Statistical analysis plan for the DREAM study - A randomized controlled trial of meniscal tears in young adults

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Statistical analysis plan

DREAM - A randomized controlled trial of meniscal tears in young adults

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Section 1: Administrative information

Title & trial registration

- 1a: Danish Rct on Exercise vs Arthroscopic Meniscal surgery for young adults (The DREAM study)
  DREAM is a parallel group, superiority, randomized controlled trial (RCT) investigating if a strategy of early arthroscopic meniscal surgery is superior to a strategy of individualized supervised exercise therapy and patient education, with the option of later surgery if needed, in improving pain, function and quality of life in young patients (18–40 years of age) with meniscal tears.
- 1b: Trial registration: ClinicalTrials.gov ID: NCT02995551 (originally registered 16.12.2016)

Version

- 2: Version 2.0. Date: 18.02.2021

Protocol version

- 3: This statistical analysis plan (SAP) has been written based on the protocol approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20160151; 05.02.2020) and the published study protocol for the RCT (21.08.2017)[1]. This SAP adheres to the Guidelines for the content of statistical analysis plans in clinical trials[2]. The SAP was made publicly available before any outcome analyses commenced and before unblinding the data.

Revisions

- 4a: Revision history
- 4b: Justification for revision
- 4c: Timing of revision

Two versions of this SAP is available, one with and one without tracked changes.

Protocol version	Updated SAP version no.	Section number changed	Reason	Date changed
1.0	2.0	5	The statistician had to withdraw from the study of personal reasons	18.02.2021
1.0	2.0	20	Due to the COVID-19 situation, a sentence on the definition of the study population was added	18.02.2021
1.0	2.0	20, 25, 27, 28, 32	Following discussions with the new statistician as well as knowledge of loss to follow-up at the different time points the sections were updated.	18.02.2021

Roles and responsibility

- 5: Names, affiliations, and roles of SAP contributors

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Signatures

- 6a: SAP author:

  Date: 18.02.2021, 

- 6b: Statistician signature:

  Date: 18.02.2021, 

- 6c: Primary investigator signature:

  Date: 18.02.2021, 

Section 2: Introduction

Background

- 7: Synopsis of trial background

Background

Arthroscopic meniscal surgery is the most common orthopedic procedure. Numerous randomized controlled trials (RCTs) have investigated the effects of meniscal surgery compared with sham (placebo) surgery[3,4], meniscal surgery in combination with exercise compared with exercise alone[5-9] and meniscal surgery compared directly to exercise therapy[10] in middle-aged and older patients with degenerative meniscal tears with and without radiographic knee osteoarthritis. A recent meta-analysis of these RCTs did not demonstrate clinically relevant differences for any of these comparisons[11], and meniscal surgery was associated with risk of adverse events[12].

In contrast to degenerative meniscal tears in middle-aged and older adults, tears in younger adults (18-40 years) are most often of traumatic origin (i.e. such as a sports-related trauma). Evidence on anterior cruciate ligament (ACL) tears, another traumatic injury of the knee, suggest that a large proportion of young patients will have clinically-relevant improvements in pain, function and quality of life from structured and supervised exercise therapy as an alternative to surgery[13]. However, no RCTs have investigated the efficacy of meniscal surgery for younger adults in comparison to non-surgical treatments such as exercise and education.

Objectives

- 8: Description of specific objectives and hypotheses

The objective is to investigate if a strategy of early arthroscopic meniscal surgery (meniscal repair or resection) is superior to a strategy of individualized supervised exercise therapy and patient education, with the option of later surgery if needed, in improving pain, function and quality of life at 12 months in young patients (18-40 years of age) with a meniscal tear.

Hypotheses

We hypothesize that patients randomized to early surgery will improve significantly more in pain, function and quality of life from baseline to 12 months than those randomized to early exercise therapy and patient education, with the option of later surgery if needed.

Section 3: Trial methods

Trial design

- 9: Brief description of design

This is a multicentre, parallel-group RCT (1:1 ratio) conducted at seven orthopaedic departments (recruitment and surgery) and with 19 private physiotherapy clinics and municipalities delivering the exercise and education across all five health care regions in Denmark.

The primary endpoint is the between-group difference in change in the Knee Injury and Osteoarthritis Outcome Score ($KOOS_4$) between the group randomised to meniscal surgery and the group randomised to exercise therapy and patient education from baseline to 12 months follow-up. $KOOS_4$ is the mean score of the KOOS subscales Pain, Symptoms, Function in sports and recreational activities (Sport/Rec), and Quality of life (QOL)[14,15].

Adults between 18-40 years of age consulting one of the orthopaedic departments with knee pain and a MRI-verified meniscal tear, eligible for meniscal surgery (repair or resection) and willing to participate in the study were included and randomized after consenting to participate. Major exclusion criteria were previous surgery in the affected knee, MRI-verified displaced, bucket-handle tear, fracture of the affected extremity within the previous 12 months and complete rupture of one or more of the ligaments in the knee (see full list of eligibility criteria under item 22 below).

Patients between 18-40 years of age with clinical suspicion of a meniscal tear not fulfilling the other eligibility criteria or declining to participate in the RCT were asked to take part in an observational cohort with the same self-reported questionnaires as applied in the RCT, but following usual standard of care at the discretion of the patient and care providers. This SAP will only describe the analyses of the RCT as the results from the observational cohort will be analysed and reported separately.

A secondary 24-month follow-up of patients in the RCT is planned with an MRI evaluation of the knee joint structures alongside the same self-reported questionnaires as evaluated at 12 months. The strategy for analysing the self-reported measures will follow the same approach as described in this SAP, while the analysis of MRI changes will be described elsewhere.

Randomization

- 10: Randomization details

A priori, an independent statistician prepared a computer-generated randomisation schedule in random sized (4-6) permuted blocks stratified by recruitment centre and gender. The allocation numbers were concealed in opaque sealed envelopes prepared by and only accessible to the central study coordinator. The central study coordinator only opened the sealed envelopes after informed consent and baseline measures had been obtained.

Sample size

- 11: Full sample size calculation

The study is powered to detect a difference in change between the two groups of 10 points in the primary outcome ($KOOS_4$) from baseline to 12 months follow-up. This difference is considered clinically relevant and has previously been used in trials comparing surgery to non-surgical treatment for different knee pathologies[13,16,17]. To detect a 10-point difference, 59 patients in each group is needed (assuming a common SD of 16.5, power=90%, alpha level=0.05). We planned to recruit a total of 140 patients to account for loss to follow-up (19%).

Framework

- 12. Description of hypothesis testing framework

Both primary and secondary outcomes will be assessed using a superiority framework, expecting that patients undergoing meniscal surgery will improve more than patients undergoing supervised exercise therapy and patient education. A confidence interval excluding 10 points or more in the $KOOS_4$ score will be interpreted as a lack of a clinical meaningful difference.

Statistical interim analysis and stopping rules

- 13: Specification of planned interim analysis and/or stopping rules

A priori, as reported in the published study protocol, a stopping rule was defined[1]. If the intended sample size had not been reached at 30 months after recruitment had started at all participating hospitals (i.e. November 2019), the inclusion of patients would stop if at least 106 patients had been included or when this number was reached. This would ensure a power of 80% anticipating 20% loss to follow-up.

In November 2019, 122 patients (61 in each group) had been recruited, and the inclusion was terminated as defined by the stopping rule.

Timing of outcome assessments

- 14: Details of timing of all analyses

The primary follow-up (12 months) will be conducted 12 months after initiating treatment and all primary and secondary outcomes will be analyzed collectively by an independent statistician (Prof. Vach). Data from all time points (baseline, 3, 6, and 12 months) will be included in this analysis. Outcomes presented under Primary or Secondary Outcome Measures at ClinicalTrials.gov (ID: NCT02995551) will be reported in the primary 12-month RCT report, while outcomes presented under Other Outcome Measures will either be presented in the primary reported or in subsequent, secondary reports. The secondary endpoint, 24 months after initiating the treatment, will be analyzed at a later stage, when data collection for this has ended.

15: Timing of outcome assessments

Table 1 presents an overview of baseline characteristics and outcomes assessed and their timing. For a detailed overview of all outcome assessments, please refer to the published open access study protocol[1].

Table 1: Baseline characteristics and outcomes of the DREAM-trial

	Baseline	**Surgery**	**3 months**	**6 months**	**12 months**
Baseline characteristics					
Age	X				
Gender	X				
Study knee	X				
Height	X				
Weight	X		X	X	X
Education level	X				
Employment status	X				
Prior treatment of knee	X				
Smoking status	X				
Co-morbidities	X				

Symptom duration	X				
Symptom onset	X				
Joint line tenderness (medial and lateral)	X				
Thessaly's test (at 20° knee flexion)	X				
McMurray's test	X				
Surgery information					
ISAKOS meniscal tear classification		X			
Surgery reports		X			
Patient reported outcomes					
KOOS	X		X	X	X
WOMET	X		X	X	X
EQ-5D	X		X	X	X
Physical activity level	X		X	X	X
Sports participation	X		X	X	X
Pain location	X		X	X	X
Symptoms of catching and locking	X		X	X	X
Knee instability	X		X	X	X
Global perceived effect			X	X	X
Patient acceptable symptom state (PASS)			X	X	X
Treatment failure (TF)					X
Physical performance tests					
Isometric muscle strength	X		X		X
Knee-bend test	X		X		X
Jump performance (two tests)					X

Adverse events			
Patient-reported at Follow-up	X	X	X
Medical record review			X
Treatment-related variables			
Compliance with and progression of exercise (only for patients in the exercise group, registered after each session)	X		
Participation in post-surgery exercise (only for patients in the surgery group)	X		
Surgery and/or other treatments during follow-up			X

Data in the surgery column are only collected for patients undergoing surgery.
EQ-5D = EuroQol Group 5-Dimension Self-Report Questionnaire, ISAKOS = International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine—classification of meniscal tears questionnaire, KOOS = Knee injury and Osteoarthritis Outcome Score, WOMET = Western Ontario Meniscal Evaluation Tool

Section 4: Statistical principles

Confidence intervals and p values

- 16: Level of statistical significance and confidence intervals

All statistical tests carried out to assess the between-group effects, will consist of two-sided tests with a 5% significance level (p=.05).

- 17: Adjustment for multiplicity

Since this study has one clearly defined primary outcome and all other outcomes serve as supportive outcomes, no adjustments for multiplicity are needed.

- 18: Confidence intervals

All confidence intervals presented will be 95% and two-sided.

Adherence and protocol deviations

- 19a: Definition of adherence to the intervention

Poor compliance is defined as participating in less than 18 of the 24 exercise sessions (75%) in the group randomised to exercise and education. Compliance with the supervised exercise sessions will be registered by the physical therapist delivering the exercise therapy and education. In the group randomised to meniscal surgery, poor compliance was defined as not undergoing meniscal surgery.

- 19b: Description of how adherence will be presented

Adherence will be presented as the number and percentage of patients who participate in 18 or more supervised exercise therapy sessions in the group randomised to exercise and education and the number and percentage of patients who do not undergo meniscal surgery in the group randomised to meniscal surgery.

- 19c & 19d: Definition of protocol deviations and how they will be reported

The following is defined as a major protocol deviation which may compromise the scientific value of the trial:

- More than 10% of patients in the surgical group did not have a meniscal tear or had a complete rupture of one of the knee ligaments, identified during surgery
- More than 19% loss to follow-up
- Less than 50% of patients randomized to exercise therapy and education participated in at least 18 of the supervised exercise therapy sessions.

- More than 20% of patients randomized to surgery did not undergo surgery after all.

All major protocol deviations will be reported in the primary report.

Crossover to surgery will not be considered a major protocol deviation as the DREAM-trial is comparing two treatment strategies: early surgery or early exercise therapy and education with the option of later surgery. However, crossover to surgery will be registered and reported as it is important when evaluating the clinical applicability of the results.

Analysis population

- 20: Definition of analysis populations

In the primary analysis of the trial outcomes and the safety analysis (adverse events (AE)), all patients will be included according to the treatment they were randomized to receive, following the Intention-To-Treat (ITT) principle. As a consequence of the COVID-19 pandemic, one patient did not receive the treatment that he/she was randomized to until 6.5 months after inclusion and the treatment was delivered during the pandemic, thereby potentially altering the treatment course in comparison to the rest of the study population. Prior to conducting any analyses and unblinding the data, this patient was therefore excluded from the ITT population. This is the full analysis set, defined as an analysis set being as complete and as close to the ITT principle of including all randomized patients as possible[18].

In addition, the population can be divided into six disjoint sub-populations with respect to randomization and treatment experience. (The terms “poor/good compliers” refer to the definition given in section 19a. “Operated” refers to exposure to surgery prior to the 12 months follow up assessment.)

- Randomized to exercise therapy and patient education
    - A: Good compliers and not operated
    - B: Good compliers and operated
    - C: Poor compliers and not operated
    - D: Poor compliers and operated
- Randomized to meniscus surgery
    - E: Operated
    - F: Not operated

Patients randomized to exercise therapy and patient education can be further divided into

- G: Good compliers
- H: Poor compliers

or into

- I: Operated
- J: Not operated

The distribution of the primary outcome (change score in $KOOS_4$) will be visualized by dot plots and described by mean, median, SD, 10%- and 90%ile, and an 95% confidence interval for the mean for each of the 10 groups.

In the spirit of a per protocol analysis the following formal comparison will be performed:

Patients randomized to exercise treatment and patient education who are good compliers and not operated (group A)

vs

Patients randomized to meniscus surgery and operated (group E)

In the spirit of an as-treated analysis the following formal comparison will be performed:

Patients not operated (groups A, C, F)

vs.

Patients operated (B, D, E)

Patients operated within the last 3 months prior to the 12-months follow up will be excluded from all these additional analyses and reported as a separate group. A sensitivity analysis including these patients will be conducted if relevant.

Section 5: Trial population

Screening data

- 21: Reporting of screening data

The duration of the recruitment period (start and end date) and the total number of subjects screened for eligibility throughout the recruitment period will be reported. See also item 23 & 24.

Eligibility

- 22: Summary of eligibility criteria

Inclusion criteria

- Adults aged 18 to 40 years with knee pain
- Clinical history and symptoms of meniscal injury verified on magnetic resonance imaging (MRI)
- Deemed eligible for meniscal surgery by the examining orthopaedic surgeon
- Willing to participate in 12 weeks of supervised exercise twice a week and undergo surgery for the meniscal tear as soon as possible

Exclusion criteria

- Previous knee surgery in the affected knee
- Clinical suspicion (acute locking of knee AND/OR extension deficit) of displaced bucket-handle tear confirmed by MRI
- Fracture of the affected extremity within the previous 12 months
- Complete rupture of one or more knee ligaments.
- Participation in supervised systematic exercise for knee problems within the last 3 months prior to recruitment
- Other reasons for exclusion (unable to understand Danish, mentally unable to participate, etc.)

Recruitment and withdrawals

- 23 & 24: Information to be included in the CONSORT flow diagram

The CONSORT flow diagram will consist of the following:

- All patients assessed for eligibility throughout the recruitment period
- All patients meeting one or more of the exclusion criteria, with reasons
- All patients eligible for inclusion in the trial
- All eligible patients not consenting, with reasons

- All patients randomized for both treatment arms
- All patients receiving and not receiving the allocated treatment for both treatment arms
- All patients with follow-up assessments at the 3, 6 and 12 months follow-up[1]
- Withdrawals/lost to follow-up with reasons and timing for both treatment arms
- Patients included in the ITT, per protocol and as treated analyses for both treatment arms

[1]Patients with complete primary outcomes ($KOOS_4$) will be summarized at each follow-up for both treatment arms.

Baseline patient characteristics

- 25a: List of baseline characteristics to be summarized

MOCK table 1 (below) presents an overview of baseline characteristics that will be presented in the primary report. For further details, please refer to the published open access study protocol[1].

- 25b: Details on descriptive summary of baseline characteristics

Categorical and binary data will be summarized by absolute and relative frequencies . Continuous and count data will be summarized by mean, median, SD, inter quartile range, 10%ile, and 90%ile. In case of only few different values observed or unusual shape of the distribution (e.g. bimodality, extreme skewness), also absolute and relative frequencies will be reported, potentially after a suitable categorization). Number of available measurements will be reported, too. No formal tests for significant differences between groups at baseline will be performed, as this is not recommended by CONSORT[19].

Section 6: Analysis

Outcome definitions

- 26: Specification of outcomes and timing

Table 1 presents an overview of outcomes assessed and their timing. MOCK table 2 and 3 illustrate how the results of the primary and secondary outcomes and the safety analysis will be presented in the primary report. For a detailed overview of all outcome assessments, please refer to the published open access study protocol[1].

Analysis method

- 27: What analysis methods will be used

Outcomes presented under Primary or Secondary Outcome Measures at ClinicalTrials.gov (ID: NCT02995551) will be reported in the primary 12-month RCT report, while outcomes presented under Other Outcome Measures will either be presented in the primary reported or in subsequent, secondary reports.

Continuous outcomes will be analysed using a mixed model repeated measurements analysis of variance (MMRM ANOVA) with time (0, 3, 6, and 12 months) and a time dependent effect of the treatment arm (Meniscal surgery or Exercise and education) as fixed effects constraining the difference between the arms to 0 at baseline[20]. The model will be adjusted for the randomisation stratification factors (centre and gender) by including them as fixed effects. Additionally, we will adjust for age. To take the dependence among the measurements into account, a patient specific intercept and slope are added as random effects from a bivariate normal distribution with treatment arm specific variances and correlations. A common error variance is assumed for all follow up time points and treatment arms, whereas the error variance may be different at baseline The same analysis approach will be used to for assessment of muscle strength and knee-bend test, though the time points will be baseline, 3 and 12 months only. Jump performance at 12 months will be analysed using an ANOVA with adjustment for the stratification factors.

A confidence interval excluding 10 points or more in the treatment effect on the $KOOS_4$ score at 12 months will be interpreted as a lack of a clinical meaningful difference.

A figure visualizing the mean and 95% CI at all time points for $KOOS_4$ and the KOOS subscales for the six groups described in section 20, separately, will be produced.

The distribution of the primary outcome at each time point (both raw values and change scores) will be visualized by box plots, by error bar plots showing means and standard deviations, and by error bar plots showing means and 95% confidence intervals.

The individual trajectories of the patients with respect to the primary outcome will be presented in a graph. Mean and standard deviations of the slopes will be reported for both treatment arms based on a random intercept – random slope model fitted separately to each arm.

The occurrence of adverse events will be compared between groups at the 12-month follow-up using a Poisson regression model with a robust error variance[21].

Categorical outcomes will be analysed using Chi-square test, Fisher's exact test, or Mann-Whitney U test as appropriate.

As described under item 20, the primary analysis of the trial outcomes and the safety analysis, will follow the ITT principle, while secondary analyses inspired by the per protocol and the as treated principle will also be performed.

Missing data

- 28: Handling of missing data

No imputation methods will be applied, as the repeated measures mixed model allows inclusion of all subjects as long as there is at least a baseline measurement or one follow up measurement[22]. Age was included in the analysis model to take a potential dependence of non-response on age into account[20].

Loss to follow-up analysis

For each time point, the absolute and relative frequency of loss to follow-up in the primary outcome ($KOOS_4$) will be reported separated by treatment arm. In addition, these frequencies will be reported stratified by gender and age at baseline, $KOOS_4$ at baseline, $KOOS_4$ at the previous time point and change score at previous time point. The continuous factors will be categorized into three groups of equal size for these analyses.

In addition, the availability will be modelled as a function of time point, gender, age, $KOOS_4$ at baseline, and either $KOOS_4$ or the change score at the previous time point in a logistic regression model and effect estimates together with confidence intervals and p-values will be reported. This model will be fitted to all patients as well as stratified by treatment arm.

Additional analysis

- 29: Details of any additional analysis

Other Outcome Measures at ClinicalTrials.gov (ID: NCT02995551) will be reported in subsequent, secondary reports.

At the 24-month follow-up an MRI evaluation of the knee joint structures alongside the same self-reported questionnaires as evaluated at 12 months will be conducted. This will be reported in a secondary report.

Further exploratory analyses will be conducted if found relevant.

Harms

- 30: Handling of adverse events

Non-serious AEs and serious adverse events (SAE) are recorded at all follow-ups by asking patients to report any AEs using open probe questioning to ensure that all AEs are identified. Additionally, the medical records from the recruiting hospitals will be examined for all AEs occurring from inclusion until the 12 months follow-up. An AE is defined as any undesirable experience during follow-up leading to contact with the health care system (general practitioner or hospital) or death. AEs will be analysed in combination and separating index knee and other sites for AEs and SAEs separately. If an AE results in hospitalization, prolonged inpatient hospital care, result in re-surgery, or if an AE is life-threatening, result in death, permanent disability or damage, they will be categorized as SAEs, according to the FDA definition[22]. SAEs will include cardiovascular, gastrointestinal and pulmonary events, systemic and local infection (and treatment with antibiotics) and deep vein thrombosis, but also other AEs will be categorized as an SAE in accordance with the FDA definition above.

Crossover to surgery is registered and reported, but it will not be labelled as an AE as the study is comparing two treatment strategies: early meniscal surgery or early exercise and education with the option of later surgery. For all AEs, date of health care system contact is noted. Furthermore, duration of SAEs and potential consequences of SAEs are be registered if possible.

AEs will be assessed for severity, grouped into non-serious and serious AEs and categorized into sub-categories by an independent adjudication committee without accounting for whether they are casually related with study treatments. Any potential disagreements between the

adjudication committee members will be resolved by consensus. To reach consensus, additional information can be requested from the recruiting hospitals.

AEs and SAEs will be presented as illustrated in MOCK table 3.

Statistical software

- 31: Details of statistical package used for the analysis

STATA 16.1 (or an updated version if applicable) (StataCorp, College Station, TX, USA).

Operating procedures

- 32: Data management

The procedures for data collection and management was approved by the Danish Data Protection Agency (University of Southern Denmark, 16/45314). Data entry and coding of the de-identified data will be conducted by trained staff at the University of Southern Denmark. Personal information about patients is kept separate from the main data set and will not be shared with anyone outside the central study team. To protect confidentiality before, during and after the trial, all personal data is stored securely.

This SAP will form the basis for all analyses of the primary and secondary endpoints, which will be carried out by the same independent statistician, without any involvement from the investigators or study chairs (identical to the authors of the primary report from the study). The central study coordinator, will code the two treatment arms into ‘Group A’ and Group B’ before handing the data over to the statistician. This will help ensure that the statistical analyses will be performed blinded from treatment allocation.

In a first step the data will be passed to the statistician without any information on the compliance and on adverse events to ensure blinding. The statistician will finalize the report about the ITT analysis before getting information on compliance and adverse events in the second step.

To reduce risk of interpretation bias, blinded results from the ITT analysis (Group A vs. Group B) will be presented to all authors, who will agree on two alternative written interpretations, one where group A is meniscal surgery and one where Group A is Exercise and education. After finalizing the blinded interpretation, the central study coordinator will unblind who is Group A and Group B[23].

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Mock tables

Mock Table 1. Baseline characteristics

Baseline characteristics	Exercise and education	Meniscal surgery
Women		
Age (years)		
Weight (kg)		
Body Mass Index		
Symptom duration		
Symptom onset		
Meniscal surgery (resection or repair)		
Education level		
Employment status		
Prior treatment of knee		
Smoking status		
Instability		
Joint line tenderness (medial and lateral)		
Thessaly's test (at 20° knee flexion)		
McMurray's test		
Knee range of motion (flexion and extension)		
$KOOS_4$ score		
KOOS subscale scores		
WOMET		
Isometric muscle strength (kg)		
Number of knee-bends in 30s		
One-leg hop for distance (cm)		
6 m timed hoped (s)		

Mock Table 2. Outcome at 12 months

	Total no. of assessments (exercise and education group/meniscal surgery group)[1]	**Mean score at 12 months in meniscal surgery group** (95% CI)	**Mean score at 12 months in exercise and education group** (95% CI)	**Mean improvement in exercise and education group** (95% CI)	**Mean improvement in meniscal surgery group** (95% CI)	**Between-Group difference in mean improvement (crude)** (95% CI)	**Between-Group difference in mean improvement (adjusted)[2]** (95% CI)
Primary outcome							
$KOOS_4$							
Secondary Outcomes							
KOOS subscales scores							
Pain							
Symptoms							
ADL							

Sport/Rec
QOL
WOMET
Isometric muscle strength (kg)
Number of knee-bends in 30s
One-leg hop for distance (cm)
6 m timed hoped (s)

[1] There were 244 possible assessments for each group (61 at baseline, 3, 6 and 12 months)

[2] The results will be adjusted for baseline imbalance and randomisation stratification factors, i.e. recruitment centre and gender.

Mock Table 3. Serious Adverse Events

Serious adverse events[1]	**Exercise and education**	**Mensical surgery**	**P Value**
Number of patients affected			
	Number of events		
Overall			
Site other than index knee			
XXXX			
XXXX			
XXXX			
Index knee			
XXXX			
XXXX			
XXXX			

[1] This table includes all serious adverse events that occurred during the 12-month study period, but which did not necessarily have a causal relationship with the treatment administered. Serious adverse events include those that result in hospitalization, prolonged inpatient hospital care, result in re-surgery, or if an AE is life-threatening, result in death, permanent disability or damage[21]. The Supplementary appendix will present non-serious adverse events in a similar way.