the eight combination of the strata aetiology (primary, secondary), medication (regularly/no or sporadic) and laterality of the disease (one-sided, two-sided) using computer-generated random numbers (0;1) with varying block lengths and 50 subjects per stratum combination. The randomization list will be transferred to the data management system SecuTrial (Interactive Systems Berlin). Online randomization will be performed after confirmation that the respective subject fulfils all selection criteria and after entry of the stratification criteria.

Participants will not be randomized in case of exclusion before completion of the examination and tests at t0.

## Blinding

The study intervention is obvious and therefore an adequate comparable placebo intervention is not available. As such this trial is non-blinded for participants. Blinding of health care providers is not applicable as the intervention of interest is a stand-alone app without human interaction. Baseline assessments take place before randomization and data collectors for the performance test will be blinded to group allocation of the participants for follow-up assessment. All other outcomes are self-reported and blinding is not possible. The creation of the computer-generated randomization list using the software nQuery will be done by an employee of the IKEAB who is not involved in the conduction and assessment of the study. Statisticians will be blinded for the analyses of the primary endpoints and all other health outcome measures. For further analyses statisticians will be unblinded as treatment allocation is obvious (i.e. perceived human-digital interaction, logfiles etc.).

# Statistical Methods

The two primary endpoints of the statistical analyses are the KOOS Subscales Pain and KOOS ADL. They will be analyzed at t1 immediately after the termination of the intervention using a baseline adjusted analysis of covariance (ANCOVA) with the primary factor “study arm”. The level of significance will be 0.025 (two-sided, Bonferroni correction for two confirmatory outcomes). We hypothesize that the exercise intervention will be superior to the control. Additionally, the stratification factors aetiology (primary, secondary), medication (regularly/no or sporadic) and laterality of the disease (one-sided, two-sided) will be coded by binary variables. The model equation is:

$$Y = \beta_0 + \beta_1 * BL + \beta_2 * Arm + \beta_3 * aetiology + \beta_4 * medication + \beta_5 * laterality + \epsilon.$$

Y: KOOS (Pain resp. ADL) at t1, BL: baseline KOOS (Pain resp. ADL), Arm: study arm coded as 0 (control) and 1 (exercise intervention),  $\epsilon$  random error (normally distributed, equal variance, independent). Reference categories “primary”, “no or sporadic medication”, and “one-sided disease”,  $H_0: \beta_2 = 0$ ,  $H_1: \beta_2 \neq 0$  (two-sided test, scientific hypothesis: superiority of exercise intervention, i.e.  $\beta_2 < 0$ ).

Continuous secondary endpoints will be analyzed using the same statistical methods (analysis of ANCOVA, if baseline values are available, analysis of variance else). For the main results, two-sided 95% confidence limits will be given additionally to significance tests.

Success of randomization will be assessed using baseline comparisons between both study arms. The primary analysis population will be the intent to treat population. This population includes all patients, who contribute at least baseline values of the primary outcomes. Multiple imputation will be applied to subjects who drop out or do not contribute measurements of the primary outcome for other reasons. 500 imputation samples will be drawn. Baseline measurements will be included as predictor (c.f. definition of intent to treat population). The “jump to reference” method will be used for the primary analysis, i.e., patients who drop out will be assigned to the control arm in the imputation model, but not in the analysis model. Sensitivity analyses will be performed with “complete case analysis”, “baseline observation carried forward” (single imputation) and with inclusion of the correct study arm in the imputation model (multiple imputation). A per protocol analysis will be conducted with all participants of the IG complying to the study criteria and still using the app until the last two weeks of intervention phase with an overall adherence rate of 80% of the scheduled sessions. The same procedure will be done for all other secondary health outcome measures for which baseline values are complete.

Exploratory subgroup analyses will be performed for the stratification factors and patient age (18–40 years, 40–55 years, 55–65 years, older than 65 years). Additionally, in the case of frequent or differential occurrence of concomitant care (medication, physical therapy – active treatment) between the study groups, an exploratory subgroup analysis will be performed. P-values for interaction of study arm with stratification factors and patient age as well as p-values of study arms within strata will be reported but should not be interpreted confirmatory.

An additional analysis is planned for subjective ratings of overall change (general, pain, function). Response scales will be first dichotomized into improved (somewhat/much better) and not improved (unchanged or worse). Between-group comparisons will be expressed as relative risks of improvement (41). Exploratory, prognostic factors including baseline pain, age, BMI, sex, technical affinity and fear of movement will be analyzed using multiple regression models (linear regression) to identify potential responders to the training. Binary outcomes will be analyzed using similar logistic regression models.

## Data Management

Data of all participants with informed written consent will be pseudonymized. On site data will be captured with paper and pencil case report forms (CRF) and using an online-questionnaire (Questback GmbH, Köln, Germany) for PROMS. Log-Data of app usage will be captured by the software and transferred to the study team (\*.csv-file). Paper and pencil CRFs will be double entered into an electronic data sheet (Excel). Doubly-entry will be checked for errors. The data bank will be closed after the last patient out and after processing all queries. Study data are then exported via \*.csv-File to the statistical programs in use.

## Data Monitoring

There is no external data monitoring committee for this study.

## Discussion

M-health interventions such as the sensor-guided digital-based exercise intervention re.flex can be used independently from time and location and allow most patients to get access to this kind of exercise guidance. Re.flex was specifically developed to support home training in patients with knee OA. If effective, it can bridge part of the gap between recommendations for strengthening exercises in patients with knee OA and the insufficient actual care situation. However, to be classified as a digital health application reimbursed by German health insurance companies, the intervention must prove patient benefit.

## Limitations

The following limitations have to be addressed for the outlined study. All participants are allowed to make use of usual health care provided by the treating physician during the study period. This concerns IG and C. This cannot be prohibited, as all persons with a German health insurance have a right to receive physician recommended usual care treatments. An exclusive participation in re.flex or doing nothing (C) cannot be ensured. To address this issue, all concomitant care is queried retrospectively for one year and every 4 weeks until the end of the study.

Considering the intervention duration of 12 weeks, only short-term effects can be assessed. Long-term effects are not included.



## **Conclusion**

This randomized controlled trial is designed to provide conclusions on the effectiveness of re.flex for the population under study. Patient benefit is primarily related to OA-specific pain reduction and improvement of physical function. Superiority of re.flex versus control for pain and function is a prerequisite for the permanent listing of the app into the DiGA register.

In addition, this study will add important knowledge to the scientific community on the short-term effectiveness of exercise-related digital health interventions on health outcomes in general and it will further provide evidence on its usability, patient acceptance and safety. Regarding this, the sensor-based technology allows objective measures on exercise performance and may therefore help to control and analyze exercise training at home.

## **Abbreviations**

ADL	Function in daily living
AE	Adverse event
ANCOVA	Analysis of covariance
App	Application
C	Control group
CRF	Case report form
DiGA	Digital health application – Digitale Gesundheitsanwendung
DRKS	German clinical trials register - Deutsches Register Klinischer Studien
ETS	Expectation for Treatment Scale
FPS-R	Faces Pain Scale
ICD	International Classification of Disease
ICHOM	International Consortium for Health Outcomes Measurement
IG	Intervention group
IKEAB	Institute for Clinical Epidemiology and Applied Biometrics
KOOS	Knee Osteoarthritis Outcome Score
MAUQ	M-Health App Usability Questionnaire
MCID	Minimal clinically important difference
m-health	Mobile health
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PAR-Q	Physical Activity Readiness Questionnaire
PROM	Patient-reported outcome measure
QoL	Quality of life
RPE	Rating of perceived exertion
Sport/Rec	Sport and recreation
t0	Timepoint 0, collection point at baseline
t1	Timepoint 1, collection point after 12-week study phase

TA-EG	Questionnaire to assess technical affinity regarding electronic devices
TSK-GV	Tampa Scale for Kinesiophobia, German Version
VR-12	Veterans Rand 12: 12-item questionnaire assessing Health related quality of life
WOMAC	Western Ontario and McMaster Universities Arthritis Index
ZUF-8	Patient satisfaction questionnaire

## Declarations

### *Availability of data and materials*

Data and material will be made available upon reasonable request after the conclusion of the study.

### *Consent for publication*

Not applicable.

### *Declaration of interest*

The exercise intervention that is implemented into the re.flex app was designed by employees of the University Hospital (i. a. VD, IK) in the context of a previous cooperation project between with the trial sponsor Sporlastic GmbH and the University Hospital Tuebingen. The pilot study of this trial protocol was conducted during this cooperation as well. The University Hospital will be appropriately compensated for the granting of rights of use to the results generated by employees of the University Hospital (intellectual property) in the event of successful commercialization of the app. University Hospital will compensate the employees (i. a. VD, IK) who were involved in the previous collaboration and are authors of the intellectual property from these revenues. Contract negotiations are currently underway. However, the PI (PJ) of the study outlined in this study protocol as well as the biomedical statisticians (PM) do not have any conflict of interest.

### *Dissemination policy*

The University Hospital Tuebingen has a basic right of publication of study data. The study protocol and study results will be communicated at scientific congresses and/or in peer-reviewed scientific journals. The sponsor Sporlastic GmbH will use his right to make the study results public as part of his corporate communications.

### *Funding*

The study is financed by Sporlastic GmbH (Nuertingen, Germany). Sporlastic GmbH also provided the digital application and sensors that are used in the clinical trial. The trial sponsor Sporlastic GmbH has a contractual relationship with Kineto Tech Rehab SRL. Kineto Tech Rehab SRL is the manufacturer of the product (sensors & app). Sporlastic is the exclusive distribution partner for the contract area (Germany).

### ***Data privacy, ethics approval and consent to participate***

The complete final trial dataset will only be assessed by employees of the University hospital Tuebingen. Any information provided in the context of the interaction with the digital application (technical queries, log files, information given within the scope of the software use) can be assessed by the app producer and the study sponsor. However, these data are pseudonymized and cannot be re-identified by any party other than the University Hospital.

This study has been approved by the Ethics committee of the Medical Faculty of the University of Tuebingen (688/2022B02). The trial was registered on 20/01/2023 at [www.drks.de](http://www.drks.de) (ID: DRKS00030932). Participants will be informed about potential harms and benefits of the study and the voluntariness of study participation. Written informed consent will be obtained from all participants prior to the study inclusion. In case of modifications of the protocol an amendment will be sent to the local Ethics committee prior to the implementation.

### ***Contributions***

IK, VD, PM and PJ contributed to the conception and design of the study. VD drafted the manuscript. IK, PM and PJ critically revised the manuscript. All authors read and approved the final manuscript.

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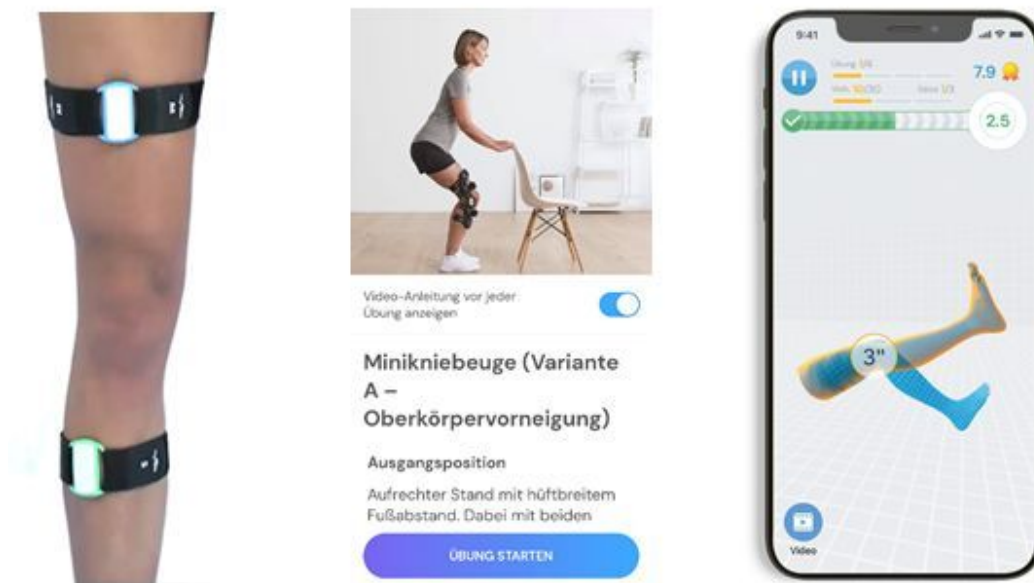
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## Figures



**Figure 1**

re.flex technology (left picture) and examples for app-guided exercise instructions (middle and right pictures).

## 12-week exercise program for patients with knee osteoarthritis

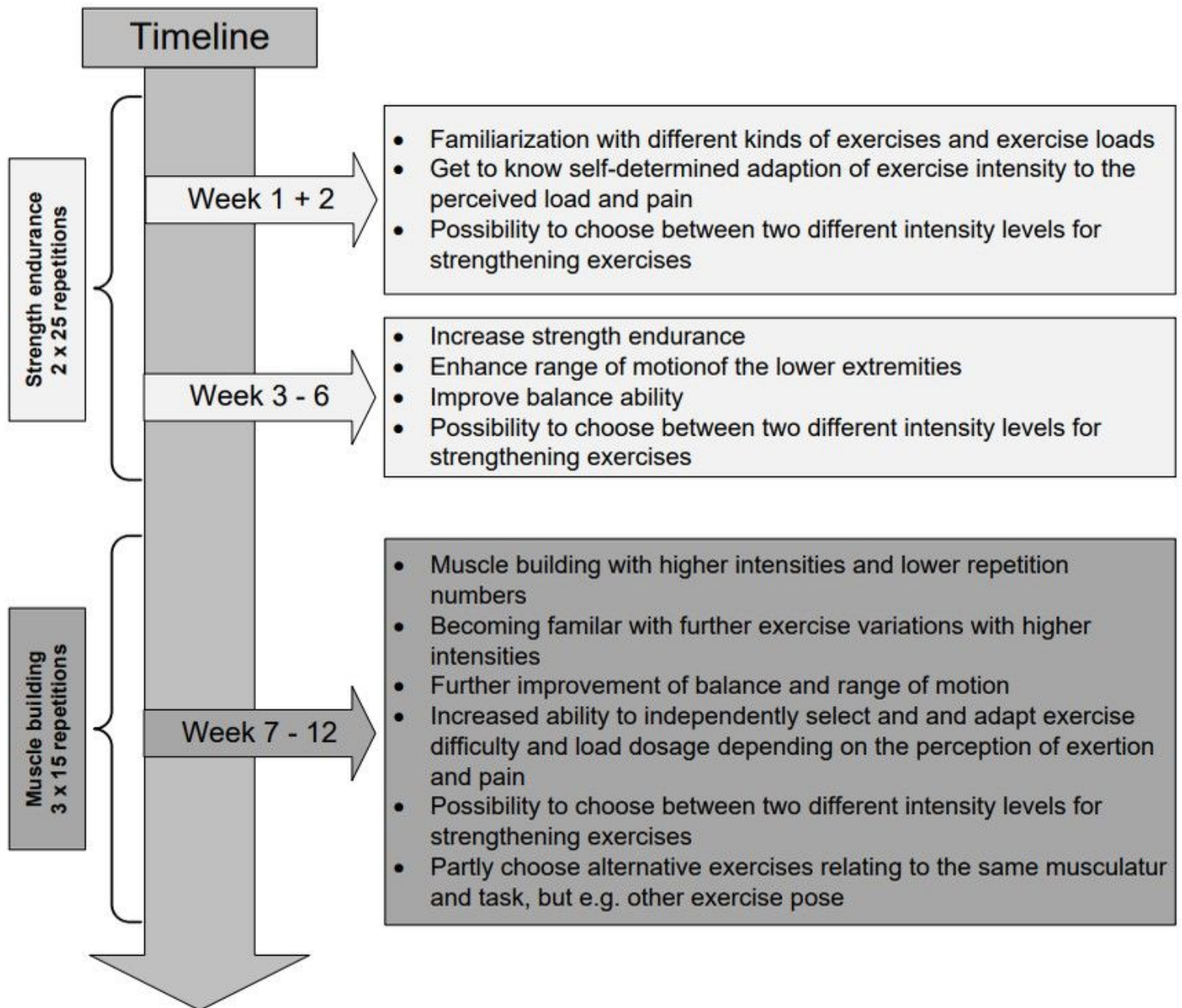
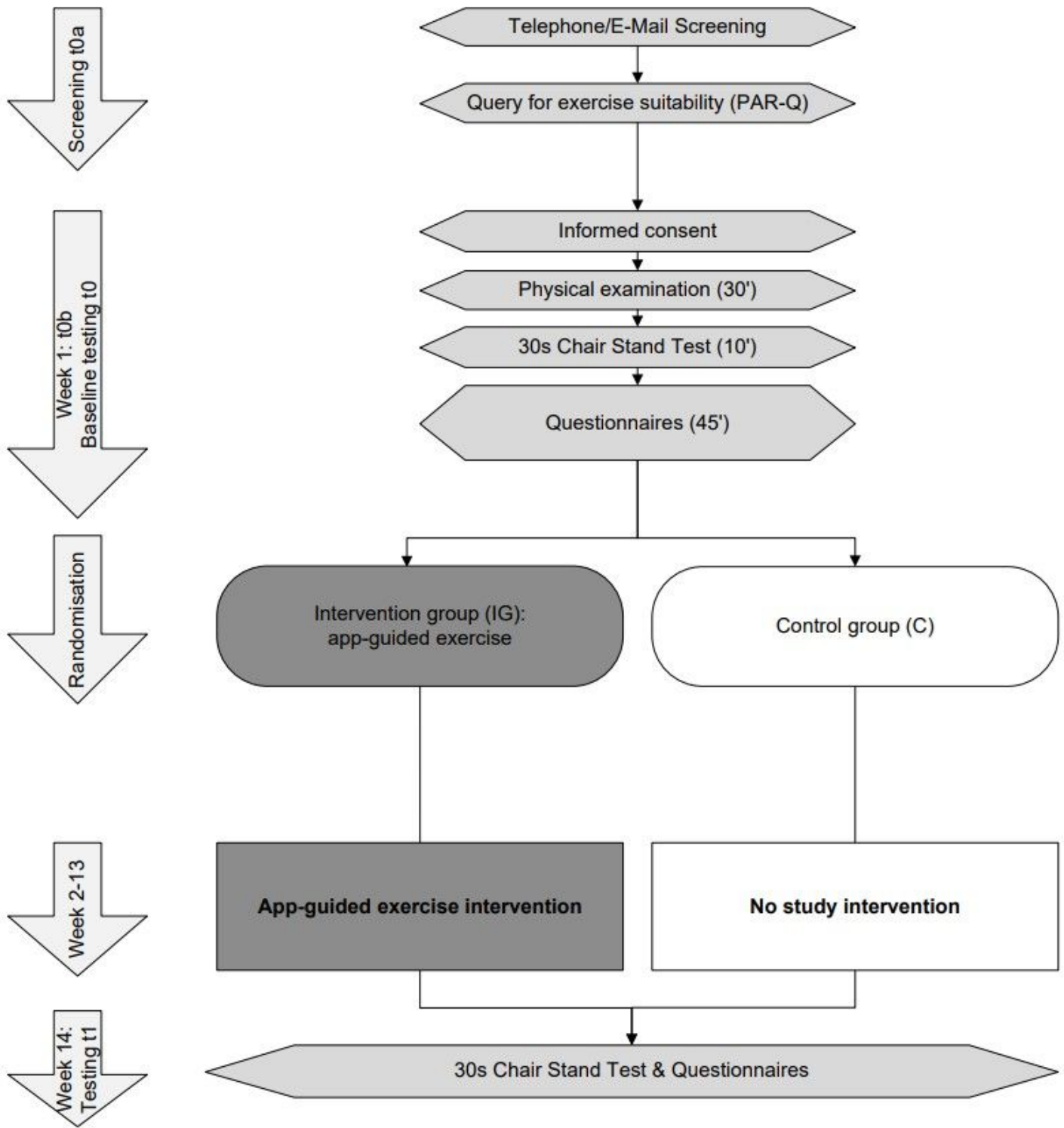


Figure 2

Objectives within the different phases of the 12-week exercise program for patients with knee osteoarthritis.





**Figure 3**

Study Flow Chart

## Supplementary Files

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- [Supplement1SPIRITchecklist.docx](#)
- [Supplement2TIDieRChecklist.docx](#)