



RESEARCH STUDY PROTOCOL

PROTOCOL TITLE: Cost and outcomes of hospital-based physiotherapy versus mHealth-based self-directed rehabilitation in patients with knee osteoarthritis: A randomized, controlled, non-inferiority trial

PROTOCOL NUMBER: NIL

VERSION NUMBER: 2

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PRINCIPAL INVESTIGATOR: Dr Pua Yong Hao

PROTOCOL SIGNATURE PAGE

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Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Pua Yong Hao

Name of Principal Investigator:



Signature of Principal Investigator:

Date:

Singapore General Hospital

Name of Study Site:

Note:

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- Signed copies of this signature page should be stored in the study file and in the respective study site's investigator file.

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1. BACKGROUND AND RATIONALE

Knee OA is common, disabling, and costly

Symptomatic osteoarthritis (OA) of the knee affects approximately one-fifth (~300K) of Singaporeans aged 50 years or older, with the disease prevalence increasing with age¹. Patients with advanced knee OA and severe disability often require a total knee replacement (TKR) surgery. With an ageing population and the high prevalence of obesity², the annual number of TKR is projected to rise³. Thus, innovative care models are urgently needed to improve patient outcomes, while managing or reducing the economic burden of this common and costly public health problem.

Unmet Need: Conservative treatment through physiotherapy rehabilitation is a key intervention but significant access limitations result in unnecessary TKRs

For patients with knee OA, consensus guidelines⁴⁻⁶ are unanimous in recommending education, exercise, and weight management (if required) as first-line intervention. Physiotherapy rehabilitation incorporates these 3 first-line interventions and is a widely advocated and evidence-based component of OA intervention⁶. Despite this, international evidence⁷⁻⁹ suggests that these core interventions are often under-utilized, with only 20-40% of community-dwelling older adults with knee OA receiving them. Locally and worldwide, suboptimal care from rehabilitation non-attendance is prevalent⁹ and costly: available research suggests that at least a quarter of TKRs could have been avoided with optimal care¹⁰. Thus, to reduce the economic burden of OA, there is a need to develop innovative and flexible rehabilitation strategies.

mHealth-based program is a likely solution to address this unmet need, but local contextualization is needed. Against this background, a mobile health (mHealth)-based OA self-management program may be a feasible solution to deliver guideline-based interventions, with minimal involvement by healthcare professionals. Whilst several app- or web-based OA self-management programs are available¹¹, few have undergone rigorous RCT evaluation¹², and still fewer¹³⁻¹⁵ provide detailed instructions to enable self-directed exercise (in particular, muscle strengthening exercises¹⁶) – despite the evidence that exercise is the cornerstone of knee OA management⁴⁻⁶. Furthermore, the reach and adoption of these programs in Singapore is limited as they are designed for English-speaking patients from Western cultures. Hence, whilst there are potential benefits in harnessing technology-enabled programs, these data emphasize the need for local co-design and adaptation to suit the Singapore context and to facilitate adoption^{17,18}.

Thus, we have, through an iterative user-centered design process, developed *Managing Osteoarthritis of the Knee using Therapist-Technology Optimized Rehabilitation* (MOKneeTOR), a blended digital rehabilitation program integrating an initial face-to-face physiotherapy assessment and a mobile health (mHealth)-enabled exercise and self-management program designed to promote first-line interventions (education, exercise, and weight management where indicated) for patients with knee osteoarthritis.

2. HYPOTHESIS AND OBJECTIVES

- Primary hypothesis: The MOKneeTOR program will be non-inferior to hospital-based physiotherapy rehabilitation at 3 and at 6 months in improving physical function (fast gait speed).
- Secondary hypothesis: The MOKneeTOR program will be more cost-effective than hospital-based physiotherapy rehabilitation in reducing total OA-related costs.

3. EXPECTED RISKS AND BENEFITS

Expected risks

To ensure safety of participants randomized to the MOKneeTOR program, our MOKneeTOR app will allow for regular monitoring to facilitate timely intervention escalation for participants who are deemed to have deteriorated and are at risk for poor clinical outcomes. Participants will also attend additional outpatient physiotherapy sessions if (i) they are deemed unsafe when performing their exercises, (ii) participants are unable to use the app competently, or (iii) participants request them.

Some participants may experience temporary discomfort, muscle soreness, or fatigue associated with the physical tests conducted in this study, which includes strength testing. These responses are common in routine physiotherapy assessments and are expected to be transient. To mitigate risks, all testing will be performed by trained clinical research coordinators following standardized protocols. Testing will incorporate appropriate instructions on technique, warm-up, and rest intervals. To summarize, the probability of discomfort is no greater than those encountered in standard clinical care.

Since the MOKneeTOR mobile app will be downloaded onto the participants' phone, usage of the mobile application may have a potential breach of their personal mobile devices and breach of privacy not related to their health. The chances of this happening, however, is very slim as the accounts will be created using a unique code. Apart from these, the application will not collect any additional data from their personal devices.

Potential benefits

Participants are expected to have a better understanding of knee OA and show a greater ability to engage in self-management. Their functional levels are expected to improve, and participants may also report subjective improvements in their knee symptoms. The primary benefit of this study is contribution to generalizable knowledge regarding the clinical and cost effectiveness of the MOKneeTOR program.

4. STUDY POPULATION

4.1. List the number and nature of subjects to be enrolled.

Study participants will be recruited from a large pool of patients who are referred by orthopaedic surgeons for conservative physiotherapy management in Singapore General Hospital (SGH). Per sample size estimation, we will recruit 80 participants per intervention arm. As our MOKneeTOR program is designed to improve the social support of patients with knee osteoarthritis, patient participants randomized to the MOKneeTOR group may optionally nominate one SP (family member/friend) to participate in the study. SPs must be ≥ 21 years, own a smartphone, and be able to receive and respond to messages via the SP version of the MOKneeTOR app. The involvement of a support person in the MOKneeTOR group is strictly

optional and depends entirely on the patient participant's preference. Therefore, the actual recruitment number for support persons will range from 0 to a maximum of 80.

4.2. Criteria for Recruitment and Recruitment Process

Study participants will be recruited from a large pool of patients who are referred by orthopaedic surgeons for conservative physiotherapy management in Singapore General Hospital (SGH). Participants who consent to join the study will be given time to consider their participation before providing informed consent. All patients will be informed that they have the option to opt out of the study. Informed consent will be taken in the presence of a witness. Consent will be taken in a quiet outpatient consultation room so that the participants will not be distracted by the bustle of clinic activities. Patients who consent to join the study will be given time to consider their participation before providing informed consent. All relevant study team members will be trained in the consent-taking process to reassure patients that participation is entirely voluntary and their decision to participate will not affect their care or management.

Patient participants randomized to the MOKneeTOR program may optionally nominate one Support Person (SP) (family member/friend) to participate in this study. If the SP is present at the consultation, the study team will introduce the study and can obtain written informed consent immediately. If absent, the study team will seek the patient's participant's permission to contact the SP separately to share information and schedule an in-person consent visit. The study team will then reach out to the SP via phone call to introduce the study. Should the SP express interest in participating, they will be scheduled to attend a subsequent study visit. During this session, the study team will address any questions, and written informed consent will be formally obtained from the SP in person. In either scenario, should the SP express interest in participating, the study team will provide ample time to review the information, address any questions, and formally obtain written informed consent in person. SPs will provide informed consent before any app access or data collection; declining (by the SP) will not affect the patient participant's care or study participation.

SPs will provide informed consent before any app access or data collection; declining (by the SP) will not affect the patient participant's care or study participation. The SP account linking process is dependent on study team's action. Even if the patient participant generates and shares a unique access code, the SP cannot access the system or link accounts unless their profile has been pre-created by the study team.

4.3. Inclusion Criteria

Patient participants:

- All patients who meet the knee OA clinical criteria:
 - aged ≥ 45 years,
 - activity-related knee pain,
 - and ≤ 30 min knee joint stiffness in the morning
- an owner of a smartphone,
- an education level of at least 8 years,
- a willingness to be randomized to either MOKneeTOR program or outpatient rehabilitation program,
- and an ability to complete baseline assessment.

Support Person:

- must be ≥ 21 years,
- own a smartphone,
- an education level of at least 8 years,
- be able to receive and respond to messages via the SP version of the MOKneeTOR app.

4.4. Exclusion Criteria

Exclusion criteria for patient participants include the following:

- (i) lower limb joint replacement surgery anticipated within the next 6 months,
- (ii) rheumatoid arthritis and other systemic arthritis, and
- (iii) a previous history of stroke and other major neurological conditions, and
- (iv) significant back or other non-knee pain
- (v) pregnant women

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

Approach and Methods

This will be an assessor-blinded, parallel design, noninferiority randomized controlled trial, with assessments done at baseline, 3 months, and 6 months after randomization. The protocol conforms to the CONSORT guidelines for eHealth interventions and non-inferiority RCTs¹⁹.

Participants

Study participants will be recruited from a large pool of patients who are referred by orthopaedic surgeons for conservative physiotherapy management in Singapore General Hospital (SGH). Informed, written consent by each participant will be obtained. Study treatments, but not the study hypotheses, will be disclosed to participants; therefore, participants will be unaware of the hypothesized direction of effect.

Randomization

To maintain allocation concealment, randomization will be undertaken only after completion of baseline outcome assessment. Participants will be randomized using minimal sufficient balance (MSB) randomization²⁰, a covariate-adaptive randomization method designed to ensure covariate balance on the key variables of age, sex, and baseline knee pain intensity. The first 20 patients will be allocated in a 1:1 ratio to MOKneeTOR program or outpatient physiotherapy rehabilitation program using simple randomization, after which the computer-generated MSB algorithm will be activated. To support an exploration of potential mechanisms through which our MOKneeTOR mobile app improves management adherence, participants randomized to the MOKneeTOR program will undergo a second randomization (1:1) to receive either (i) MOKneeTOR with the standard MOKneeTOR app configuration or (ii) MOKneeTOR with enhanced personalization of the MOKneeTOR app (e.g., personalized UI such as tailored caricature, preferred colour scheme and customizable chatbot settings that allow patients to choose between concise or detailed replies). Notably, this 2:1:1 design will optimize our ability to assess the overall effects of the MOKneeTOR program relative to outpatient physiotherapy rehabilitation program while also allow an exploration of potential mechanistic effects of the MOKneeTOR app.

Participants randomized to MOKneeTOR program may optionally nominate one adult support person (SP) (e.g., family member/friend) to receive access to an SP version of the MOKneeTOR mobile app. The SP app is a subset of the patient app and is intended to (i) improve SP's knee OA knowledge and (ii) support SP's efforts in supporting the participant's self-management. The SP app displays the participant's progress summaries (exercise and physical activity frequency) and delivers informational and encouragement messages to the SP. Participation of an SP is optional and does not affect the participant's clinical care or trial participation.

Intervention

MOKneeTOR program

Participants allocated to the MOKneeTOR program will receive 24-week access to the MOKneeTOR app. Participants with BMI > 23 kg/m² who report not owning a weighing scale will be provided one. To onboard participants on the use of the MOKneeTOR app, the MOKneeTOR program is designed to include an in-person outpatient session, during which the physiotherapist will guide participants through the system. Importantly, based on assessment findings and data input by the physiotherapist, the MOKneeTOR app will utilize a care stratification approach by selecting educational materials tailored to the participant's needs. During the onboarding session, participants will be provided with resistance bands, and they will be instructed on a home exercise program designed to improve (i) lower limb strength, (ii) postural balance, and (iii) physical function. Participants will be instructed to perform the exercises at least 2 times weekly. Over the period of self-management, the MOKneeTOR app will combine both self-reported outcomes and performance-based outcomes to provide objective exercise feedback and criterion-based personalized exercise progression recommendations. Participants randomized to receive MOKneeTOR with enhanced personalization of the MOKneeTOR app will receive an app experience with an education chatbot that adapts tone, reading level, and format (text, infographics, short videos) to participants' preferences and engagement. Minor person-centred features (e.g., treating therapist caricature avatars and name-badged messages) will also be incorporated to strengthen therapeutic alliance without altering clinical guidance.

Hospital-based outpatient rehabilitation program

Participants will attend, over a 12-week period, a minimum of 3 outpatient physiotherapy sessions, with up to 3 additional sessions if patients are deemed to require them. This reflects a realistic, optimal treatment dosage and timeframe in our local context. During the sessions, participants will receive patient education, exercises, manual therapy, and other modalities. Participants will also be instructed on a home exercise program in which they will exercise at least 3 times weekly. During each session which will last around 40 minutes, the project physiotherapist will (i) review the home exercise program, (ii) observe the participants performing the exercises and correct their form and techniques when necessary, and (iii) work with the participants to set goals and progress the exercise program. Because of the nature of the intervention, it is not feasible to blind participants or the treating physiotherapists. To reduce bias, the research assistant collecting assessment data will be blinded to treatment allocation. Participants will also be instructed not to reveal details about their group assignment to the outcome assessor to maintain blinding.

The outcome measures listed below will be collected from participants of MOKneeTOR program and Hospital-based outpatient rehabilitation program.

Primary outcome measure (all time-points)

Gait speed: This provides a performance-based measure of physical function. Participants will walk at their usual pace (warm-up) and fast pace along a 4-metre walkway, with a 2.5-metre acceleration distance before and a 2.5-metre deceleration distance after the timed section. Gait timing will be captured concurrently using both a stopwatch and a time-of-flight sensor. Gait speed (m/s) will be calculated for both walking conditions; however, time-of-flight sensor-based fast-paced gait speed will be the primary outcome measure.

Secondary outcome measures (all time-points)

Short Form of the Western Ontario and McMaster Universities Osteoarthritis Index (ShortMAC-F): The ShortMAC-F is an OA-specific questionnaire designed to measure physical function.

Knee Pain: Knee pain intensity will be measured using numeric pain rating scales (NPRS) that inquire about the average pain intensity level over the past 1 week.

Knee strength: Maximum quadriceps strength will be assessed on a seated knee-extension machine using a standardized one-repetition maximum (1RM) protocol.

Lower limb strength and mobility: This will be measured by the 5-times sit-to-stand test. Participants will perform the tests at their usual (warm-up) and fast pace, and their timing will be concurrently captured using both a stopwatch and a smartphone.

Health-related quality of life - EuroQol Group 5-Dimension (EQ-5D-5L): The EQ-5D-5L is a health-related quality of life instrument with established psychometric properties in Singaporeans. Quality-adjusted-life-years (QALY), derived from the EQ-5D-5L scores, will be the primary economic outcome and it will be used in the cost utility analysis

Secondary outcome measures (Week 12 only)

Treatment satisfaction: Participants will rate their satisfaction with rehabilitation on a 11-point numeric rating scale, with 0 indicating "not at all satisfied" and 10 indicating "totally satisfied".

Treatment recommendation: Participants will rate how likely they are to recommend this treatment to a friend or family member with knee arthritis using an 11-point numeric rating scale (allowing for 0.5 increments). A score of 0 indicates "Not at all likely," and a score of 10 indicates "Extremely likely."

Global perceived effect (GROC) GROC of overall change in pain and change in physical function since baseline will be measured using a 9-point ordinal scale, with 1 indicating "Much better" and 9 indicating "Much worse"

Exercise Compliance: Participants will respond to the question "I do my knee strengthening exercises as often as recommended/ advised," using a 0-10 scale (0=strongly disagree, 10= strongly agree).

Secondary outcome measures (Week 12 and 24)

Exercise Compliance: They will also report their knee strengthening exercise frequency (days per week)

Mechanistic outcomes (all time-points)

These measures are being collected as part of the study to undertake exploratory mediation/ moderation analyses post study completion.

Body weight and overall muscle mass/strength measurements: This will be measured using a calibrated scale for body weight and bioelectrical impedance analysis (BIA) to assess body composition (e.g., fat mass, lean mass). As a proxy measure of overall muscle strength, handgrip strength of the dominant hand was measured using a Jamar Plus digital dynamometer. In the sitting position with the elbow flexed at 90degrees, each participant will perform three maximal trials with 30 s rest between trials, and the highest reading will be analyzed. These measures will help explore whether changes in body composition mediate improvements in physical function and pain.

Perceived TKR Necessity: Participants will respond to the question *“Based on your knee symptoms in the past week, how willing would you be to have knee surgery if you were medically fit to do so?”* using a 0–10 scale (0 = not at all willing, 10 = definitely willing). They will also respond to the question *“How necessary do you think knee replacement surgery is for your condition?”* using a 0–10 scale (0 = not at all necessary, 10 = totally necessary).

Pain self-efficacy: This will be measured by the pain subscale of Arthritis Self-Efficacy Scale, which measures a person’s confidence in managing arthritis pain symptoms.

OA knowledge: This will be measured using the Knee Osteoarthritis Knowledge Scale (KOAKS)²¹

Fear of Movement: This will be measured by the Brief Fear of Movement Scale for Osteoarthritis²².

Psychological distress: This will be measured by the Four-Dimensional Symptom Questionnaire (4DSQ)²³.

Family support: This will be assessed using the Multidimensional Scale of Perceived Social Support (MSPSS), a validated 12-item questionnaire designed to measure perceived social support from family. In addition to the MSPSS, we will use a study-specific scale developed by our research team to assess supportive or unsupportive behaviors from family and friends related to knee osteoarthritis management.

Planned Walking Activities (IPEQ-W): Participants will report their planned walking activities using the walking subscale of the Incidental and Planned Exercise Questionnaire (IPEQ-W). They will indicate the frequency and duration of planned walking sessions over the past week. This measure captures structured walking exercise intended for health or fitness purposes, rather than incidental walking (e.g., walking for transport).

Knee range-of-motion: A long-arm goniometer will be used to measure active-assisted knee flexion and extension range-of-motion with the participants in supine position.

Weight bearing symmetry: This assesses the ability of the participants to weight bear on both limbs. With their feet on 2 portable force plate, participants will stand up from a standard chair, and weightbearing symmetry is calculated by expressing the peak force produced by the involved leg as a percentage of that produced by the uninvolved leg.

Support Person exploratory measures (baseline and Month 3)

For SPs of MOKneeTOR participants who opt in, we will assess (i) SP confidence in supporting the participant’s OA self-management, (ii) perceived support burden, and (iii) OA knowledge (as measures using the KOAKS). Note that these measures are exploratory and will not be included as primary or secondary endpoints of the RCT comparison.

Cost outcomes (follow-up timepoints)

Healthcare utilization costs: Between the baseline and the Month-6 assessment, we will use the modified OA Cost and Consequences Questionnaire (OCC-Q) to measure the use of other health and home care services, including hospitalizations, co-interventions, visits to healthcare providers (e.g., doctors and other healthcare professionals), and prescribed or over-the-counter medications. We will also collect information on participants' employment and income status and assess productivity losses, including restricted activity days (such as sick leave taken by participants and leave of absence taken by their caregivers).

Other measures

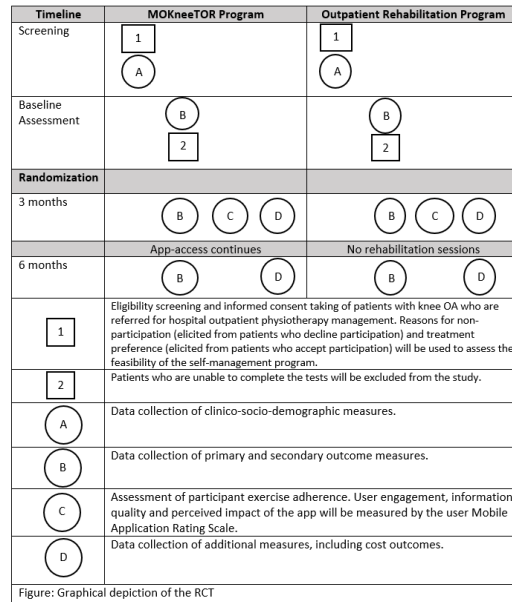
App usability: The usability of the MOKneeTOR app will be measured using the System Usability Scale (SUS), which is a validated 10-item questionnaire that assesses perceived usability. Qualitative feedback from participants will be collected to help identify intervention elements that are perceived to be useful. Additionally, user engagement and usage metrics will be automatically captured by the system backend throughout the study.

Descriptive measures A range of descriptive measures will be collected at baseline assessment including age, gender, symptom duration, ethnicity, education level, employment status, comorbidities, treatment preference, and confidence using technology.

Adverse effects: For participants randomized to the hospital-based rehabilitation group, adverse effects, such as falls or reports of injuries during the exercises, will be monitored by questioning participants at each outpatient visit by the treating physiotherapists. For participants randomized to the MOKneeTOR group, they will be contacted by telephone on a weekly basis by a research coordinator. As we are evaluating a low-risk intervention, there are no specific interim analysis plans or associated stopping guidelines.

Study duration and procedures

The participants will be directly involved in the study for ~6 months (from the recruitment date). Please refer to the Figure below which outlines our proposed study procedures.



6. SAFETY MEASUREMENTS

6.1. Definitions

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

6.2. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

The reporting requirements will be in accordance to the reporting requirements published on CIRB website at the time when the event took place.

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the research.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

6.3. Safety Monitoring Plan

The principal investigator and the co-investigator would perform the data and safety monitoring. There are no major safety issues in this study as the assessments are non-invasive and physical activity has been shown to be safe in older adults. However, we will monitor for any physical injuries (muscle aches, strains or sprains) that may be possibly attributed to the physical fitness tests on the day of the assessment.

To ensure safety of participants randomized to the MOKneeTOR program, our app will allow for regular monitoring to facilitate timely intervention escalation for participants who are deemed to have deteriorated and are at risk for poor clinical outcomes. Participants will also attend additional outpatient physiotherapy sessions if (i) they are deemed unsafe when performing their exercises, (ii) participants are unable to use the app competently, or (iii) participants request them.

6.4. Complaint Handling

Complaints received with regard to this study will be taken seriously. All comments to further improve the flow of this study will be taken into serious consideration and implemented wherever possible to refine recruitment and study process.

6.5. Collecting, Recording and Reporting of Reportable Adverse Events relating to Medical Device to the Health Sciences Authority (HSA)

The reporting requirements will be based on the reporting requirements published on HSA website at the time when the event took place.

All adverse events relating to medical device which meets the three basic reporting criteria listed below, is considered as a reportable adverse event to HSA:

- An AE (or potential AE) has occurred.
- The medical device is associated with the AE.
- The AE leads to one of the following outcomes:
 - It becomes a serious threat to public health.
 - The death of a patient, user or other person.
 - Serious deterioration in state of health of patient, user or other person.
 - There is no death or serious injury in the initial AE but it might lead to death or serious injury of a patient, user or other person if the AE recurs.

7. DATA ANALYSIS

7.1. Data Quality Assurance

The data will be counter checked by the principal investigator and co-investigator.

7.2. Data Entry and Storage

Data collection from the assessment will be stored electronically. The research data will be kept in a password-locked hospital computer (for softcopy data) and a locked cupboard (for hardcopy data). All data will be kept for at least six years after the study completion.

Data collected will only be viewed and accessed in the password protected hospital computer in co-investigator's and principal investigator's office.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

Our primary endpoint will be 4-metre fast gait speed at 3 months. Based on our previous work²⁴, we estimate a between-subject standard deviation of 0.30 m/s and a correlation of 0.70 between baseline and follow-up gait speed. Using an ANCOVA model²⁵ and setting a one-sided 2.5% significance level and 80% power, the required sample size to test comparative efficacy with a non-inferiority margin of 0.10 m/s is 72 participants per group. Allowing for an approximately 10% attrition rate, we will recruit 80 participants per arm. Given the relatively short 6-month follow-up period, we anticipate a drop-out rate < 10%.

8.2. Statistical and Analytical Plans

Data will be analyzed using both intention-to-treat and per-protocol approaches²⁵. Between-group difference in primary and secondary outcomes at 3- and 6-months post randomization will be analyzed using Bayesian linear mixed-effects models which include the baseline outcome measures, treatment group, age, sex, baseline knee pain intensity, follow-up timepoint, and timepoint-by-treatment interaction as independent variables. To avoid assuming linearity, all baseline outcome measures are modelled flexibly using a restricted cubic spline with three knots. To account for multiple observations from each patient, all models will use participant-level random intercepts. In the gait speed model, a non-inferiority margin of 0.10m/s is set. For the "treatment group" term, a weakly informative normal prior distribution centred at 0 with a 95% prior interval -0.20m/s to 0.20m/s will be used to reduce the likelihood of estimating unrealistic values without excluding reasonable values²⁶. Non-inferiority is established when there is $\geq 95\%$ posterior probability that fast gait speed is not more than 0.10m/s greater (faster) in the outpatient physiotherapy arm than in the MOKneeTOR arm. Table 1 provides the non-inferiority margins for all the outcomes.

As the ordinal secondary outcomes of treatment satisfaction, treatment recommendation, exercise compliance, and global rating of change (GROC) scores at 3 months post intervention are likely to show data clumping, we will fit separate Bayesian proportional odds logistic regression models²⁷ that will include as covariates age, sex, and baseline knee pain intensity level. For treatment satisfaction, treatment recommendation, and exercise compliance, the common odds ratio (OR) will be estimated and used to derive between-group differences in mean scores. Specifically, the OR will be transformed to an expected outcome score on the original scale through a weighted mean of the possible response levels with weights equal to the model-derived cell probabilities. For GROC, we will estimate for each group, the marginal probability of exceeding the threshold of achieving at least a minimally meaningful improvement (level 7), and we will compute the absolute between-group difference in exceedance probabilities, with corresponding posterior credible intervals.

In all analyses, weakly informative normal priors were specified for the regression coefficients of treatment group to reduce the likelihood of estimating unrealistic values without excluding reasonable values²⁶. Specifically, in linear mixed-effects models, we specified a normal prior distribution with a mean of 0 and a 95% prior interval with a half-width that was 2 times the non-inferiority margin of the outcome measure (Table 1). In ordinal regression models, we will specify a prior distribution centred at an odds ratio (OR) of 1.0 with a 95% prior interval of 0.33 to 3.0.

Economic evaluation

The primary economic evaluation will be a cost utility analysis involving the incremental cost per extra quality-adjusted-life-years (QALYs) gained (using the EQ-5D-5L over a 6-month follow-up). A societal perspective on costs will be taken. To estimate intervention cost, we will obtain, from medical records, data on the number of outpatient physiotherapy rehabilitation sessions received by each participant. We will use the modified OA Cost and Consequences Questionnaire (OCC-Q) to measure other health and home care services used, including the use of co-interventions and medications. We will use the absenteeism and presenteeism items from the Work Productivity and Activity Impairment Questionnaire (WPAI) to measure productivity losses (indirect costs). In sensitivity analyses, we will exclude from our sensitivity analyses the cost of productivity losses, with indirect costs evaluated as a clinical secondary outcome (in terms of time-off-work).

To compare the disaggregated costs between groups, Bayesian robust linear regression analyses will be used, adjusting the differences for age, sex, baseline utility, and employment status. To minimize influence of extreme values on the analyses, all models will use the Student t-distribution. To relax the assumption of homoscedasticity in linear regression, we will model the residual variance to vary with treatment groups. To simultaneously examine the between-group differences in total cost and effect, we will fit a Bayesian multivariate robust linear regression model, adjusting the differences for the same set of covariates. To limit the influence of extreme cost values, total costs will be winsorised at the 99th percentile prior to analysis, with the same threshold applied across treatment group. We will compute incremental cost-effectiveness ratios (ICER) and construct the cost-effectiveness (CE) plane by using the posterior samples of total cost and effect by treatment groups (CE pairs) from the Bayesian regression model. To complement the interpretation of the ICER, we will also calculate the net monetary benefit values for each treatment, based on a willingness to pay (WTP) threshold of S\$45,000/QALY. In sensitivity analyses, we will take a healthcare and personal social services perspective and exclude from our analyses the cost of productivity losses, with indirect costs evaluated as a clinical outcome (in terms of time-off-work).

Missing data management

Missing data were handled using full likelihood estimation in mixed-effects modeling. In other analyses (ordinal regression and economic evaluation), missing data will be handled using treatment group-stratified,²⁸ predictive mean-matching multiple imputation with 20 replications. Finally, we will perform modified intention-to-treat (mITT) analyses which included only patients with at least one follow-up outcome.

Table 1. Non-inferiority margin for individual outcome measures		
Outcome	Description	Non-inferiority Margin
Fast gait speed	The 4-metre fast-paced walk test will be measured using a time-of-flight sensor, with a 2.5-metre acceleration and deceleration zone before and after the timed section	0.10m/s ²⁹
Short Form of the Western Ontario and McMaster Universities Osteoarthritis Index function scale (ShortMAC-F)	The ShortMAC-F is a 7-item questionnaire designed to measure physical function. Each item was rated from 0 (none) to 4 (extreme), and the ShortMAC-F will be re-scaled to range from 0 to 100 points, with higher scores representing greater function	9.3 points ³⁰
Knee pain intensity	An 11-point numerical pain rating scale that enquires about the average knee pain over the past 1 week (range, 0-10, with 0 anchored at "no pain" and 10 anchored at "extreme pain")	0.95 points ³¹
5-times sit-to-stand test	The time taken to perform 5 chair stands will be measured using a phone accelerometer sensor. This timing (seconds/5 repetitions) will be transformed to the repetition scale (total repetitions/30 seconds), with higher scores representing better sit-to-stand performance	0.7 repetitions/30s ²⁹
Table 1. Non-inferiority margin for individual outcome measures		
Outcome	Description	Non-inferiority Margin
Quadriceps strength	Maximum quadriceps strength will be assessed on a seated knee extension machine using a standardized one	0.025kg/kg ³²

	repetition maximum (1RM) protocol. The strength value (in kg) will be normalized to participant's body weight.	
Quality-adjusted life year (QALY)	QALY was computed from the EuroQol-5D-5L (EQ-5D-5L) questionnaire	0.028 ³³
Treatment recommendation	Treatment recommendation is measured by how likely participants are to recommend their treatment to a friend or family member with knee arthritis using an 11-point numeric rating scale. A score of 0 indicates "Not at all likely," and a score of 10 indicates "Extremely likely."	1point*
Treatment satisfaction	Satisfaction with rehabilitation measured using a 11-point numerical rating scale, with 0 indicating "no satisfaction" and 10 indicating "complete satisfaction"	1point
Exercise adherence	Self-reported adherence with strengthening exercises is measured by the question "I do my knee strengthening exercises as often as recommended/advised". A 11-point numerical rating scale is used, with 0 indicating "strongly disagree" and 10 indicating "strongly agree".	1point
Global rating scale of change	This is measured using a 9-point ordinal scale, where 1 indicates "much worse" and 9 indicates "much better." Patients are considered improved if they rate themselves as at least "somewhat better, enough to be an important improvement." ($\geq$ Level 7).	0.10 [†]
<p>*The common odds ratio (OR) estimated from the ordinal regression models will be used to derive between-group differences in mean scores on the 11-point scale.</p> <p>[†]Treatment comparison is represented by the absolute between-group difference in the probabilities of meeting or exceeding a Level 7 rating.</p>		

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Principal investigator and co-investigator will check every fortnightly that this research study is carried out as per planned. Data collected will be critically evaluated by the principal investigator and co-investigator to ensure its accuracy and data quality.

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Study Protocol, including the final version of the Participant Information and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principal investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

11.1. Informed Consent

The participants will be recruited during their outpatient appointment session at the SGH rehab centre. Participants who consent to join the study will be given time to consider their participation before providing informed consent. All patients will be informed that they have the option to opt out of the study. Informed consent will be taken in the presence of a witness.

11.2. Confidentiality of Data and Patient Records

Patients recruited will be de-identified to ensure the confidentiality of recruited patients. Research data will be retained in a secured storage facility for minimum of 6 years after completion of research study or date of publication of the research using the research data, which is later.

12. PUBLICATIONS

Study team members and collaborators will be rightfully acknowledged for their contribution into this study. Singapore General Hospital will also be recognised as the contributing institution in this research study.

13. RETENTION OF STUDY DOCUMENTS

Research data will be kept in a password locked computer in the institution for soft copy data sets and locked cupboard for hard copy data sets. Research data will be kept for at least six years after the completion of this research study.

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