Statistical analysis plan for: The efficacy of strength training and stationary cycling on quality of life and knee function in patients with knee osteoarthritis. A multi-arm randomized controlled trial.

1. Administrative information

Clinical trials registration number: NCT01682980
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This statistical analysis plan (SAP) is a supplement to the study protocol[1]. We have followed the guidelines for the content of statistical analysis plans in clinical trials [2], all the recommended items are described either in this SAP or in the study protocol.

Contributors to SAP:
I hereby declare that I have reviewed and approved the statistical analysis plan:

Name	Role	Signature	Date
Britt Elin Øiestad[1]	Primary investigator		
May Arna Risberg[2,3]	Coordinating investigator and contributor to SAP		
Nina Østerås[4]	Contributor to SAP		
Margreth Grotle [1,5]	Contributor to SAP		

[1] Department of Physiotherapy, Oslo Metropolitan University, Norway, [2]Department of Orthopedics, Oslo University Hospital, [3]Department of Sports Medicine, Norwegian School Sport Sciences, [4]National Advisory Unit on Rehabilitation in Rheumatology (NKRR) [5]Research and Communication Unit for Musculoskeletal Health (FORMI), Oslo University Hospital, Norway

Statistical advisors: Milada Cvancarova Småstuen and Are Hugo Pripp, Oslo Metropolitan University

Research coordinator and assistants from Norwegian Institute of Sports Medicine: Kristin Bølstad, MSc, (research coordinator), Marte Lund, PT, MSc (research assistant), and Even Jarstad, Physiologist (research assistant).

List of abbreviations

Abbreviation	Explanation
BMI	Body mass index
CI	Confidence interval
EQ-5D-5L	The EuroQol 5-dimension, 5-levels
KL	Kellgren and Lawrence radiological classification system
KOOS	Knee injury and Osteoarthritis Outcome Score
OA	Osteoarthritis
RCT	Randomized controlled trial
QoL	Quality of life
VO_{2max}	Maximal oxygen consumption

The statistical analyses will be conducted by the primary investigator (Britt Elin Øiestad) and first authors with help from statistical advisor at the Oslo Metropolitan University (Milada C. Småstuen and Are Hugo Pripp). Along with our study protocol, this statistical analysis plan will be used as a work description for the statistical analyses. Results will be presented to co-authors of the studies where any uncertainties will be clarified and discussed. SPSS will be used for statistical analyses.

2. Introduction

Background

Despite an extensive literature on exercise interventions for patients with knee osteoarthritis, studies comparing the efficacy of specific exercise programs, for instance aerobic exercise or strength training, with usual care on quality of life (QoL), knee function and cost-effectiveness are few. The study protocol for this multi-arm (RCT) was published in 2013[1]. The methods are described in detail in the study protocol and will not be repeated here. There have been protocol changes that are described under *Study objective and outcomes*. Statistical analysis plan for subgroup analyses, explorative and predictor analyses will be published separately.

Study objectives and outcomes

The objective of this multi-arm RCT is to evaluate the efficacy of two exercise programs compared to usual care on knee related QoL (primary outcome), knee function, radiographic changes, and cost-effectiveness in patients with mild to moderate knee osteoarthritis. In addition, the aim is to evaluate the clinically important change for the subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS). The objectives and hypotheses will be described in detail in the planned studies below.

Outcomes

The primary outcome is knee-related QoL measured by the KOOS[3] at the 1 year follow-up.

Secondary outcomes and exploratory variables

Assessments are performed before randomization (baseline), and then at post-intervention (4 months), and at 1 and 2 years after the baseline assessment.

- Knee function measured by the KOOS subscales: pain, other symptoms, activities of daily living (ADL), and function in sport/recreation
- Health-related quality of life measured by EuroQoL-5D-5L and 3L
- Quality adjusted life years (QALYs) measured by EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) at 12 months
- Kellgren and Lawrence radiographic classification
- Total knee replacement (TKR)
- Isokinetic muscle strength (Newton meters)
- Maximal oxygen consumption (VO_{2max})
- Global rating of change scale (GRC)
- Self-efficacy for pain (Arthritis Self-Efficacy Scale, ASES)

Importantly, there have been changes in the study protocol:

- Due to lack of resources, we were not able to do the planned *magnetic resonance imaging (MRI) assessments and blood samples* of the study participants. Thus, the secondary aims of assessing cartilage quality and biochemical composition as

explanatory variables have been removed.

- The inclusion criterion for age has been extended from initially 45-65 years of age to 35-70 years of age to reach out to more eligible participants.
- The hypothesis: "*Strength exercise is more effective than cycling in improving knee function"* is removed due to that the study was not designed to test this hypothesis.
- The hypothesis "*Patients with mild radiographic osteoarthritis at baseline will respond significantly better to the interventions compared to those with moderate radiographic osteoarthritis at baseline on KOOS pain and QoL during the 2-year follow-up"* has been removed due to updated literature on weak associations between radiographic findings and symptoms.
- The hypothesis involving TKR will probably not be tested because we will not have enough numbers with TKR.
- We do not have funding to the 5-year follow-up.
- A feasibility study describing the exercise interventions will be published separately.

3. Study design

Trial methods

The study is a multi-arm RCT according to the Extension of the CONSORT 2010 Statement[4]. Participants are randomized to either strength training, stationary cycling, or usual care. Block sizes of 6 participants was prepared before study start.

The RCT was designed as a superiority trial between each of the intervention group and the usual care group, i.e. we expect difference between each exercise group and the usual care group, but we expect no difference between the two exercise groups.

The sample size was calculated to detect a clinically important difference on the KOOS QoL of 10 points (β = 0.2, two-sided $\alpha = 0.05$) with standard deviation of the mean for the groups of 20 points. This estimation gave 63 in each group. With an estimated 10% drop-out, we needed 69 participants in each group (n=207).

Analyses of the planned hypotheses in this trial will be conducted after all participants have finished their 1-year visit and data monitoring has been completed.

4. Statistical principles and planned articles

All analyses described in this plan are considered a priori analyses as described in the protocol before the data collection started.

All statistical tests will be two-sided and p-values, and 95% confidence intervals (CI) will be reported. Data distributions will be checked for normality. The intention-to-treat principle will be implemented in analyses of group comparisons.

In the following, the objectives, hypotheses and statistical approaches for each article are presented.

Study 1. Reporting of exercise interventions in a randomized controlled trial – descriptions, adherence and outcomes

In all studies evaluating the effect of exercise interventions the quality of descriptions of interventions in publications remains remarkably poor. The completeness of intervention description is often worse for non-pharmacological interventions. One study found that 67% of descriptions of drug interventions were adequate compared with only 29% of non-pharmacological interventions[5]. Without a complete published description of the intervention, other researchers and clinicians, patients, and other decision makers are left unclear about how to reliably implement the intervention and cannot replicate or build on research findings. Furthermore, the validity of systematic reviews and meta-analyses could be threatened due to the heterogenous exercise interventions included in exercise trials for knee osteoarthritis. Many systematic reviews cannot perform meta-analyses due to lack of information of the different exercise interventions included in the clinical trials. Hence, a study on the two exercise interventions is needed to describe the exercise interventions, including duration, dose or intensity, mode of delivery, monitoring, and adverse events in line with the TIDier [6] and CERT [7] checklists.

Objective

The objective of this study is to describe exercise type, frequency, duration, adherence of the two exercise interventions, adverse events, and progression and outcomes in the strength training group and the stationary cycling group from baseline to 4 months and 1 year.

The reporting of study includes data from the training dairies, and the test results at baseline and 4 months and 1 year, and includes the following objectives:

1) Describe recruitment and data collection procedures.

2) Describe type, frequency, duration, dosage (number of sessions, repetitions, and resistance), and progression for exercises included in the strength training group and the frequency, duration, watts and heart rate for the stationary cycle group. The participants in the strength training group filled in a training diary for each session for: number of repetitions per exercise, and weight load for the different strength exercises. The participants in the stationary cycling group reported duration (time), watts, and heart rate for each exercise session. Dosage was reported as sessions/week. Additionally, for the strength training group the training volume was calculated as number of exercises x (repetitions x sets x weight) (kg). Progression was defined as increase in weight load (kilos, kg) and volume or watts over the 12 weeks intervention period for the strength training group and the stationary cycle group, respectively.

3) Describe adherence: Adherence was determined by attendance of at least two exercise sessions per week for at least 10 weeks, in accordance to the American College of Sports Medicine's (ACSM) guidelines, suggesting that a minimum of 80% of the exercise sessions should be completed[8].

3) Describe adverse events and pain during the exercise sessions. The numeric rating scale (NRS) for pain during training was included (0 = no pain, and 10 = worst possible

pain) weekly over the 12-week period. Average level of ≤ 5 on the pain NRS was defined as acceptable throughout the training sessions[9]. The training diary also included questions about why the program was not followed, if patients did not attend or perform the exercises as described.

4) Describe improvement in isokinetic quadriceps muscle strength and VO_{2max} and self-reported knee function (by the 4 secondary outcomes of the KOOS pain, other symptoms, function in daily living and function in sport/recreation), and GRC (Knee pain from baseline to the next visit: "very much worse", "much worse", "worse", "unchanged", "better", "much better" and "completely recovered"[10]).

Statistical analyses

Data from the training diaries for the two intervention groups as well as the above given outcome measurements of participants who complete assessments at the 4-month follow-up and at the 1-year follow-up will be included. No data for the control group will be included in these analyses. The sample size of 69 participants in each group is adequate to detect clinically meaningful changes in muscle strength as previously found for 20 participants with degenerative meniscal tears[11], and in 48 participants with cartilage lesions after three months of strength training[12].

We will present means and standard deviations (SD) for normally distributed data and median and minimum-maximum values for skewed data. Paired t-tests or non-parametric Wilcoxon test will be used for paired comparisons between pre- and post-intervention examinations of quadriceps strength, VO_{2max} and the self-reported scores depending on data distribution, group sizes and drop-out rates. Feasibility data will be reported for women and men separately.

Study 2. Efficacy of the interventions

Primary objective

The overall objective of this study is to evaluate the efficacy of a standardized strength exercise program or standardized stationary cycling program compared to a control group doing as usual on knee related QoL after 1 year in patients with symptomatic knee osteoarthritis.

Secondary objectives

The secondary objectives are to investigate the efficacy of respectively the strength exercise program to usual care and cycling exercise to usual care on physical function after 4 months and 1 year, and over time. Furthermore, cost-effectiveness, cost-utility and cost-benefit analyses will be conducted comparing the exercise interventions to the usual care group up to the 1-year follow-up. The following hypotheses (H1-H8) will be included in this study.

Hypotheses

In patients with mild to moderate knee osteoarthritis:

- H1: Strength exercise is more effective than doing as usual in improving knee-related QOL after 1-year follow-up (main hypothesis)

- H2: Stationary cycling is more effective than doing as usual in improving knee-related QOL after 1-year follow-up (main hypothesis)

- H3: Strength training is more effective than doing as usual in improving knee function during a 1-year follow-up (at 4, months, at 1 year and over time).

- H4: Stationary cycling is more effective than doing as usual in improving knee function during a 1-year follow-up (at 4, months, at 1 year and over time).

- H5: Strength training has superior effect on radiographic joint space compared to the control group.

- H6: Stationary cycling has superior effects on radiographic joint space compared to the control group.

- H7: There is a significant difference in cost-effectiveness, cost-utility and cost-benefit in favour of the strength exercise group compared to usual care during 12 months of follow up.
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- H8: There is a significant difference in cost-effectiveness, cost-utility and cost-benefit in favour of the cycling group compared to usual care during 12 months of follow up.

Descriptive data

Patient flow will be presented in a CONSORT figure (e.g. Figure 1). Baseline patient characteristics will be presented as suggested in Table 1. The outcome variables, and other variables will be described as suggested in Table 2.

All outcomes will be checked for normality and statistical methods will be dependent on data distribution. Assumptions for mixed linear regression analysis will be checked before analyses are conducted.

Statistical analyses for primary outcome

Data from the two intervention groups will be statistically tested against the usual care group in separate analyses. To test the hypotheses, intention-to-treat mixed linear models will be applied using KOOS QoL data from baseline, 4 months and 1 year. The baseline score for KOOS QoL will be included as a covariate, the participants will be included as random effect and the treatment condition as a fixed factor. A mixed-method linear model includes all participants with at least baseline and one follow-up value and includes both fixed and random factors. The mixed-methods approach has higher statistical precision in analyzing data from a RCT, than other imputation methods such as last observation carried forward and multiple imputation[13]. The intention-to-treat approach ensures that the patients stay in the group they were randomized to for all

time points regardless of cross-over[13]. The purpose of this principle is to preserve the theoretical basis for the validity of the statistical results, specifically by eliminating the possibility that patients with known or unknown prognostic factors are systematically selected to a treatment[14]. Treatment effect will be determined as mean difference in KOOS QoL at the 1-year follow-up between respectively the strength training group and usual care group, and the cycling group and usual care group. Superiority will be tested using the two-sided 95% confidence interval (CI) of the mean difference in KOOS QoL between the two intervention groups versus the usual care group. The KOOS will be presented graphically for its development over the 1-year period.

Statistical analyses for secondary objectives

Between-group differences will be statistically assessed for the secondary outcomes similarly to the primary outcome, with intention-to-treat linear mixed-models using data from baseline, 4 months and 1 year. We will discuss to adjust the analyses for adherence, i.e. evaluate the efficacy in those that followed the planned program vs. those that did not follow the planned program. We expect little cross-over between the two exercise intervention groups as the participants are follow-up by physiotherapists.

Cost utility, cost-benefit and cost-effectiveness analyses

Cost-effectiveness, cost-utility, and cost-benefit analyses will be conducted from a health and societal perspective, and according to the intention-to-treat principle. To measure treatment effects and health utilities during 1 year the EuroQoL 5D (EQ-5D-5L) utility index will be used[15]. The EQ-5D-5L is a generic and preference-weighted measure of health-related quality-of-life based on five dimensions: mobility, self-care, activities of daily life, pain, and anxiety and/or depression. For each dimension, the patient assesses five possible levels of problems (from none to severe). The participants completed the EQ-5D-5L at baseline, and at 4, and 12 months follow-up. Health gains will be expressed as QALYs, which will be derived from the EQ-5D-5L utility scores, using the UK tariff[16] (a Norwegian tariff is not available). QALYs range from -0.59 to 1, where 1 corresponds to perfect health, and -0.59 to worst imaginable health. Combining utility indexes and time, the QALYs will be estimated as area under the curve using the trapezoidal method[17].

The willingness-to-pay threshold for OA will be based on the Norwegian governmental report No. 34 to the parliament with a value of NOK 275,000 (Euro (€) 27,500/USD 35,628) per QALY (Norwegian Ministry of Health and Care Services, 2016)[18]. Health care utilization and productivity loss will be assessed by self-report of:

- Number of visits to a general practitioner, medical specialist, physical therapist, manual therapist or other physical therapy specialist, and other therapists (specified)
- Use of medication (both prescription and over-the-counter medication)
- Type of medication (name of medication, dosage)
- Work status in terms of working time (percentage of position), partial sick leave (percentage, duration), complete sick leave (duration and reason), disability pension (percentage, duration), unemployment (yes, no), and student/other/unknown (yes, no)

Number of days of sick leave due to knee problems will be calculated for each follow-up period and adjusted for part-time work (employment rate), as well as percentage sick leave in the period. The costs of productivity loss will be estimated as the number of days absent from work multiplied by the average wage rate in Norway by sex. Costs for absence from work will be estimated from official statistics of average wage by sex and age groups as obtained from Statistics Norway. Cost categories, units, valuation, and unit price will be presented as shown in Table 3.

An incremental cost-effectiveness ratio (ICER) will be calculated, defined by the incremental costs (costs in the intervention groups – costs in the control group) relative to QALYs gained (QALYs intervention group – QALYs control group). Differences between the two groups in QALYs gained will be estimated using the trapezoidal method (the area under the curve combining utility indexes and time)[17]. Uncertainty will be analysed using the bootstrap method with 10,000 replicated datasets.

To illustrate the statistical uncertainty surrounding ICERs, the bootstrapped cost and effect pairs will be plotted on a cost-effectiveness plane (CE plane) with the ICERs on the y-axis and the incremental effects on the x-axis.

The intention-to-treat (ITT) method will be used. Missing values will be imputed with a multiple imputation model. To assess the robustness of the results, the following sensitivity analyses will be carried out:

1) Complete case analysis (without adjustment for missing data)
2) Without outliers (if relevant)
3) Uncertainty of the ICER will be tested by bootstrapping with 10,000 repetitions (probabilistic sensitivity analysis, PSA).
4) In a multiple one-way sensitivity analysis, the relevant costs and QALYs will be varied 20% below and above the estimates used in the main analyses. Results will be presented in a Tornado diagram showing the number of one-way sensitivity analyses in one graph.

Planned figures and tables are presented below.

Figure 1. CONSORT 2010 Flow Diagram

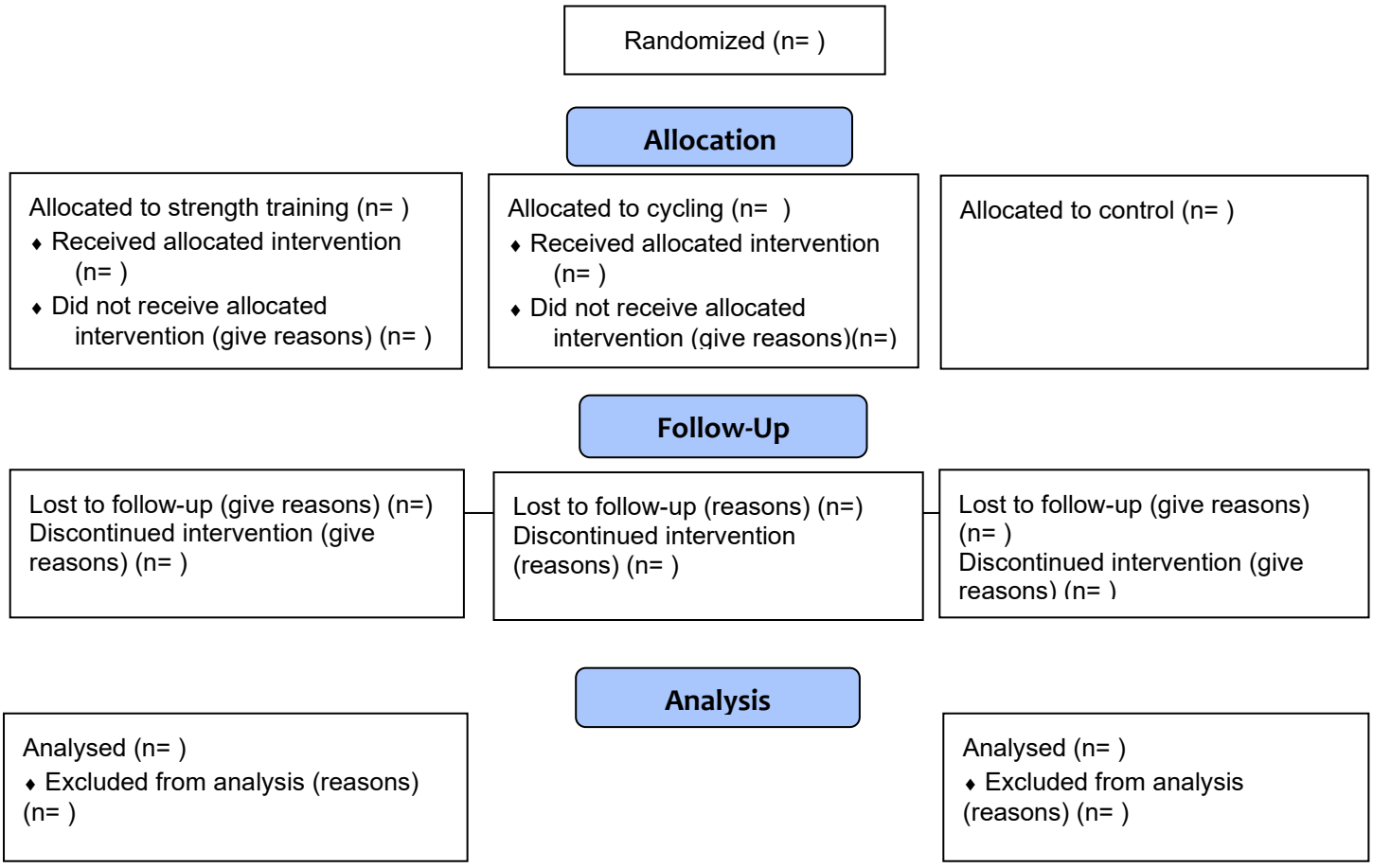

Table 1. Baseline descriptive characteristics of trial participants (*may be extended*).

Characteristics	All (n=)	Strength training (n=)	Cycling (n=)	Usual Care (n=)
Men, n (%)				
Age (years), mean (median)				
Body mass index, mean (median)				
Smoking, n (%)				
Comorbidities				
High education, n (%)				
Low education, n (%)				
Occupational status (work/sick leave/retired)				
Activity level, mean (range)				
Sessions per week				
Hours per week				
Intensity level				
Pain last week (0-110)				
Pain (0-10)				
Radiographic severity (Kellgren-Lawrence), n (%)				
Grade 2				
Grade 3				
Other				

Table 2. Outcomes and explanatory variables (variables with continuous values)*(may be edited)*

	Scores for all follow-ups for each group (mean, standard deviation)									Mean score change within group (95% CI)						Difference in change between groups			
	Baseline			4-months			1-year			4-months			1 year			4-months		1 year	
Outcomes and explanatory variables	**STG (n=)**	**CG (n=)**	**UCG (n=)**	**STG (n=)**	**CG (n=)**	**UCG (n=)**	**STG (n=)**	**CG (n=)**	**UCG (n=)**	**STG**	**CG**	**UCG**	**STG**	**CG**	**UCG**	**STG vs UCG**	**CG vs UCG**	**STG vs UCG**	**CG vs UCG**
KOOS Quality of life																			
KOOS Pain																			
KOOS Symptoms																			
KOOS activities of daily living																			
KOOS Sport/Rec																			
Self-efficacy (ASES)																			
Quality of life (EQ-5D-5L)																			
Quadriceps muscle strength																			
Oxygen consumption																			

STG= strength training group, CG= cycling groups, UCG=usual care group (control group)

Table 3. Cost categories, units, valuation and unit price

Cost categories	Unit	Valuation	Unit price Euros, €	Unit price NOK	Reference (source)
Direct costs of strength exercises	Per patient	Cost			
Direct costs of aerobic exercises	Per patient	Cost			
Direct costs of usual care (control)	Per patient	Cost			
Non-opioid medication (NSAIDs: ibuprofen, paracetamol, other A-prescription medicines)	Per daily defined dose	Cost			Pharmacy Selling Price (over-the-counter)
Opioid medication (codein)	Per daily defined dose	Cost			Pharmacy Selling Price
General practitioner	Per visit	Cost			NOMA, general practitioner consultation
Medical specialist	Per visit	Cost			NOMA, Specialist health service consultation (fee*2, + 20 min)
Chiropractor	Per visit	Cost			Norsk Kiropraktorforening estimated average
Physiotherapist	Per visit	Cost			The Norwegian Physiotherapy Association, estimated average
Manual therapist	Per visit	Cost			The Norwegian Physiotherapy Association, estimated average
Acupuncture	Per visit	Cost			Average estimate from private pricelists
Other therapists	Per visit	Cost			Average estimate from private pricelists
Surgery	Per surgery	Cost			DRG215B
Hospitalizations (non-surgery)	Per day	Cost			DRG247 (/2) per patient
Rehabilitation stay (outpatient)	Per day	Cost			UniCare price list, adjusted for health region authority supplements
Production loss (225 work days per year)	Per day	Wage rate adjusted for age and gender			Statistics Norway
Total healthcare costs					
Production loss (225 work days per year)					
TOTAL COSTS (healthcare + production loss)					

Study 3. Minimal important change for the KOOS subscales

Objective

To calculate the minimal important change (MIC) for the KOOS subscales by comparing patient-reported change from baseline to the 4-month visit with The Global Rating of Change scale (GRC).

- H9: A change in the Knee injury and Osteoarthritis Outcome Score (KOOS) subscales of 8–10 points are clinically important differences in patients with mild to moderate knee osteoarthritis.

Statistical analyses

The change score distributions for each KOOS subscale will be investigated using descriptive statistics and illustrated with boxplots. The proportion of patients who reports to be improved vs. unchanged vs. deteriorated on the GRC will be described. The association between the KOOS subscale change scores and GRC (with the seven response categories) will be analyzed with Spearman's correlation.

The GRC variable will further be used as an anchor response when investigating the MIC for improvement for the KOOS subscales. Patients will be classified as being importantly improved when answering "much better" or "completely recovered". The primary method for determining MIC values will be the predictive modeling method (MIC_{pred})[19]. MIC_{pred} values will be calculated using logistic regression analyses with patients classified as being importantly improved vs. not importantly improved as dependent variable. The prediction model enables adjusting for the proportion improved, as an unadjusted model may be biased if the proportion of improved is lower or higher than 50%[20]. Further, the MIC_{pred} method permits sensitivity analyses to be done with adjustments for very low vs. very high symptom or function scores at baseline. KOOS subscale scores at baseline will be included together with the change score in interaction terms in the MIC_{pred} models and considered to be effect modifiers if p-values are < .05. Bootstrap replications (n=1000) will be used to obtain 95% confidence intervals (CI) for the MIC_{pred} values. Sensitivity analyses with a different definition (cut off) of being importantly improved, i.e. classifying patients reporting "better", "much better" or "completely recovered" as being importantly improved, will be done.

The MIC_{pred} results will be compared with the more commonly used mean change method ($MIC_{mean\ change}$)[21] and the receiver operating characteristics (ROC) method (MIC_{roc})[22]. The $MIC_{mean\ change}$ with 95% CI will be calculated as the KOOS mean change score in the subgroup of patients responding "much better" ±1.95 ($SD_{change}/\sqrt{n}$). The ROC analysis will use the proportions of patients classified as being importantly improved vs. not importantly improved as anchor together with the KOOS subscale change scores. The MIC_{roc} values will correspond to the least degree of misclassification of sensitivity and specificity (Youden criterion) with 95% CI calculated from bootstrap replications (n=1000).

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