PROTOCOL TITLE:

Feasibility, acceptability, and preliminary efficacy of combined transcranial direct current stimulation and mindfulness for pain after total knee arthroplasty

PRINCIPAL INVESTIGATOR:

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	6/7/23	Removing fNIRS data collection	Yes

Table of Contents

1.0 Study Summary

Study Title	Feasibility, acceptability, and preliminary efficacy of combined transcranial direct current stimulation and mindfulness for pain after total knee arthroplasty
Study Design	Pilot randomized controlled trial
Primary Objective	Assess feasibility/acceptability of the intervention
Secondary Objective(s)	Assess preliminary effectiveness on pain intensity and pain interference with activities
Research Intervention(s)/ Investigational Agent(s)	Combined Mindfulness-based intervention (MBI) + transcranial direct current stimulation (tDCS) vs sham MBI+sham tDCS
IND/IDE #	
Study Population	Preoperative patients undergoing total knee replacement (TKR)
Sample Size	40
Study Duration for individual participants	1 month
Study Specific Abbreviations/ Definitions	CPSP: chronic post-surgical pain MBI: mindfulness-based intervention tDCS: transcranial direct current stimulation EG: experimental group CG: control group

2.0 Objectives*

2.1 The goal of this project is to assess the preliminary feasibility, acceptability, and efficacy of self-administered preoperative tDCS+MBI in older adults (50+) undergoing TKR. The central hypothesis is that combined preoperative tDCS+MBI will decrease postoperative analgesic consumption, postoperative clinical pain severity, as well as preoperative pain-related cortical response. We will accomplish three aims using a randomized controlled trial.

2.2 Hypotheses:

To determine the effects of 5, 20-minute preoperative self-administered tDCS sessions combined with brief MBI on analgesic medication consumption following TKR

Hypothesis 1: participants receiving preoperative active tDCS+MBI will show reduced postoperative analgesic consumption.

To determine the effects of 5, 20-minute preoperative self-administered tDCS sessions combined with brief MBI on postoperative pain severity following TKR

Hypothesis 2: participants receiving preoperative active tDCS+MBI will show reduced postoperative pain intensity and pain interference with physical and emotional function 5 days and 1 month after TKR.

To explore the effects of 5, 20-minute preoperative self-administered tDCS sessions combined with brief MBI on preoperative endogenous pain modulation

Hypothesis 3: participants receiving preoperative active tDCS+MBI will show improved preoperative endogenous pain modulation.

3.0 Background*

Osteoarthritis (OA) is a leading cause of disability with 32.5 million adults diagnosed in the United States (US)[1] and the number of people affected is predicted to climb conjointly with life expectancy[2]. TKR is among the three most common inpatient surgeries performed in the US[3], and patients undergoing TKR commonly experience acute pain and consume analgesic medications after surgery, more importantly in the first 48-72 hours[4,5]. While acute pain in the surgical context is expected, greater pain predicts worse outcomes for TKR patients, including chronic post-surgical pain (CPSP)[4,6] in up to 44% of patients, thus impacting their quality of life[6-8]. Opioid analgesics have traditionally been used to manage pain related to a TKR procedure[13,14]. However, the iatrogenic potential of opioids in the perioperative (e.g., respiratory depression, delirium) and postoperative phases (e.g., misuse, addiction, cognitive impairment, decreased level of activity)[15], particularly in older adults, has led to efforts in examining non-pharmacological pain management strategies [16,17]. Moreover, the current biopsychosocial framework for pain management calls for a multimodal approach[18].

4.0 Study Endpoints*

4.1 Measures will be taken by a research assistant via a telephone interview using a Qualtrics® survey. Outcome measures will be taken at 4 time points: 1) baseline (before preoperative active/sham tDCS+MBI), 2) after 5 sessions of preoperative active/sham tDCS+MBI, 3) after surgery, and 4) 1 month after surgery (see table below)

4.2 Primary endpoint: Analgesic consumption. The dose of every opioid received within 5 days postoperatively will be transcribed and converted into standardized parenteral morphine equivalents using the Centers for Disease and Control Prevention Guidelines on opioids [42]. A total in milligrams will be calculated for each day and means will be obtained for all groups.

4.3 Secondary endpoints: pain severity (numeric rating scale 0-100), pain interference with activities (numeric rating scale 0-10), depression and anxiety (PHQ-4), pain catastrophizing (Pain Catastrophizing Scale), multimodal quantitative sensory testing (QST) including heat pain (e.g., threshold, tolerance), pressure pain threshold, punctate mechanical pain (e.g., suprathreshold ratings and temporal summation), and Conditioned Pain Modulation (CPM), acceptability and feasibility

Day/month	B	Preoperative phase	Postoperative phase

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 1	Day 2	Day 3	Month 1
Medical History Questionnaire	X									
Analgesic consumption (primary outcome)							X	X	X	X
Clinical Pain severity (secondary outcome)										
NRS	X					X			X	X
BPI	X					X			X	X
PHQ-4	X					X			X	X
PCS	X					X			X	X
Pain-related Cortical Response (secondary outcome)										
QST measures	X					X				
Acceptability and feasibility										
tDCS + MBI experience questionnaire						X				
Side effects questionnaire		X	X	X	X	X				

5.0 Study Intervention/Investigational Agent

5.1 Dr Ahn's laboratory research coordinator, Lindsey Park, who is the research coordinator for previous and ongoing tDCS studies (R01NR019051 and R15NR018050), will be responsible for coordinating and supervising the intervention sessions. Equipment will also be provided by Dr Ahn's lab. Participants will receive a brief training at the lab to explain the procedure and how to use the device at the time of enrollment (after their preoperative visit at the clinic). Participants will go home with the tDCS device and videoconference meetings will be scheduled for the monitoring of sessions. Each session will start with tDCS and end with a brief mindfulness meditation using audio recording, i.e., 3-minute breathing space. This exercise is a well-established strategy that is being used in MBI for acute pain[19] and chronic pain[35].

6.0 Procedures Involved*

6.1 This study will use double-blind randomized sham-controlled design with an allocation ratio of 1:1 with repeated measures at 4 time points. Participants will be randomly assigned to one of 2 arms as follows: 1) preoperative active tDCS+MBI or 2) preoperative sham tDCS+MBI. Participants will be recruited at their preoperative visit (see letter of collaboration). A clinician (registered nurse or surgeon) or a research coordinator from the clinic will review the preoperative

clinic schedule, conduct a pre-screening of potentially eligible participants, and introduce the study to potential participants at their preoperative visit by using a flyer. If the individual agrees to learn more, the PI or RA (Katherine Lewis) will enter the room to discuss study, answer questions and sign the consent. If they agree to participate, after signing the consent, they will be invited to come to the brain stimulation laboratory (FSU innovation park) where a baseline assessment will be done before randomization by the RA or lab research coordinator (Lindsey Park). The tDCS device along with instructions will then be provided. The baseline visit will take approximately 2 hours. The preop procedures will be as follows with T = day of surgery:

T-7: Recruitment/Consent
T-6: Baseline lab measurements & tDCS fitting and training
T-5: AM & PM remote tDCS/MBI
T-4: AM & PM remote tDCS/MBI
T-3: AM remote tDCS/MBI + Post-intervention lab measurement & collect tDCS equipment

6.2 Measures:

Usual sociodemographic variables (i.e., age, sex, civil status, living conditions, education level, and employment status) will be assessed. Relevant medico-surgical information during hospitalization will be collected: type of surgery, postoperative complications, and current involvement in a rehabilitation program. The presence of chronic pain before surgery will also be documented.

Outcome measures will be taken at 4 time points: 1) baseline (before preoperative active/sham tDCS+MBI), 2) after 5 sessions of preoperative active/sham tDCS+MBI, 3) after surgery, and 4) 1 month after surgery. Table 1 gives an overview of all measures for the preoperative and postoperative phases.
Analgesic consumption. The dose of every opioid received within 5 days postoperatively will be transcribed and converted into standardized parenteral morphine equivalents using the Centers for Disease and Control Prevention Guidelines on opioids [42]. A total in milligrams will be calculated for each day and means will be obtained for all groups.
Pain severity. Pain intensity is a global indicator of the pain experience. It will be assessed with *a numerical rating scale (NRS) (0-100)* with the anchors being no pain at all (0) and worst possible pain (100). This type of scale is recognized for its reliability, validity and sensitivity in various clienteles and settings [41,43,44] and is a reliable and well-validated measure with good ability to detect pain change in adults with knee OA [45]. Four different measures of pain intensity will be taken: 1) average pain upon movement in the past 7 days, 2) worst pain upon movement in the past 7 days, 3) present pain upon movement, and 4) present pain at rest. As suggested by the IMMPACT group in regard to pain core domains in clinical trials [41,46], the impact of pain on various aspects of daily living will be assessed with interference items of the *Brief Pain Inventory (BPI)* [47]. The BPI has been successfully validated patients suffering from OA and undergoing TKR [6,48]. It includes seven items and evaluates the *impact of pain on general activity, mood, walking, work, relationships, sleep, and enjoyment of life via a NRS (0-10)*. Each item represents a subscale and can be scored and analyzed individually (0-10), with the anchors being “does not interfere” (0) and “completely interferes” (10). A total interference score can also be calculated by taking the sum of all the items. Additionally,

with regards to emotional function, considering established relations between pain, anxiety, and depression [49], measures of anxiety and depression will be taken with the *Patient Health Questionnaire-4 (PHQ-4) for depression and anxiety* at all time points [50]. Total score is determined by adding together the scores of each of the 4 items. Scores are rated as normal (0-2), mild (3-5), moderate (6-8), and severe (9-12). Total score ≥3 for first 2 questions suggests anxiety. Total score ≥3 for last 2 questions suggests depression. The validity and reliability of the Patient Health Questionnaire-4 has been well established including with surgical clienteles [51,52]. The *Pain Catastrophizing Scale* [53] will be used to assess patients' pain-related catastrophic thoughts. It includes 13 items divided into three subscales: rumination (4 items), magnification (3 items), and helplessness (6 items). Each item is rated on a 5-point scale with the end points not at all (score=0) and all the time (score=4). The total score and scores for each subscale can be calculated by taking the sum of the items. The Pain Catastrophizing Scale has demonstrated an excellent internal consistency, and its sensitivity in the context of chronic pain has been established [54,55]. Pain severity will also be measured 1 month after surgery to explore sustained efficacy of combined tDCS+MBI on the incidence and severity of persistent post-surgical pain.

A *multimodal Quantitative Sensory Testing (QST)* battery will be completed: heat pain (e.g., threshold, tolerance), pressure pain threshold, punctate mechanical pain (e.g., suprathreshold ratings and temporal summation), and Conditioned Pain Modulation (CPM). These measures, which were utilized in our previous and ongoing study (R01NR019051 and R15NR018050), will be assessed using equipment and methods available at the Dr. Ahn's laboratory, including a Medoc TSA-II Neurosensory Analyzer and Wagner pressure algometer.

Acceptability and feasibility. We will collect data on *participants' tDCS experience* via a questionnaire, at the conclusion of tDCS treatment on a 0 (strongly disagree) to 10 (strongly agree) scale: 1) It was easy to prepare the device and accessories; 2) The device was unnecessarily complex; 3) The device was easy to use; 4) I felt the video conferences with a technical person were helpful; 5) I would imagine that most people would learn to use this device quickly; 6) The device was cumbersome to use; 7) I felt confident using the device; 8) I needed to learn a lot of things before I could get going with this device; 9) The effectiveness of the treatment increased over the course of treatment; 10) Overall, I felt that transcranial electrical stimulation treatment benefited me. Moreover, we will evaluate the presence and severity of possible side effects of treatment at the end of each session on a 0 (not at all) to 10 (highest degree) scale. By using open-ended questions, the participants will be asked whether they experienced any side effects, and they will then be asked specifically about tingling, itching sensation, burning sensation, pain at the stimulation site, fatigue, nervousness, headache, difficulty concentrating, mood change, and changes in vision or visual perception. If any side effects are reported, the degree of relatedness to the intervention will be assessed on a 5-point scale. This approach has been used in our previous study and frequently in other studies [58-60]. Regarding *feasibility,* we will calculate the percentage of participants who a) met the inclusion criteria, b) agreed to be randomly assigned, c) completed the full tDCS+MBI protocol, and d) attended the follow-up assessment.

6.3 Treatment conditions:

The Food and Drug Administration (FDA) has ruled that the aforementioned tDCS stimulator is a "non-significant risk" device, a requirement for Investigational Device Exceptions. For pain treatment, tDCS is typically delivered

with the anode electrode placed over the primary motor cortex (M1) and with the cathode electrode placed over the supraorbital region (SO)[36,37]. A panel of experts from the European Chapter of the International Federation of Clinical Neurophysiology recommends 20-minute M1-SO stimulation using 2 mA electrical current intensity for possible efficacy among populations with chronic pain[38]. tDCS with a constant current intensity of 2 mA will be applied for 20 minutes per session twice a day for 2.5 days before surgery (preop tDCS) via the Soterix 1x1 tDCS mini-CT Stimulator device (Soterix Medical Inc., NY; 6.5 inches long, 3 inches wide, 0.7 inches thick) with headgear and 5x7 cm saline-soaked surface sponge electrodes. The sponge electrodes snap into the custom headgear, which is secured to the participant's head for simple and fail-safe electrode preparation. This single-position headgear with clearly labeled sponge markers eliminates room for user error and helps conserve the placement of the montage. Participants can only administer a stimulation session via the Soterix 1x1 tDCS mini-CT Stimulator device after being provided a single-use unlock code by the research staff once proper contact quality is achieved (only the on/off button is adjustable by the study participants; they will not able to adjust the device settings). After the participant enters the unlock code, the screen on the device will show a timer that counts down the minutes until the end of the session. At 20 minutes, the device will turn off automatically, and study staff will instruct the participant to remove the headset and discard the sponges and to safely store all materials for the next session.

For preoperative sham stimulation, the electrodes will also be placed twice a day for 2.5 days in the same positions as for active stimulation, but the stimulator will only deliver 2 mA current for 30 seconds. This sham stimulation method has been shown to be reliable and indistinguishable from active treatment[39,40]. Regarding sham brief MBI, participants will be invited to practice a standard relaxation exercise for 3 minutes by listening to an audio recording.

7.0 Data and Specimen Banking*

7.1 Data (questionnaires, sociodemographic and clinical info) will have identifiers removed and banked indefinitely. Data will be available to research team, PI, RA, statistician. Data will be stored on a password-protected computer. The computer will be stored in a locked room.

8.0 Sharing of Results with Subjects*

8.1 Data will be released to participants upon request and approval by PI (HIPAA). De-identified datasets will be available to the scientific community upon request (depending on the journal policy in which results will be published).

9.0 Study Timelines*

- *The duration of an individual subject's participation in the study: 1 month*
- *The duration anticipated to enroll all study subjects: 6 months*
- *The estimated date for the investigators to complete this study: 7 months*

10.0 Inclusion and Exclusion Criteria*

Inclusion criteria: elective unilateral knee total replacement, (4) mentally capable of reading, giving consent and following instructions, (5) being able to answer questions in English, (6) not pregnant. Exclusion criteria include: (1) history of brain surgery, brain tumor, seizure, stroke, or intracranial metal implantation, (2) systemic rheumatic disorders, including rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia, (3) alcohol/substance abuse, (4) current use of sodium channel blockers, calcium channel blockers and NMDS receptor antagonists, (5) hospitalization within the preceding year for psychiatric illness, and (6) no access to a device with internet access that can be used for secure videoconferencing for real-time remote supervision.

Following populations will not be included:

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

11.0 Vulnerable Populations*

11.1 N/A

12.0 Local Number of Subjects

12.1 N=40 (completers)

13.0 Recruitment Methods

An experienced research assistant (RA) and/or the PI will be responsible of participants' recruitment and informed consent procedures.
The research coordinator (Phillip Worts) will review the preoperative clinic schedule. The individual will conduct a pre-screening of potentially eligible participants (see attached HIPAA waiver). A clinician (Registered nurse, Victoria Haley) will introduce the study to potential participants at their preoperative visit by using a flyer. If the individual agrees to learn more, the PI or RA will enter the room to discuss study, answer questions, sign the consent and schedule the visit to the lab. Before any in-person interaction, COVID-19 screening will be conducted.

The PI and RA are fully vaccinated, they will use the CDC self-checker tool and wear a mask at all times, as well as respect the clinic's current policies. Patients usually receive a COVID screening before starting their visit at the clinic and the clinician will inform them about FSU COVID-19 precautions and distribute the FSU Information sheet.

13.1 Source of subjects: community/outpatient clinics

13.2 Participants in both groups will receive gift cards of $100 at the end of the study.

14.0 Withdrawal of Subjects*

14.1 Participants will be withdrawn without their consent if complications occur during their postoperative recovery and they need to be re-admitted to the hospital.

15.0 Risks to Subjects*

15.1 No adverse events have been reported in relation to mindfulness-based intervention or tDCS. We have conducted several studies on tDCS and patients minimal side effects such as slight itching (present in 30% of people as reported by systematic reviews) or tingling on the scalp (present in 70% of people as reported in systematic reviews). Although we have not observed other side effects. Systematic reviews report the possibility of dizziness in 10% of people, nausea in 3% and headache in 11% of people. The Food and Drug Administration (FDA) has ruled that the aforementioned tDCS stimulator is a "non-significant risk" device, a requirement for Investigational Device Exceptions.

15.2 Patients may feel tired while completing questionnaires, but they can pause and resume at any time. Individual interviews and some items from questionnaires may allow emotions related to the experience of a major surgery to emerge. If psychological distress becomes obvious (verbatim or score on a questionnaire), the provider will be informed for follow-up and the patient will be encouraged to communicate with the clinic.

16.0 Potential Benefits to Subjects*

16.1 Based on previous studies, participants may use less opioids and experience less pain and anxiety. This reduction may allow for a better recovery and return to activities.

17.0 Data Management* and Confidentiality

17.1 The protocol will favor an intention-to-treat approach for the analysis of results.

Data analysis will be performed with R (Vienna, Austria) version 4.1+. Baseline demographic information will be summarized using descriptive statistics. Continuous variables will be summarized with means and standard deviations. Categorical variables will be summarized with counts, proportions, and medians (interquartile range). The distribution of all variables will be examined before any analysis, using appropriate statistical tests like Shapiro's test for normality checking. If the assumption of normality is not met, equivalent non-parametric approaches or data transformation will be employed. The multiple testing problem will be accounted for using Bonferroni correction. All testing will be two-sided and 0.05 will be used as the familywise significance level. If needed, statistical analysis will also be conducted after controlling for baseline demographics and clinical characteristics (e.g., age, sex, and race).

For Aim 1, analgesic consumption measured on 3 consecutive days will be summarized into one number for each subject. Two-sample t-test (or non-parametric alternative) will be employed to determine the significance of the difference between the active and the sham tDCS+MBI groups. Multivariate linear regression will be further employed to account for potential confounding factors, including selected baseline demographics and clinical characteristics (e.g., age, sex, race, and body mass index). For Aim 2, we will conduct multivariable regression analysis to compare the change in clinical pain intensity (NRS, BPI, PHQ-4, PCS) from baseline to Day 3 in the postoperative phase after controlling for baseline and other confounding factors (e.g., age, race, sex, baseline NRS, consumption of pain medications). We will also determine whether the improvement conferred by active tDCS+MBI can be sustained by comparing the clinical pain intensity changes from baseline to 1 month between the active and the sham groups. We will also conduct sex-stratified analysis and explore whether there exists sex difference in these effects. For Aim 3, the QST dataset for endogenous pain modulation will be analyzed using multivariate linear regression for changes in each of the QST measures against potential confounding factors, and backward stepwise variable selection will then be performed to identify the parsimonious model structures. Spearman rank-order correlation will be used to quantify the association between changes in each of the QST measures and the changes in clinical pain intensity (NRS).

17.2. The PI, RA and research coordinator received the CITI training. Data will be de-identified and a code will be assigned to each participant.

17.3 Data entry will be validated at random.

17.4 Data (questionnaires, sociodemographic and clinical info) will have identifiers removed and banked for a minimum of 3 years per Federal regulations. Deidentified data will be available to research team: PI, co-I (Dr Ahn and Dr Johnson), RA, statistician (Dr Miao, CON). Data will be stored on a password-protected computer. The computer will be stored in a locked room. Any data collected online will be stored on an encrypted data server at the CON. Any downloaded data will be stored on a password protected computer. The RA supervised by the PI will be responsible for data receipt. Dr Ahn and Dr Johnson will assist with results interpretation.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

Dr Martorella has the primary responsibility for monitoring study research staff. Research team will receive training on the study design, recruitment and protocol. Weekly meetings will take place with study staff to ensure protocol adherence and monthly meetings with co-investigators to discuss any issues. Patients' experiences and any potential adverse events will be reviewed and discussed. Each treatment session will be remotely supervised via zoom and after each session any potential side effects will be investigated and documented by the research coordinator (see questionnaires), Lindsey Park. This monitoring will be continued after surgery for the remainder of the data collection (up to 1 month).

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Privacy interest protection is increased by the use of online data collection and intervention tools. Regarding individual interviews, we believe that the questions will not be perceived as intrusive as they only address the intervention and its convenience for patients. However, we will highlight that there is no obligation to answer. Also, if participants prefer not to be recorded, we will take notes on their response and not use the recorder.

19.2 We will explain to the participants that they can complete questionnaires and strategies at their own pace and that if they feel that a question is making them uncomfortable, they have no obligation to respond.

20.0 Compensation for Research-Related Injury

20.1 N/A

21.0 Economic Burden to Subjects

21.1 N/A The intervention is provided remotely. All necessary materials and equipment will be provided. Data collection will be remotely as well. The only time participants will travel to the lab is at the time of the preoperative visit so they can get equipment and baseline data can be collected.

22.0 Consent Process

22.1 If the patients are interested in participating,

A clinician/research coordinator from TOC will introduce the study to potential participants at their preoperative visit by using a flyer, and if the individual agrees to learn more, the PI or RA will enter the room to discuss study, answer questions and have the participant sign the consent

on a printed copy. Once the study team member will have countersigned the consent, a copy will be provided to the participant and a copy will be kept by the study team in a locked cabinet in the PI's office. the *Before any in-person interaction, COVID-19 screening will be conducted. Although, the PI and RA are fully vaccinated, they will use the CDC self-checker tool and wear a mask at all times. Patients usually receive a COVID screening before starting their visit at the clinic and the clinician will inform them about FSU COVID-19 precautions. An FSU information sheet on FSU COVID-19 precautions will also be distributed at the time of consent.*

We believe that the study will be perceived as being independent from the clinical setting and that participants will not experience undue influence. Moreover, it will be underlined that participating in the study or not will not affect the care they receive.

22.2 Participants will be adults, not cognitively impaired, who can understand and read English and able to consent. No vulnerable populations will be involved.

23.0 Process to Document Consent in Writing

23.1 The consent will be obtained and signed on paper at the preoperative clinic or at the lab baseline visit.

24.0 Setting

24.1 Participants will be recruited in the community during their preoperative visit. All intervention and assessment procedures will be performed remotely, online or via telephone, except for the consent and baseline questionnaire (baseline visit) and one follow-up visit before surgery (after the preoperative intervention). Telephone/zoom interviews will be done from Dr Ahn's lab at innovation park.

24.2 The FSU CON is well equipped for any size research project. The CON provides significant research resources for faculty including, 1) computers and computer technical support; 2) day-to-day financial oversight of grants; 3) assistance with financial reporting for project annual and final reports; and 4) consultation on research design, data analysis and dissemination. Dr. Martorella (PI) maintains individual office in the center. Each office contains a computer and laser printer. The center also houses a research conference room that can be used to meet with members of the research team. Telephone and video-conferencing equipment and programs (i.e., Skype, GoToMeeting) are also available in each of the research team member's offices. Designated office space for federally funded research is available within the TMH Center for Research and Evidenced-Based Practice, in addition to a dedicated

file room to store study-related documents and participant files. The College of Nursing provides staff experienced in processing (i.e., collecting, inputting, coding and cleaning) high volumes of data including a dedicated data analyst who works solely on CON research, systems for instrument development and piloting including large scale distribution of surveys, servers and clusters for high demand computing, and network bandwidth to accommodate high volume Internet traffic.

25.0 Resources Available

25.1 Dr David Bellamy (TOC) does an average of 4 knee surgeries per week. Considering a potential refusal rate of 30%, it is anticipated that the recruitment will require at least 14 weeks if they meet all criteria.

25.2 A RA will be trained and fully devoted to the project

25.3 Participants are being followed by a team of clinicians (clinic and/or rehab) because of their recent major surgery, thus they have access to medical resources.

26.0 Multi-Site Research*

This is not a multicenter study.