A multidisciplinary intervention in total knee arthroplasty - a multicenter, randomized controlled trial in osteoarthritis patients (MULTI-KNEE trial).

This is a protocol for a multicenter, three-armed, randomized controlled trial (RCT). An estimated one in five patients undergoing total knee arthroplasty (TKA) does not improve in pain and function, suggesting that among the 6466 patients who underwent primary TKA in Norway in 2016, more than 1200 patients derived little or no benefit from the surgery and continue to experience chronic pain. In addition, these numbers suggest that more than 100 000 000 NOK are spent every year on an invasive treatment with questionable effect[1]. This study will evaluate the effect of a multidisciplinary intervention delivered either as a substitute, or in addition to, TKA for patients identified as being at risk for non-improvement after TKA.

Hypotheses, aims and objectives

The overall aim of this study is to test the effectiveness of a 12-week integrated Physiotherapy (PT) group exercise program in combination with cognitive behavioral therapy (CBT) support, delivered by physiotherapists, in patients with knee osteoarthritis (OA) who are on a waiting list for TKA and who are identified as being at risk for non-improvement based on a set of preoperative criteria. The effects of the integrated PT exercise program and CBT will be evaluated both as a substitute for TKA and as a supplement to TKA in comparison to TKA alone. We hypothesize that for patients identified as being at risk for postoperative non-improvement: 1) the effect of PT exercise and CBT alone will be equivalent to surgical treatment alone, and 2) the effect of PT exercise and CBT in combination with surgical treatment will be better than surgical treatment alone. The effects of the three treatments will be evaluated in terms of pain relief (primary outcome), functioning and quality of life (QOL) (secondary outcomes) at 12-month follow-up. The study includes a pilot study with 15 participants prior to the full-scale study.

This large study consists of four sub-studies and a pilot study, each with individual aims.

The pilot study has the following aims:

- To evaluate the feasibility of the multidisciplinary intervention alone and as a supplement to TKA
- To evaluate the rate of recruitment, patients' willingness to participate and adherence to the intervention
- Investigate patients' experiences with participation in the study

Sub-study 1 has the following aims:

1a) Investigate the effectiveness of the multidisciplinary intervention alone and as a supplement to TKA in comparison with TKA alone, on pain measured by the Knee Injury and OA Outcome Score (KOOS) at 1-year follow-up (primary outcome)
1b) Investigate the effectiveness of the multidisciplinary intervention alone and as a supplement to TKA on the KOOS subscores function and stiffness
1c) Evaluate adverse events in the three study arms during the first year following randomization

S**ub-study 2** has the following aims:

2a) Evaluate the adherence and feasibility of the multidisciplinary intervention in a feasibility study
2b) Determine the effects of the multidisciplinary intervention, on lower extremity strength and range of motion at 12 months follow-up
2c) Investigate the effects of the multidisciplinary intervention on health-related quality of life at 12 months follow-up

Sub-study 3 has the following aims:

3a) Investigate the cost-effectiveness of the multidisciplinary intervention alone and as a supplement to TKA, in comparison with TKA alone
3b) Assess the use of health care resources at 2-year follow-up in the 3 treatment arms
3c) Assess the use of medication at 2-year follow-up in the 3 treatment arms

S**ub-study 4** has the following aims:

4a) Compare the effect in the 3 treatment arms on sports and recreation, walking and physical performance 2 years following the intervention
4b) Investigate the longitudinal relationship between pain catastrophizing, fear of movement and depression, on functional levels in the 3 treatment arms during the 2 years following the intervention
4c) Identify barriers to and benefits of increased adherence to physical activity in patients with painful knee OA

Methods/Design

This is a multicenter randomized controlled trial with three arms: 1) PT + CBT intervention alone, 2) PT + CBT in combination with TKA, and 3) standard care control group receiving TKA. The protocol adheres to the CONSORT guidelines and to the principles of the Declaration of Helsinki, and is approved by the The Regional Medical Research Ethics committee of Health East of Norway (2017/968).

Project arrangements, method selection and analyses

Intervention

The PT component of the intervention will be based on the evidence-based AktivA program, which is the Norwegian equivalent of Sweden's Better Living with OsteoArthritis (BOA)[2] and Denmark's Good Life with OsteoArthritis (GLA;D) programs[3], developed specifically for hip and knee OA. The GLA;D program reduced pain in patients with hip and knee OA and the results were sustained for 12 months[3].

The CBT component of the intervention will be delivered as an e-therapy program using text combined with animated videos. The e-learning program is currently under development for this study in close cooperation with Braive A/S and will be based on Linton's standardized CBT intervention program for pain-related disability and pain chronicity[4], modified for OA patients[5].

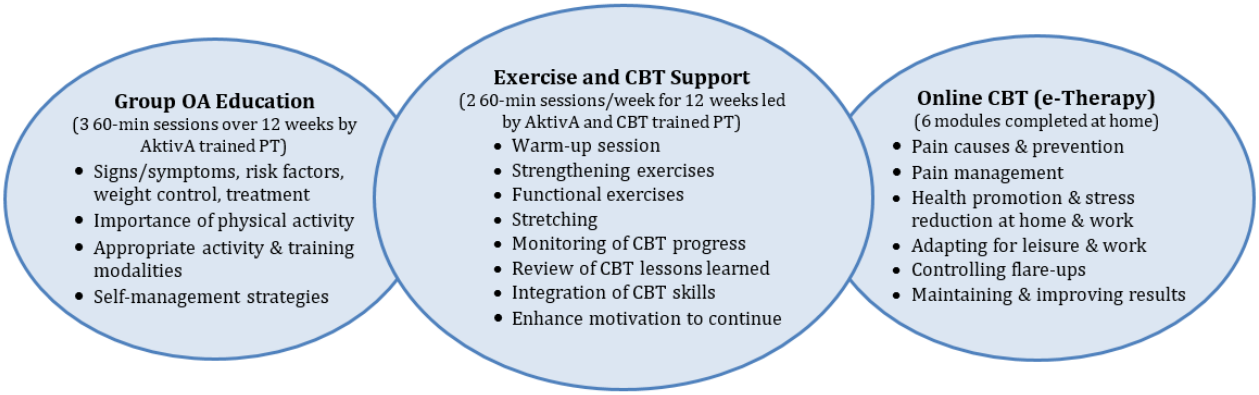
Physiotherapist certification: PTs who will deliver the intervention will participate in a full day interdisciplinary certification course delivered by an orthopedic surgeon, PTs, a nutritionist, and a patient with OA to provide a user perspective. Upon completion, the PTs will be certified AktivA providers.

All physiotherapists will also participate in a CBT education program led by a psychologist. The goal is to enable the PTs to be mentors for the participants' progress in their e-learning program, monitor the patients' progression and help the patients to integrate their new skills into their physical activity program. A manual will be developed and made available for the physiotherapists. The psychologist will then serve as a consultant to the physiotherapists.

The intervention will consist of the following elements (See Figure 1):

- Group OA education (a theoretical patient education program).
- Exercise therapy program consisting of a physical activity program with integration of CBT skills) [6]. This part of the intervention is led by an AktivA certified PT who is also trained to support and integrate the CBT e-therapy program.
- CBT e-therapy program that consists of 12 modules focused on training in a number of pain coping skills. Participants complete this part of the intervention at home and at their own pace.

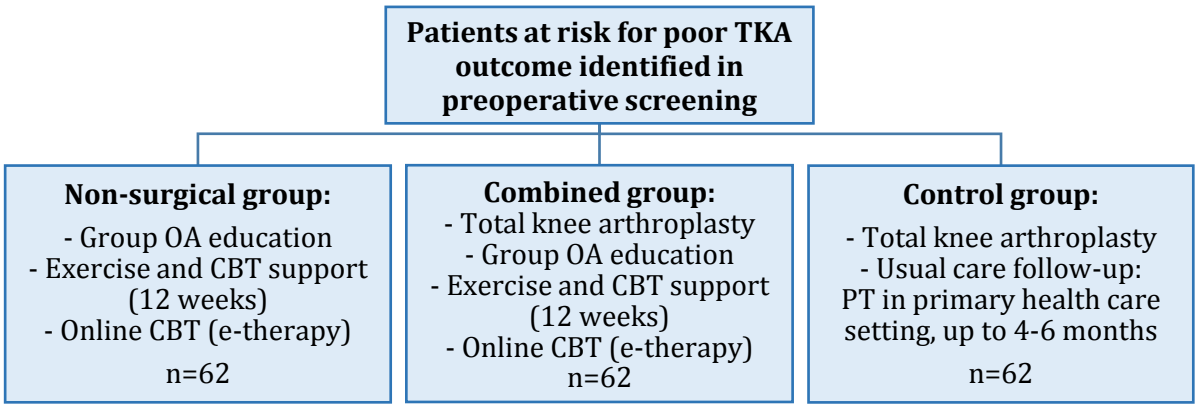
Figure 1 – overview of the components of the intervention.



Recruitment and allocation

All patients scheduled for TKA at the two surgical clinics (i.e., Lovisenberg Diaconal Hospital (Lovisenberg), Kysthospitalet Hagevik (Hagevik)) will be screened prior to their consultation with their orthopedic surgeon. The screening will be performed using a validated prioritization algorithm developed by Escobar and Riddle[7-9], using the following preoperative predictors: preoperative pain and function; presence of widespread pain; and the following additional factors: anxiety/depression; pain catastrophizing; coping strategies. The additional predictors were selected based on findings from our previous studies[10, 11] and the literature[12]. Based on this screening, each patient will be categorized as either inappropriate/inconclusive, or appropriate for surgery. The surgeon and patient will be blinded to the result of the screening during the consultation. The surgeon will receive a sealed envelope with the result of the screening. After the surgeon and the patient have jointly decided to schedule the patient for TKA, the surgeon will open the envelope. Patients categorized as inconclusive/inappropriate will be invited to participate in the study. Patients who consent to participate will then be randomly allocated to one of the intervention groups or the control group using allocation numbers in sealed envelopes. The envelopes will be prepared before initiation of the trial by an independent staff member, and distributed to the two study sites (Lovisenberg and Hagevik). The envelopes will be kept in a locked location only available to the research assistants at each study site. Reasons for not participating will be recorded.

Figure 2 – allocation of patients into 3 treatment arms



Patients who meet the following inclusion criteria will be eligible for the study: 1) scheduled for TKA for OA at Lovisenberg or Kysthospitalet Hagevik, Bergen, 2) Charnley comorbidity classification A, B or C, 3) ASA grade 1 and 2, and 4) BMI<40, 5) able to read and write in Norwegian. In addition, the patient must be identified as being at high risk for an unsuccessful outcome after TKA based on cutoff scores on 2 or more of the following screening criteria, whereof one must be within the physical components, and one must be within the psychological components of the screening criteria:

- Age <55 years
- Preoperative pain and function level: The Knee Injury and OA Outcome Score (KOOS) pain and physical scale combined[9], cutoff ≤22.
- Presence of multiple painful sites/widespread pain (number of painful sites, cutoff score= ≥2)
- Tendency for pain-related catastrophizing (Pain Catastrophizing Scale (PCS), cutoff ≥30)
- Pain-related fear of movement (Fear-Avoidance Belief Questionnaire (FABQ), cutoff >14,9)
- Anxiety/depression (Hospital Anxiety and Depression (HADS) subscale scores: >11)

Exclusion criteria: Diagnosis of dementia, rheumatic disease, prior or current participation in a CBT or AktivA program.

Baseline data will be collected as a part of the screening, prior to consultation with the orthopedic surgeon. The remaining baseline data will be collected after inclusion in the study. Blinding of participants and health personnel to the allocation groups will not be possible due to the nature of the intervention. Follow-up measurements will be performed after 3, 6, 12 and 24 months and self-reported data will be collected electronically using ipads connected to a secure wireless net using the TellMe system. Data will be stored in secure research databases at Lovisenberg and Hagevik.

Pilot study (Feasibility study).
A pilot study will be performed prior to the full-scale study. The pilot study will take place at Lovisenberg and will include 15 patients who will be randomized to one of the three allocation groups and followed according to the above described protocol. The aim of the pilot study is to evaluate the feasibility of the study, assess patients' willingness to participate in the study and estimate expected rate of inclusion, adherence to the intervention among participants, and patients' experiences with participating in the study. The results will be used to modify and optimize the study protocol for the full-scale study.

Primary outcome
The primary outcome will be the pain subscore from the KOOS at 12 months. The KOOS is a knee joint specific questionnaire developed in 1998 for the purpose of evaluating short-term and long-term symptoms and functioning in subjects with knee injury and OA. KOOS is a 42-item survey designed to assess people's opinions about the difficulties they experience with activity due to problems with their knees during the past week. Each of the 42 items carries equal weighting (0–4), with higher scores indicating better outcomes. KOOS has 5 subscales: pain, other symptoms, activities of daily living (ADL), function in sport and recreation, and knee-related QOL. Scores are transformed to a 0-100 scale, with 0 representing extreme knee problems and 100 representing no problems. The KOOS has been validated for use in TKA and has been shown to be a valid, reliable and responsive measure[13].

Secondary outcomes will include the 4 remaining KOOS subscales and the following additional measures:
Patient-reported outcomes
Pain intensity and interference with functioning: the Brief Pain Inventory[14].
Sleep quality: the Pittsburgh Sleep Quality Index (PSQI)[15].
Pain Catastrophizing: the Pain Catastrophizing Scale (PCS)[16].
Pain-related fear of movement: the Fear-Avoidance Belief Questionnaire (FABQ)[17].
Mood states (depression and anxiety): the Hospital Anxiety and Depression Scale (HADS) [18].
Health-related quality of life (HRQoL): EuroQol-5D-3L (EQ-5D-5L)[19].

The Health Locus of Control Scale (HLCS) will be used to measure patients' anticipations between own health and disease behavior and consequences of the behavior[20].
The Forgotten Joint Score will be used to assess how natural the prosthesis feels after TKA[21].
Anchor measures: Patient acceptable symptom state, treatment failure, global perceived effect.

Clinical assessments
Knee functioning: the new American Knee Society Score (AKSS)[22].
Comorbidity will be measured with the Self-Administered Comorbidity Questionnaire (SCQ-19)[23].
Time in activity, number of steps: ActivePal Professional single-axis accelerometer[24].
Functional lower extremity strength: the 30-second sit to stand test[25].
Walking speed will be measured using the 6 minutes walk test.

Radiological assessments
X-rays including weightbearing AP, lateral view, Rosenberg view and long leg weightbearing AP view (HKA), preoperative and at 24 months. OA grading according to Kellgren-Lawrence and Ahlbachs[43].

Table 1 study measures

Construct assessed	**Data collection instrument**	**Time of collection**
Primary outcome measure	*Proms*	
Pain	Pain subscale of the KOOS	0, 3, 6, 12 and 24 months
Secondary outcome measures	**Data collection instrument**	**Time of collection**
	Proms	
Pain, symptoms, ADL, QOL, sport & recreation	The five individual subscales of the KOOS	0, 3, 6, 12 and 24 months
Self-reported level of physical activity	HUNT2, Stages of Change physical activity	0, 3, 6, 12 and 24 months
Co-morbidity	The Self-Administered Co-Morbidity Questionnaire	0 months
Pain, interference with functioning, number of painful sites	Brief pain inventory	0, 3, 6, 12 and 24 months
Sleep	Pittsburgh Sleep Quality Index	0, 3, 6, 12 and 24 months
Catastrophic thinking related to pain	Pain Catastrophizing scale	0, 3, 6, 12 and 24 months
Locus of control	The Health Locus of Control Scale	0, 3, 6, 12 and 24 months
Pain-related fear of movement	The Fear-Avoicance Belief Questionnaire	0, 3, 6, 12 and 24 months
Mood states	The Hospital Anxiety and Depression Scale	0, 3, 6, 12 and 24 months
Health-related quality of life	EuroQol-5 (EQ5D-5L)	0, 3, 6, 12 and 24 months
Natural feeling of joint	Forgotten Joint Score	0, 3, 6, 12 and 24 months
Anchor measures of satisfaction	Patient acceptable symptom state	0, 3, 6, 12 and 24 months
	Treatment failure	0, 3, 6, 12 and 24 months
	Global perceived effect	0, 3, 6, 12 and 24 months
	Objective measures	
Functional lower extremity test	The 30 second sit to stand test	0, 3, 6, 12 and 24 months
Walking	6 minutes walk test	0, 3, 6, 12 and 24 months
Body mass index	Weight from baseline to follow-up	0, 3, 6, 12 and 24 months
Time in active position/number of steps	The ActivePal Professional Single Axis accelerometer	0, 3, 6, 12 and 24 months
Radiological measurements	Weightbering AP, lateral view, Rosenberg view and long leg weightbearing AP view (HKA)	0 and 24 months
Other measurements		
Adverse events	Physiotherapy-reported, patient-reported, medical records	0, 3, 6, 12 and 24 months
	Registry-based data	
Use of health care resources	The KUHR-system	0, 3, 6, 12 and 24 months
	The Norwegian Patient Registry	0, 3, 6, 12 and 24 months

	FD trygd social security data base	0, 3, 6, 12 and 24 months

Outcomes, Feasibility study		
Adherence to intervention	Records, physiotherapists. Data, eTherapy.	0, 3, 6, 12 and 24 months
Acceptability of the intervention	Questionnaires, interviews	0, 3, 6, 12 and 24 months
Adverse events	Patients, physiotherapists, medical records	0, 3, 6, 12 and 24 months
Recruitment, screening, randomization	Flow chart, inclusion and exclusion	0, 3, 6, 12 and 24 months
Retention in study/loss to follow-up	Loss to follow-up, crossover	0, 3, 6, 12 and 24 months

Registry-based data

Use of health care resources: registry data from the KUHR-system (i.e., control and payment of reimbursements to health service providers), the Norwegian Patient Registry (NPR) and FD Trygd social security database. All information will be anonymized and linked to each patient using a unique ID number generated prior the start of this study. Data on revision surgery and deep prosthetic infections will be retrieved from the Norwegian Arthroplasty Registry[26].

Other measures

Adherence with AktivA: The physiotherapists will monitor patients' adherence with the AktivA program during the 12 weeks. Adherence will be measured as the total number of the 24 sessions completed. Good compliance will be defined as participation in 75% or more of the exercise sessions, medium compliance will be defined as participation in 50-74% of the sessions, and poor compliance will be defined as participation in less than 50% of the sessions.

Compliance with the e-therapy program: Good adherence to the e-therapy program will be defined as completing 75% of the content; medium compliance will be defined as completing 50-74% of the program, and poor compliance will be defined as completing less than 50% of the sessions. In addition, time used in the program will be assessed.

Power calculation and sample size

The primary outcome measure is KOOS pain subscale, 12-month follow-up. The minimal perceptible clinical improvement (MPCI) for KOOS has been determined to be 10 points[13] which will be considered a minimal clinically important change. The power will be set to 80%, the level of significance at 1%, and the standard deviation of the measurements considered equal in both groups at 16, resulting in a sample size of 62 patients in each treatment group. The attrition rate will be set to 20% to account for drop-out and crossovers. Therefore, we will include and randomize a total of 230 patients.

Statistical analysis

Data analyses will be performed using SPSS version 24.0 (IBM, Armonk, NY) and STATA version 14.2. Differences between the intervention and control group will be analyzed using responder analysis based on the OMERACT-OARSI responder criteria[27, 28]. Differences between the intervention and control groups at 12 months will also be analyzed using ANOVA. Non-normally distributed data will be analysed using the Kruskal-Wallis test. Differences over time at 3, 6 and 12 months will be analysed using mixed models for repeated measures to account for dependencies caused by each patient being measured several times. P-values <0.05 will be considered statistically significant, and all estimates with be reported with 95% confidence intervals. Effect sizes will be calculated for group differences using Cohen's coefficient *d*. A d-value ≥ 0.40 will be considered a clinically meaningful difference[29]. All analyses will be performed based on the intention to treat principle.

Economic evaluation

The cost-effectiveness analysis will be based on the Norwegian healthcare system. A societal perspective will be used as recommended by Russel et al[67]. A Markov decision model will form the theoretical framework for a cost-effectiveness analysis to estimate the costs and benefits for patients in the two intervention groups and the control group. With this model, simulation will be performed of long-term health benefits, health care costs and cost-effectiveness of the specified interventions. The main variables will be QALYs based on the EQ5D, combined with use of health care resources and use of medication. The incremental cost-effectiveness ratio (ICER) will be used to summarize the cost-effectiveness of each of the intervention groups, compared to the control group. Sensitivity analyses will be performed to test the stability of the conclusions.
According to the literature, a clinically relevant difference in EQ5D between the groups would be 0.08 [68]. Keeping alpha to 5% and power to 80%, we would need 42 individuals in each group.

Given we plan to enroll 62 in each group, our study is sufficiently powered to reveal a clinical relevant difference also for this secondary aim.

Timelines

Ethical approval was obtained from the The Regional Medical Research Ethics committee of Health East of Norway in June 2017. Recruitment and training of physiotherapists for the pilot study started in March 2018, and recruitment of physiotherapists for the full-scale study is expected to start in Jan 2019. Recruitment of patients to the pilot study is expected to start in Nov 2018, and recruitment for the full-scale study is expected to start in April 2019. Final completion of the 12-week follow-up is expected in August 2020.

7. References:

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