

Statistical analysis plan for the 5- and 10-year follow-up assessments of the FIDELITY trial

Raine Sihvonen

Tampere University Hospital

Roope Kalske

University of Helsinki

Martin Englund

Lunds Universitet

Aleksandra Turkiewicz

Lunds Universitet

Pirjo Toivonen

University of Helsinki

Simo Taimela

University of Helsinki

Teppo Järvinen (✉ teppo.jarvinen@helsinki.fi)

University of Helsinki <https://orcid.org/0000-0003-3713-956X>

Study protocol

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Abstract

Background: The research objectives of the 5- and 10-year assessments of the Finnish Degenerative Meniscal Lesion Study (FIDELITY) are two-fold: 1) to assess the long-term efficacy of arthroscopic partial meniscectomy (APM) in adult (age 35 to 65 years) patients with a degenerative meniscus tear, and 2) to determine the respective effects of APM and degenerative meniscus tear on the development of radiographic and clinical knee osteoarthritis (OA). **Methods and Design:** FIDELITY is an ongoing multi-centre, randomized, participant and outcome assessor blinded, placebo-surgery controlled trial of 146 patients. This statistical analysis plan (SAP) article describes the overall principles for analysis of long-term outcomes (5- and 10-year follow-ups), including how participants will be included in each analysis, the primary and secondary outcomes and their respective analyses, adjustments for covariates, and the presentation of the results. In addition, we will present the planned sensitivity and subgroup analyses. **Discussion:** To study whether APM (resection of torn meniscus tear) per se accelerates or delays the development of knee osteoarthritis in patients with an arthroscopically-verified degenerative tear of the medial meniscus, we are carrying out pre-registered long-term (5- and 10-year) follow-up of our placebo-surgery controlled FIDELITY trial according to statistical principles outlined in detail in this document. We have also outlined the analyses intended to assess our second primary objective, the long-term efficacy of APM on knee symptoms and function.

Introduction

Trial overview and purpose of the statistical analysis plan

Finnish Degenerative Meniscal Lesion Study (FIDELITY) is a trial to assess the efficacy of arthroscopic partial meniscectomy (APM) for patients with a degenerative meniscus tear. The primary outcome assessment point of the trial was at 1-year post surgery. The original study protocol [1] and the results of 1- and 2-year analyses [2, 3], as well as a secondary analysis focusing on mechanical symptoms [4], are published.

To safeguard against the imminent risk of outcome reporting bias, selective reporting, and data-driven interpretation of results, this statistical analysis plan (SAP, Version 1.0) of the 5- and 10-year follow-ups is published as an update to the previously published protocol [1]. The original study protocol [1] provides more details on the trial rationale, eligibility criteria, interventions, data management and methods for limiting bias. This SAP follows the guidelines for writing SAPs provided by Gamble et al [5] and describes the overall principles for analysis of long-term outcomes (5- and 10-year follow-ups), including how participants will be included in each analysis, the primary and secondary outcomes and their respective analyses, adjustments for covariates, and the presentation of the results. In addition, we will present the planned sensitivity and subgroup analyses. The trial results will be reported according to the Consolidated standards of reporting trials (CONSORT) guidelines for RCTs [6].

Background

By the end of the 21st century, arthroscopic partial meniscectomy (APM) had become the most common orthopaedic procedure with well over half a million such surgeries performed annually in the US alone [7, 8], most to middle-aged and older patients [8]. According to conventional wisdom, APM was thought to result in short-term improvement in knee function and quality of life. However, a series of rigorous trials, summarized in three recent systematic reviews and meta-analyses, provide compelling evidence that APM offers little short- to medium-term benefit for most patients with knee pain and degenerative meniscus tear above sham surgery or non-surgical management [9, 10]. Recent evidence thus convincingly contradicts the widely-held contentions on the asserted benefits of APM on knee symptoms or function, but uncertainty still exists on the possible undesirable consequences of the procedure [11]. Overall, the risk of adverse events within 90 days of the procedure appears low, but serious adverse events (including pulmonary embolism and infection) have been associated with the surgery [12, 13].

However, there is mounting evidence to suggest that APM is associated with increased risk of accelerated progression of knee OA and earlier need for “corrective” surgery (high tibial osteotomy, HTO or total knee replacement, TKR) in this patient category of middle-aged to older patients [14, 15]. It still remains unclear whether the increased risk is due to the meniscus tear *per se*, the surgical procedure (APM), or if there is an interaction between the two. This question cannot be addressed simply by evaluating the outcome of patients who have undergone APM, because the role of the underlying degenerative process and the surgical procedure cannot be disentangled in such design [16]. Given the existing uncertainty regarding the potential effect of APM on the development or progression of knee osteoarthritis (OA), we are planning to address this particular issue by carrying out an adjunct, pre-registered analyses of the FIDELITY trial at 5- and 10-years from randomization. The biological rationale behind these studies is that the resection of torn meniscus tear (APM) has an effect on the progression of degenerative knee disease: some argue that APM cures symptoms and slows down the development of OA while others assert the contrary.

Objectives

The following two research questions capture the primary objectives of these 5- and 10-year follow-up investigations:

- 1) What is the long-term efficacy of APM (vs. placebo surgery) on functional outcome and knee symptoms in patients with an arthroscopically-verified degenerative tear of medial meniscus?
- 2) Does APM either accelerate or delay the development/progression of radiographic and clinical knee OA in these patients?

Trial Design

FIDELITY is a multicenter, randomized, participant and outcome assessor blinded, placebo-surgery controlled trial. This study is carried out at five orthopedic clinics of Tampere University Hospital

Hatanpää, Kuopio University Hospital, Helsinki Central Hospital (Jorvi), Turku University Hospital, and the Central Finland Central Hospital in Jyväskylä, all in Finland. The study group at each center consists of a main investigator (an orthopedic surgeon experienced in knee arthroscopy) who took care of the recruitment of the patients and all surgical procedures, a study nurse, an orthopedic surgeon for possible postoperative problems and another for scheduled follow-up examinations, the latter two both blinded to the treatment allocation. Patients were enrolled between 2007 and 2012 and all the follow-ups were carried out between October 2013 and January 2017. The study was approved by the Pirkanmaa Hospital District's committee of ethics (n:o R06157). The two research questions were registered as separate studies in the ClinicalTrials –database (Clinical trials.gov identifiers NCT00549172 and NCT01052233).

The study process shown in Figure 1 provides a brief outline of the trial. The eligibility criteria for the study are presented in Table 1.

Table 1.

Inclusion criteria
<p>Age: 35-65 years of age</p> <p>Persistent (>3 months) pain on the medial joint line of the knee</p> <p>Pain provoked by palpation or compression of the joint line or a positive McMurray sign</p> <p>MRI showing signals characteristic of medial meniscus injury</p> <p>Degenerative injury to the medial meniscus confirmed at arthroscopy</p>
Exclusion criteria
<p>Trauma-induced onset of symptoms</p> <p>Locked knee (that cannot be straightened normally)</p> <p>Previous surgical procedure on the affected knee</p> <p>Clinical osteoarthritis (OA) of the knee (American College of Rheumatology criteria)</p> <p>Radiological OA of the knee (Kellgren-Lawrence grade >1) at clinical site readings</p> <p>Acute (within the previous year) fracture of the affected extremity</p> <p>Decreased range of motion of the knee</p> <p>Instability of the knee</p> <p>MRI assessment shows pathology other than degenerative knee disease requiring treatment other than arthroscopic partial meniscectomy (APM)</p> <p>Arthroscopic examination reveals pathology other than a degenerative injury to the medial meniscus requiring intervention other than APM</p>

Methods

Outcomes

Objective #1: Efficacy of Arthroscopic Partial Meniscectomy (NCT00549172)

To assess the efficacy of APM (vs. placebo surgery) on the functional outcome and knee symptoms in patients with an arthroscopically-verified degenerative tear of medial meniscus, we will be using the same three patient-relevant outcomes (PROMs) that were used as our primary outcomes in the previous, 1-year and 2-year follow-up publications from this data [2, 3].

Primary outcomes:

1. **Western Ontario Meniscal Evaluation Tool (WOMET)** score, a disease specific quality of life – instrument developed and validated for patients with meniscal pathology [17, 18]
2. **Lysholm knee score**, the most commonly used outcome instrument for various knee conditions [19, 20] and a tool that has also been validated for patients with meniscal injury [21]
3. **Knee pain after exercise**, assessed on an 11-point scale ranging from 0 (no pain) to 10 (extreme pain).

Secondary outcome:

- The **frequency of unblindings** in the two study groups: Patients with inadequate relief of symptoms underwent unblinding of the treatment-group allocation

These outcomes and their justifications have been elaborated in detail previously [1-4].

Objective #2: Development of knee OA (NCT01052233)

To assess whether APM either accelerates or delays the development/progression of radiographic and clinical knee OA in these patients, we will use radiographs and established clinical criteria to assess the progression of knee OA at the 5- and 10-year time point after the index surgeries as follows:

Primary outcomes:

1. **Development/progression of radiographic OA:**

An increase of one grade or more in the Kellgren-Lawrence (KL) knee OA grading (dichotomous outcome: Yes or No)

The KL scale is a semi-quantitative instrument (ordered categorical grades 0-4) to assess the severity of radiographic tibiofemoral knee OA [22]. Patients who have undergone an osteotomy or a total knee replacement during follow-up will be considered to have progressed radiographically according to the definition above.

2. **Radiographic *progression* based on the sum of marginal tibiofemoral osteophyte grades and tibiofemoral joint space narrowing (JSN) grades** (Osteoarthritis Research Society International, OARSI) atlas (continuous outcome, hypothetical range 0-18)

The OARSI atlas is a semi-quantitative instrument (ordered categorical grade 0-3) with focus to assess the severity of JSN and osteophytes, respectively, in knee OA [23].

Secondary outcome:

1. **Knee OA according to the American College of Rheumatology Clinical Criteria [24]**

Auxiliary (secondary) outcomes:

2. Development/progression of radiographic OA by an increase of 0.5 grade or more in the Kellgren-Lawrence (KL) knee OA grading (dichotomous outcome: Yes or No);
 1. More sensitive than a full one grade (above) but may potentially capture “too many” patients as progressed in the two treatment arms, in particular at the 10-year follow-up.
3. Quantitative analysis of the joint-space width based on radiographs
4. Time-to-event analysis (OA-related surgery, arthroplasties or osteotomies)
5. MRI-based progression by semi-quantitative scoring (MOAKS) [25]
6. MRI-based progression of knee degeneration by quantitative assessment of change in OA features (cartilage, bone, bone marrow lesions, synovitis, and meniscus integrity and extrusion)
7. Lower extremity alignment (mechanical axis): change from baseline to 5-years
8. Patient satisfaction and self-rated improvement
9. Patients’ return to normal activities
10. The presence of mechanical symptoms [4]
11. Clinical knee examination
12. Serious adverse events
13. Frequency of re-APMs, and the number of osteotomies and knee arthroplasties
14. Possible derivatives from the above noted outcomes

For all radiographic outcomes, two experienced musculoskeletal radiologist (JK, NS), unaware of the treatment allocation and clinical data, will grade the baseline, and the 5- and 10-year radiographs of the operated (index) knee of all participants. After readings by both readers, a consensus will be sought.

All the analyses of secondary outcomes are supportive, exploratory and/or hypothesis-generating.

Rationale for outcomes to be reported and for the statistical analyses

For the assessment of the efficacy of APM (NCT00549172), we will use the same PROMs used in the previous publications depicting the 1-year [2] and 2-year [3] follow-up findings. To safeguard against potential multiplicity effects [26] in this analysis, we will interpret the treatment effect estimates and their 95% CIs for all our three primary outcomes.

As for the evaluation of the development/progression of knee OA (NCT01052233), the 5-year follow-up is the first time point one can reasonably expect any OA-related changes to take place/to be quantifiable. Having said that, the outcome measures we originally registered in the ClinicalTrials.gov database (i.e., Kellgren-Lawrence grade and OA by ACR clinical criteria) are quite insensitive to change, we have decided to add the sum of OARSI atlas osteophyte grades and JSN grades as an additional primary outcome of radiographic progression of OA.

Statistical analysis

All the analyses will be performed according to the intention to treat (ITT) principle or, if impossible, using full analysis set [27]. In sensitivity analysis also per protocol (PP) analyses will be performed. For all outcomes, 95% confidence intervals for the relevant between group differences will be presented.

For the analysis of continuous outcomes related to the objective #1 (efficacy of APM), a mixed model linear regression will be used. In this model the patient will be included as random effect and time point (6, 12, 24, 60 and 120 months), treatment arm (APM or placebo) and their interaction, and randomization stratification factors, i.e., the age [35 to 50 years or 51 to 65 years], sex, absence or presence of minor degenerative changes on a radiograph [Kellgren–Lawrence grade 0 or 1], and study centre, will be included as fixed effects. The model will be adjusted for baseline values of the respective outcome variable.

For the analysis of the binary outcomes a logistic regression model will be used. The model will be adjusted for the baseline randomization stratification factors (age [35 to 50 years or 51 to 65 years], sex, and absence or presence of minor degenerative changes on a radiograph [Kellgren–Lawrence grade 0 or 1]). To obtain the adjusted risk ratio and the adjusted risk difference from the logistic model, the method of standardization will be used [28]. Although the randomization was also stratified by the study site, the site will *not* be adjusted for in the logistic regression analysis due to the low number of participants in some centres and anticipated sparse data. A sensitivity analysis including the study site as a covariate will be performed.

For the analysis of continuous outcomes related to the objective #2 we will use a linear regression model adjusted for randomization stratification variables and the baseline value of the outcome.

Also, serious adverse events will be reported.

Study power considerations

We note that we originally powered the study to detect a minimal clinically important difference in the efficacy (patient-reported) outcomes – the Lysholm and WOMET scores (differences of at least 11.5 and 15.5 points, respectively) and in the score for knee pain after exercise (difference of at least 2.0 points) – between the APM and placebo-surgery groups. The original sample size calculation for the FIDELITY trial – which was geared at assessing the (short-term) efficacy of APM on pain and function – yielded a sample size of 70 patients per group. At the moment, having completed the 5-year follow-up, we know that we have a 96% adherence to follow-up (68/70 in the APM and 72/76 in the Placebo-surgery groups, respectively). Based on this, we anticipate the loss to follow-up to be no more than 5 additional patients per group at the end of the follow-up period (at 10 years), thus leaving approximately 63-67 patients per group for the final analyses. These values provide us with 80% power, based on a two-sided type 1 error rate of 5%, to detect a 20 per cent unit difference in the proportion of knee OA between APM and placebo-surgery. However, we consider that the estimates of the difference with a measure of uncertainty (such as 95% confidence intervals) are important to report, even if smaller differences cannot be declared as statistically significant in a conventional way. This is due to two reasons: 1) even a statistically non-significant difference can potentially exclude clinically relevant difference in one direction (ex. with a 95% CI of -3% to 15% for comparison between APM and sham APM in the frequency of knee OA at 5 years, we can exclude existence of clinically relevant difference favoring APM); 2) even if the results of this particular study will be inconclusive, they can inform any future meta-analysis, as, due to the stringent design of the study, the estimate can be expected to be unbiased.

Blinded data interpretation

Given the widely acknowledged importance of adequately blinding of all stakeholders in eliminating potential bias from the findings of RCTs [29], we have decided to add another safeguard, a procedure we coined blinded data interpretation [30]. In brief, our trial statistician (AT) will perform all statistical analyses using unblinded treatment groups and then provides the Writing committee of the trial with blinded results (groups labelled group A and group B). The Writing Committee then contemplates on the interpretation of the results until a consensus is reached and agrees in writing on all alternative interpretations of the findings. We record the minutes of this meeting in a document coined statement of interpretation, which will be signed by all members of the Writing Committee. Only after a common agreement is reached, the data manager and the trial statistician will break the randomization code and the correct interpretation is chosen. Draft of the manuscript will then be finalized. Detailed minutes of blinded data interpretation meetings will be provided as a supplement to the manuscript. As our co-PI (RS), research coordinator (PT), and trial statistician (AT) have performed statistical analyses for the previous publications of this trial [2-4], they will abstain from taking an active role in the blinded data interpretation meeting.

Ethical considerations

The study was approved by the Pirkanmaa Hospital District's committee of ethics (n:o R06157). Our application contained a specific, six-point ethical analysis focusing on the methodological rationale for

use of placebo surgery, risk-benefit assessment and informed consent (for detail, see [1]).

Dissemination

The findings of this study, whether positive, negative or neutral, will be disseminated widely through peer-reviewed publications and conference presentations.

Trial Status

The enrollment for the study was carried out between December 2007 and January 2012, and subsequently, the follow-up examinations took place between December 2013 and January 2017. We have now completed the 5-year follow-up examinations and data management and are ready to carry out blinded data interpretation of the 5-year data. The 10-year follow-up examinations are ongoing.

Discussion

Arthroscopic partial meniscectomy (APM) to treat middle-aged and older patients with persistent knee pain is one of the most common orthopaedic surgical procedures in use despite mounting evidence of no or only marginal benefits on patient-relevant outcomes. A degenerative meniscal tear has been reported to be an independent risk factor for progression of cartilage damage and the subsequent development of knee osteoarthritis. However, the respective roles and individual contributions of meniscal tear and APM on the progression of OA remain unclear. Current evidence, primarily based on observational data and unblinded randomized controlled trials, suggest that APM increases the risk of development of knee osteoarthritis, but the studies are hampered by confounding by indication or high crossovers rate and high loss to follow-up.

Our multicenter, randomized, placebo-surgery controlled FIDELITY trial that involves patients with an arthroscopically-verified degenerative medial meniscus tear provides an exceptionally rigorous design to address the above noted questions, namely whether arthroscopic partial meniscectomy is associated with an increased risk of progression of radiographic knee osteoarthritis and whether APM has any beneficial effect on knee pain or function or other symptoms.

Declarations

Ethics approval and consent to participate

Central ethical approval was confirmed from the Pirkanmaa Hospital District's committee of ethics (ref approval no. R06157) and we did not begin recruiting at other centres in the trial until local ethical approval was obtained. Informed consent was obtained from all study participants at trial entry.

Consent for publication

Not applicable.

Availability of data and material

Given that the informed consent forms of the FIDELITY trial did not include a provision for data sharing (trial launched in 2007), the full dataset cannot be shared due to a potential breach of the Finnish Personal Data Act. Scientists with a specific question regarding the trial data are encouraged to contact the corresponding author (TLNJ).

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Authors' contributions

FIDELITY Investigators

Department of Orthopedics and Traumatology, Tays Hatanpää, Tampere University Hospital, Tampere, Finland

Raine Sihvonen, MD, PhD

Kari Kanto, MD

Timo Järvelä, MD, PhD

Janne Lehtinen, MD, PhD

Outi Päiväniemi, MD, PhD

Marko Raivio, MD

Pirjo Toivonen, PT

Department of Orthopedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Mika Paavola, MD, PhD

Juha Kalske, MD

Anna Ikonen, MD

Janne Karhunen, MD

Roope Sarvilinna, MD, PhD

Sikri Tukiainen, MD

Ville-Valtteri Välimäki, MD, PhD

Roope Kalske, MD

Simo Taimela, MD, PhD

Teppo LN Järvinen, MD, PhD

Department of Orthopedics and Traumatology, Tampere University Hospital, Tampere, Finland

Tero Järvinen, MD, PhD

Department of Radiology, Tampere University Hospital, Tampere, Finland

Niko Sillanpää, MD, PhD

Center for Health and Social Economics, National Institute for Health and Welfare, Helsinki, Finland

Antti Malmivaara, MD, PhD

Department of Orthopedics and Traumatology, Turku University Hospital, Turku, Finland

Ari Itälä, MD, PhD

Jani Knifund, MD

Ville Äärimaa, MD, PhD

Department of Orthopedics and Traumatology, Kuopio University Hospital, Kuopio, Finland

Antti Joukainen, MD, PhD

Tommi Kääriäinen, MD

Heikki Kröger, MD, PhD, Professor

Janne Sahlman, MD

Department of Orthopedics and Traumatology, Central Finland Central Hospital, Jyväskylä, Finland

Heikki Nurmi, MD

Jukka Nyrhinen, MD

Juha Paloneva, MD, PhD

Department of Radiology, University of Tartu, Tartu, Estonia

Jaanika Kumm, MD, PhD

Clinical Epidemiology Unit, Orthopedics, Department of Clinical Sciences, Lund University, Lund, Sweden

Martin Englund, MD, PhD

Aleksandra Turkiewicz, MSc

Writing committee: R. Sihvonen, R. Kalske, S. Taimela, P. Toivonen, A. Turkiewicz, M. Englund and T.L.N. Järvinen.

Trial concept and design: R. Sihvonen, A. Malmivaara, M. Paavola and T.L.N. Järvinen.

Provision of study materials or patients: T.L.N. Järvinen.

Statistical and epidemiological expertise: A. Turkiewicz and M. Englund

Obtaining of funding: T.L.N. Järvinen.

Administrative, technical, or logistic support: T.L.N. Järvinen and S. Taimela.

Patient enrollment: R. Sihvonen, A. Itälä, A. Joukainen, H. Nurmi, J. Kalske and J. Karhunen.

Acquisition, collection and assembly of data, responsibility of participants' follow-up:

2-year follow-up: T. Järvelä, T.A.H. Järvinen, J. Lehtinen, O. Päiväniemi, and M. Raivio (Hatanpää Hospital, Tampere, Finland); J. Nyrhinen and J. Paloneva, (Central Finland Central Hospital, Jyväskylä, Finland); S. Tukiainen and A. Ikonen (Helsinki University Central Hospital, Helsinki, Finland); H. Kröger and J. Sahlman (Kuopio University Hospital, Kuopio, Finland); J. Knif Sund and V. Äärimaa (Turku University Hospital, Turku, Finland), and P. Toivonen (all sites).

5-year follow-up: K. Kanto (Hatanpää Hospital), T. Kääriäinen, (Kuopio University Hospital); V-V. Välimäki (Helsinki University Hospital); Ville Äärimaa, MD, PhD (Turku University Hospital) , and P. Toivonen (all sites).

Radiographic readings: J. Kumm (Tartu University, Tartu, Estonia)

Research coordination: P. Toivonen.

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Figures

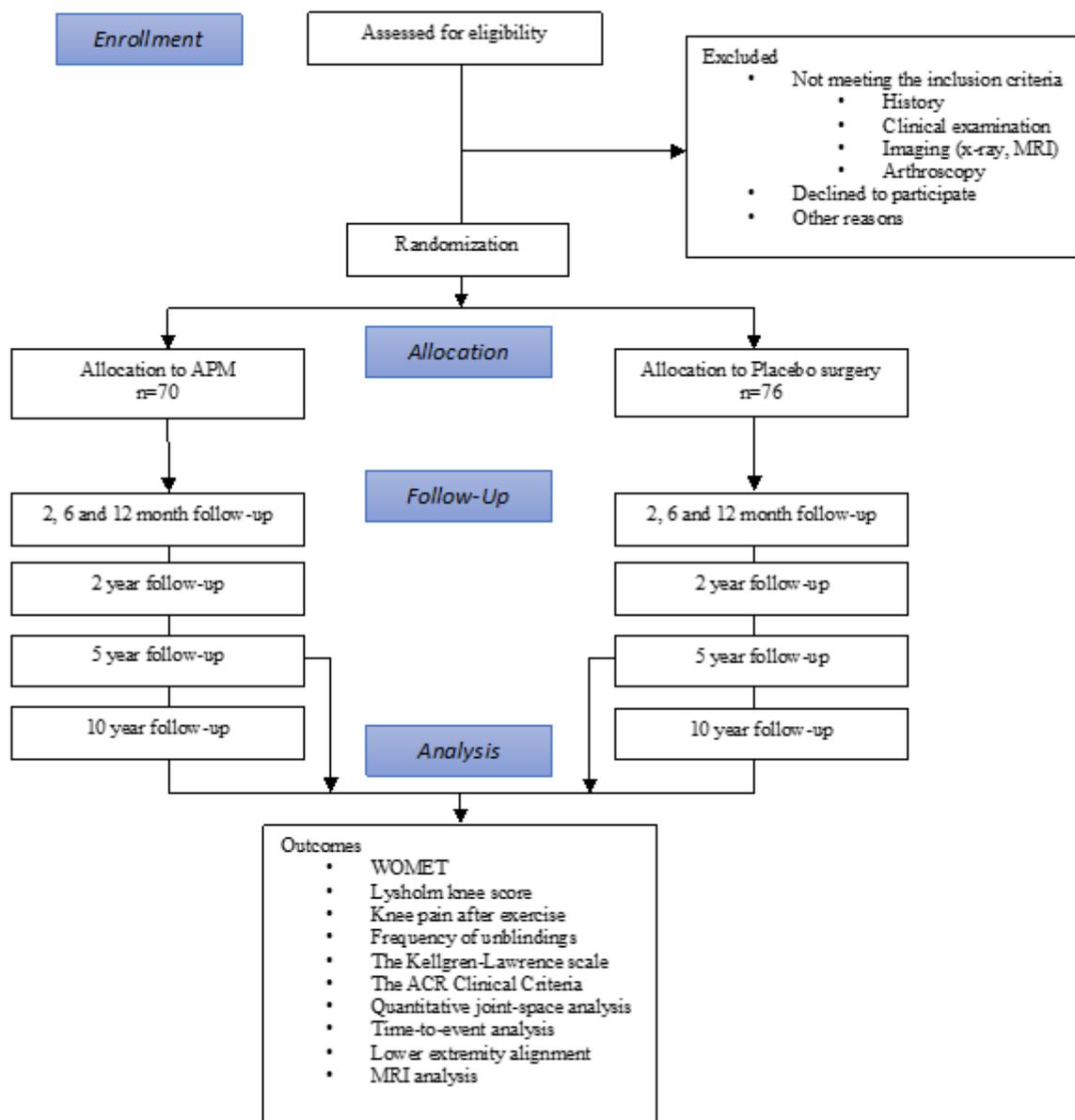


Figure 1

Figure 1 provides a brief outline of the trial. The eligibility criteria for the study are presented in Table 1.

Supplementary Files

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