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Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with degenerative meniscus lesions: a protocol for an individual participant data meta-analysis

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Abstract

Introduction

Arthroscopic partial meniscectomy (APM) after degenerative meniscus tears is one of the most frequently performed surgeries in orthopedics. Although several randomized controlled trials (RCTs) have been published that showed no clear benefit compared to sham treatment or non-surgical treatment, the incidence of APM remains high. The common perception by most orthopedic surgeons is that there are subgroups of patients that *do* need APM to improve, and they argue that each study sample of the existing trials is not representative for the day-to-day patients in the clinic. Therefore, the objective of this individual participant data meta-analysis (IPDMA) is to assess whether there are subgroups of patients with degenerative meniscus lesions who benefit from APM in comparison with non-surgical or sham treatment.

Methods and Analysis

An existing systematic review will be updated to identify all RCTs worldwide that evaluated APM compared to sham- or non-surgical treatment in patients with knee symptoms and degenerative meniscus tears. Time and effort will be spent in contacting principal investigators of the original trials and encourage them to collaborate in this project by sharing their trial data. All individual participant data will be validated for missing data, internal data consistency, randomization integrity and censoring patterns. After validation, all datasets will be combined and analyzed using a one- and two-staged approach. The most important outcome will be the difference between APM and control groups in knee pain, function and quality of life 2 years after the intervention. Other outcomes of interest will include the difference in adverse events and mental health.

Ethics and dissemination

This IPDMA will provide the evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons consider APM. The results will be submitted for publication in a peer-reviewed journal.

Registration

Prospero registration number: CRD42017067240

Keywords

Arthroscopic surgery; Meniscectomy; Osteoarthritis; Individual Participant Data Meta-Analysis; IPDMA

Article Summary

Strengths and limitations of this study

- To our knowledge, this is the first study that combines the individual participant data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery.
- The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of existing studies is combined to achieve large patient numbers.
- Trial data might not be available, not accessible or sharing is not possible due to a stringent informed consent that only enables the use of the data for the original study. This might limit the amount of trials we can include.
- We are dependent on the outcomes that have been used in the included studies. These can differ between studies.

Background

Arthroscopic partial meniscectomy (APM) is a well-established surgical procedure intended to treat symptoms believed to be caused by degenerative meniscus lesions. [1–3] Degenerative lesions are typically observed in middle-aged and older people, and are caused by chronic degenerative processes. [4,5] Over the past decade, evidence has accumulated that questions both the rationale for, and the effectiveness of APM for degenerative meniscus lesions. [6,7] Additionally, concerns have been expressed on the harms associated with the procedure [7–9] and the potential detrimental effect of the procedure on the progression of osteoarthritis. [10–12] Still, the number of surgical procedures performed in the treatment of degenerative meniscus lesions remains high. [13–17]

Orthopedic surgeons have expressed concerns about the generalizability of the trial results and point out that the study samples are not representative of the subjects they select for surgery in their day-to-day clinical practice.[18–24] The common perception by most surgeons is that there are subgroups of patients that *do* need the procedure to improve.[8] Hence, applying the mean effects of randomized controlled trials (RCTs) to individual patients in day-to-day practice runs against the intuitive approach of doctors to use the specific characteristics of a particular patient to tailor management accordingly. Unfortunately, the identification of subgroups of patients that may/may not benefit from the procedure has been problematic, as the individual trials performed so far were too small to perform valid and reliable subgroup analyses.

An individual participant data meta-analysis (IPDMA), i.e. a meta-analysis on the original individual participant data of previously performed trials, has been described as the gold standard of systematic review and meta-analysis. An IPDMA offers the unique opportunity to recode, and re-analyze all original trial data, and evaluate the effectiveness of surgical treatment of degenerative meniscus lesions and to identify potential subgroups more likely to benefit from the intervention. Identifying these subgroups can assist physicians to make personalized treatment decisions and thereby improving the overall quality of life of patients that are currently selected for APM.

Therefore, the objective of this IPDMA is to assess whether there are subgroups of patients with degenerative meniscus lesions who benefit from APM in comparison with non-surgical or sham treatment.

Methods

The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) statement and is registered in PROSPERO with registration number: CRD42017067240. [25] The first part of the method section describes a regular systematic review to identify eligible papers and invite the study authors to collaborate and contribute data. The second part describes the analysis with the individual participant data.

Patient and Public Involvement

Patients and members of the public were not involved in development of the protocol. A panel of patient representatives will provide detailed input regarding outcomes and the interpretation of the results from this IPDMA.

Part 1: Identifying eligible papers & data collection

Eligibility criteria

This IPDMA will include RCTs that evaluated the effectiveness of (partial) meniscectomy compared to non-surgical or sham treatments in persons with MRI-verified degenerative meniscus lesions. Degenerative meniscus lesions are typically observed in middle-aged and older people and may be the result of early degenerative knee disease. Persistent knee symptoms may encompass knee pain, limitation of function, and mechanical symptoms such as the sensation of catching or locking of the knee. Non-surgical or sham treatments may include, but are not limited to, sham surgery, pain and/or anti-inflammatory medication, exercise programs, and/or watchful waiting. Trials that included persons with traumatic meniscal lesions, defined as being the result of a specific traumatic incident will be excluded. There will be no restrictions on publication date, type of setting, length of follow up, or language.

Identification and selection of eligible trials

The search strategy described by Thorlund et al. [7] will be adopted to systematically search for eligible trials in Medline, Embase, CINAHL, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). (Additional file 1) The identified studies will be exported to EROS (Early Review Organizing Software, developed

by Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina) to remove duplicates, and randomly allocate references to two independent reviewers responsible for screening and selection. The two reviewers will independently screen all titles and abstracts of identified reports for eligibility. Full-text copies of all publications regarded as potentially eligible for inclusion, or where there is any uncertainty, will subsequently be assessed. Trials will be included when they meet the eligibility criteria. Any discrepancies between reviewers will be resolved by discussion, and if necessary, a third reviewer will be consulted. In addition, the reference lists of included studies will be reviewed to identify additional eligible trials. The electronic database search will be supplemented by searching for additional eligible trials in the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, which contains the trial registration datasets provided by several registries. This portal includes 16 national and international primary registries, including ClinicalTrials.gov, ANZCTR, JPRN, and ISRCTN. The corresponding authors of eligible trials will be invited to collaborate in the current IPDMA by sharing their data.

Collection of individual participant data

Data collection and transfer

Time and effort will be spent in tracing and encouraging original investigators to share their trial data. If no reply is received on a first invitation, additional inquiries will be sent, including inquiries sent to alternative email addresses identified for the corresponding author, inquiries sent to listed co-authors, and to the institution of the corresponding author listed in the original publication. The principal investigators of the original trials collaborating in the current project will be encouraged to actively participate in the IPDMA and discuss and finalize the definitions and outcomes to be assessed and the analytical processes proposed. Where possible, a face-to-face collaborator meeting will be scheduled, at which key decisions, including the project design, analysis plan, and interpretation of findings will be discussed. Before sharing of the de-identified data, we will sign a data sharing agreement with those principal investigators of the original trials that are interested in collaboration, in which we will arrange that the research data will be used for the declared purposes and the data will be stored on secured servers located in the Netherlands.

Data check and risk of bias

All received data will first be validated to match the results of the original publication. Statistical tests will be repeated and analyzed in R (R Foundation for Statistical Computing, Vienna, Austria). The trial data provided by original investigators will be checked for consistency, plausibility, integrity of randomization, and reproducibility of published trial results. The aims of checking data are to increase the probability that data supplied are accurate, and to confirm that trials were appropriately randomized. Inconsistencies will be discussed and resolved with the individual investigators. All checked and de-identified data of randomized participants will be entered into a pooled database, and every trial will be assigned a trial number. Data will include characteristics relating to the participants (age, gender, body mass index (BMI)); radiographic information on knee osteoarthritis; onset, duration, and severity of symptoms; generic and disease-specific health-related quality-of-life); non-surgical or sham procedure; trial (sample size, setting, allocation concealment); and outcome measures of interest. For eligible trials of which original data is not available the aggregated data from trial reports will be collected.

Checking the IPD directly can provide more reliable investigations of key potential biases, some of which might be reduced or alleviated in the process. The risk of bias in included trials will be independently assessed by checking the IPD directly. Randomization and allocation concealment will be assessed by checking if both treatment arms are balanced in every study.[26] The advantage of an IPDMA is that we can also include outcomes not reported by the original journal article, possibly reducing outcome reporting bias by checking all relevant outcomes at the same time. In order to avoid ecological bias, the within-trial information will be examined for individual predictors of treatment effect, separately from the across-trial information.[27] The potential for publication bias and small study effects will be examined, in the context of visual inspection, using a contour-enhanced funnel plot.[28,29] To avoid availability bias, aggregated data from studies lacking individual participant data will be used to consider their potential impact.

Missing data

The final IPDMA dataset will have a multilevel (i.e. clustered) structure, where the individual trials are the levels (i.e. clusters). A foreseen feature of this dataset will be that some variables will be systematically missing, that is missing for all individuals in one or more trials. Next to systematically missing variables, we may also encounter sporadically missing variables, that is missing for some but not all individuals in one or more trials.

In order to optimally use the available participant data, reduce bias, and to increase statistical efficiency, incomplete data will be imputed using imputation methods that handle both systematically and sporadically missing covariates in a two-level structure using hierarchical multiple imputations by chained equations (MICE). [30–33]

Outcomes variables

The most important outcomes according to surgeons and patients is treatment effect, determined as the difference between the intervention (surgery) and control group (non-surgical treatment) in knee pain, function and quality of life 2 years after the intervention. The preferred outcome measure instrument will be the Knee injury and Osteoarthritis Outcome Scale (KOOS). The KOOS is an instrument developed with the purpose of evaluating short-term and long-term symptoms and function in subjects with a knee injury and osteoarthritis. The KOOS consists of 5 subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee-related quality of life and a composite score can be calculated (referred to as the KOOS5). The KOOS has been validated for several orthopedic interventions such as anterior cruciate ligament reconstruction, meniscectomy and total knee replacement. [34] The score of the KOOS pain subscales will be compared between the intervention and control group across the included studies. Other measurement instrument targeted at quantifying pain will be standardized and combined in one single pain outcome. The functional outcome will be measured by using the KOOS function subscale or equivalent outcome aimed to measure function. The health quality of life will be measured by using the EuroQol-5 dimensions (EQ5D) questionnaire or the 36-Item Short Form Survey (SF-36).

Other outcomes of interest will include the difference between intervention and control group in adverse events (defined as deep venous thrombosis, pulmonary thromboembolism, venous thromboembolism, infection, and death) associated with the intervention from baseline to 2 years after intervention; difference in mental health; difference in risk for future knee replacement surgery between groups (feasibility will depend on whether the follow up of the trials will be long enough to capture the events), and the effect of follow-up time after the intervention on the treatment effect.

Part 2: Analysis

Treatment effect

The IPDMA will be used to assess the general effectiveness of APM in comparison with non-surgical or sham treatments in patients with knee symptoms and degenerative meniscal lesions. For this part, we will apply both a two-stage and one-stage approach.[35] In the two-stage approach, we will perform regression analyses for each study to obtain effect estimates separately. Thereafter these are pooled in a random effects model (to account for heterogeneity) like a regular meta-analysis. The random effects models in the two-stage will be analyzed using the restricted maximum likelihood (REML) approach with the Hartung-Knapp-Sidik-Jonkman method for continuous outcomes to account for uncertainty due to heterogeneity.[36] The two-stage approach is ideal for assessing pooled treatment effect and detect heterogeneity. However, it is difficult to detect non-linear trends or account for correlating covariates.

In the one-stage approach, the IPD from all studies will be analyzed simultaneously by adopting a single statistical model (random effects model) that fully accounts for heterogeneity across studies whilst accounting for the clustering of participants within studies. The one-stage approach is more flexible and more exact compared to the two-stage but can face computational difficulties. Therefore, the results from the one-stage will be compared to the results of the two-stage and differences will be investigated. The random effects models in the one-stage will be analyzed using the REML approach with the Kenward-Rogers approach for continuous outcome and the maximum likelihood method (ML) with quadrature for binary or survival outcomes.[35,37,38] Heterogeneity will be addressed by I^2 and τ^2, reflecting the heterogeneity between studies. To reflect the variation of the treatment effect in a different setting, 95% prediction intervals will be reported to provide more information on the expected effect in future patients.[39]

A key advantage of a one-stage approach is the flexibility in terms of the models that may be fitted compared to a two-stage approach. One-stage models allow for the inclusion of multiple covariates in a single model, multiple random-effects on different parameters, correlation between covariates and the separation of within and across-trials information. It is this flexibility that is essential to the primary objective of this IPDMA. [40]

Heterogeneity in treatment effect (subgroups)

To investigate which patients may benefit from (partial) meniscectomy we will assess whether the treatment effect is modified by baseline patient characteristics. First, relevant baseline patient characteristics will be identified. Modern regression procedures with penalization of estimated regression coefficients will be applied

for the selection of those characteristics that are independent predictors of the treatment effect.[41,42] A full list of the baseline patient characteristics that will be taken into consideration are listed in Additional file 2. Second, it will be assessed whether these identified independent baseline predictors, (individually or in combinations) modify the treatment effect. Effect modification will be assessed with a random effects model. In this model, a dummy for the particular study will be the random effect and APM (yes vs. no), the potential effect modifier, and an interaction term (APM * potential effect modifier) will be included as fixed variables and the treatment effect as dependent variables.[33] The illustrated approach will allow assessment of effect modification without overfitting the data and reducing the risk of type I errors.

In addition, we want to ensure that patient characteristics deemed to be of high clinical relevance in day-to-day clinical practice are ultimately evaluated for effect modification. For this purpose, alongside the procedure described above, we will also assess a set of predefined patient characteristics deemed to be of high clinical relevance for effect modification. To define these characteristics the IPDMA collaborators will be asked to provide a top-3 of characteristics that they regard as most clinically relevant. Subsequently, it will be assessed whether the overall top-3 of these predefined patient characteristics modify the treatment effect. Predefining these characteristics will be performed before actual analysis of the data.

Sensitivity analysis

To analyze the robustness of the results from the IPDMA, several sensitivity analyses will be performed. First, to evaluate the impact of including aggregated data of published trials (of which the IPD was not available in the meta-analysis), analyses will be performed in which we either only include studies with IPD available or only studies of which only aggregated data was available.

Second, to determine the effect of imputation of missing values on the study outcome, analyses will be performed in which we impute either only systematic missing variables, only sporadically missing variables (within trials) or not impute at all.

Publication considerations

The draft version of the final manuscript will be circulated among the collaborators for further discussion prior to submission for publication. The authors of the IPDMA paper(s) will be the project team managing the

IPDMA, followed by the collaborators, whom are the principal investigators that collaborated in the current project by sharing their trial data and commenting upon the results and draft of the papers.

Discussion

In the last decade, several RCTs found no or very little benefit of APM compared to non-operative or sham treatment in patients with degenerative meniscus tears. [43–52] These findings started a discussion on the effectiveness of the surgery and the methodology used in those RCTs by both orthopedic surgeons and other health care professionals.[19–23,53] The published studies were not able to adequately tease out whether or not there are subgroups that do additionally benefit from APM. This has resulted in a deadlock: APM is continued to be performed, despite Level I evidence that discourage the treatment.[13]

The proposed IPDMA provides the opportunity to evaluate the relationship between potential clinically-relevant baseline characteristics and the effectiveness of the APM of all patients that have been included in the trials, and to possibly detect subgroups that may benefit from APM. IPDMA is the gold standard of systematic review and meta-analysis that provides more power and is less prone to bias compared to meta-analysis on aggregated data. To our knowledge, this is the first study that combines the individual participant data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery. The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of existing studies is combined to achieve large patient numbers. This prevents additional trials and patient involvement. Moreover, combining individual patient data enables us to analyze the effects of within-study and between-study moderators of effect sizes, even though the original studies were too small to analyze such samples.

Although IPDMA is the best method to detect possible subgroups, performing an IPDMA also comes with several challenges. First, all individual patient data from the eligible trials have to be collected. This time-intensive task often requires us to contact the principal investigators multiple times to invite them to collaborate. Unfortunately, data is sometimes not available, not accessible or sharing is not possible due to a stringent informed consent that only enables the use of the data for the original study. While there are guiding principles for open data management and sharing (Findable, Accessible, Interoperable and Reusable data principles (FAIR principles)) these often conflict with the rules of the informed consent or national legislations,

creating a tension between privacy and reuse of (anonymous) medical data.[54] This might limit number of studies that can be included in this IPDMA. Second, there are multiple ways to measure knee pain, knee function or general quality of life. Every researcher can or will use their own set of outcome parameters, dependent on the experience of the researcher with a certain questionnaire/scoring system, preference or the time-dependent academic insights of the optimal questionnaire/scoring system (especially if studies have been published in different time periods, i.e. different research paradigm). As a result, we are dependent on the outcomes that have been used in the included studies in the IPDMA and cause systematic missing variables in the final pooled dataset of an IPDMA. These missing variables pose a methodological challenge, because they require advanced imputation that preserve the hierarchical structure of the data followed by the one-stage meta-analysis.[55]

In conclusion, the aim of this project is to identify potential subgroups of patients with degenerative meniscus lesions who may benefit from APM. It will provide the evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons consider APM. Identifying potential subgroups can improve the quality of life of patients who *do* truly benefit from the treatment, and can perhaps be implemented with a clinical decision aid. In case we do not find a subgroup that has additional benefits from the treatment, it can help to reduce the number of APMs, and thus less risk of, e.g. complications.[9,56]

List of abbreviations

APM	Arthroscopic partial meniscectomy
RCT	Randomized controlled trial
IPDMA	Individual participant data meta-analysis
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols
CENTRAL	Cochrane Central Register of Controlled Trials
EROS	Early Review Organizing Software
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
BMI	Body mass index
MICE	Multiple imputations by chained equations
KOOS	Knee injury and Osteoarthritis Outcome Scale
EQ5D	EuroQol-5 dimensions questionnaire

SF-36	36-Item Short Form Survey
REML	Restricted maximum likelihood
ML	Maximum likelihood
FAIR	Findable, Accessible, Interoperable and Reusable data principles

Declarations

Ethics approval and consent to participate

All principal investigators provided written confirmation that all participants included in the original trials had given informed consent.

Consent for publication

Not applicable

Availability of data and material

Following the ICMJE's data sharing statement policy, de-identified individual participant data will be made available at the end of the research project, including the study protocol, beginning 9 months and ending 36 months following article publication. The data will be shared with investigators whose proposed use of the data has been approved by a review committee to be identified for this purpose. Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse without investigator support other than deposited metadata.

Competing interests

The authors declare that they have no competing interest

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Authors' contributions

SW, MR, JR, and GH drafted the manuscript. All authors read, reviewed and approved the manuscript before submission.

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Additional files:

File name: Additional file 1

File format: Additional_file_1.doc

Title: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

Description: The systematic search strategy in Medline (PubMed), Embase, CENTRAL, CINAHL, Web of Science and WHO trial register to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

File name: Additional file 2

File format: Additional_file_2.doc

Title: Potential clinically relevant baseline characteristics

Description: A list of all identified potential clinically relevant baseline characteristics divided into 5 categories: General characteristics, patient history, meniscus information, symptoms and quality of life.

Additional file 1: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

	Medline (Pubmed)	Embase	Cochrane Database of registered trial (CENTRAL)	Cumulative Index to Nursing and Allied Health Literature (CINAHL)	Web of Science (Thomson Reuter)	WHO trial register
1	"Menisci, Tibial/surgery"[Mesh]	Arthroscopic meniscectomy.ti,ab,kw.	MeSH descriptor: [Menisci, Tibial] explode all trees and with qualifier(s): [Injuries – IN, Surgery – SU]	TI "Degenerative meniscal tear" OR AB "Degenerative meniscal tear"	arthroscopy AND knee	"Menisc*" in the title
2	"Menisci, Tibial/injuries"[Mesh]	Arthroscopic debridement.ti,ab,kw.	MeSH descriptor: [Arthroscopy] explode all trees	MH "Arthroscopy" OR "arthroscopy"	arthroscopic meniscectomy	"Menisc*" in the condition
3	"Degenerative meniscal tear" [TIAB]	Arthroscopic lavage.ti,ab,kw.	MeSH descriptor: [Knee] explode all trees	MH "knee" OR AB "knee" OR TI "knee"	arthroscopic debridement	"Menisc*" in the intervention
4	"Arthroscopic lavage"[TIAB]	Degenerative meniscal tear.ti,ab,kw.	2 and 3	2 AND 3	arthroscopic lavage	1 OR 2 OR 3
5	"Arthroscopic debridement"[TIAB]	knee meniscus/ or meniscus tibial.mp	Degenerative meniscal tear:ti,ab,kw (Word variations have been searched)	MH "Meniscal Injuries" OR AB "meniscal Injuries" OR TI "meniscal Injuries"	degenerative meniscal tear	
6	"arthroscopic meniscectomy"[TIAB]	exp knee arthroscopy/	Arthroscopic lavage:ti,ab,kw (Word variations have been searched)	MH "Menisci, Tibial" OR AB "tibial meniscus" OR TI "tibial meniscus"	menisci, tibial AND surgery	
7	"Arthroscopy"[TIAB] AND "Knee"[TIAB]	1 or 2 or 3 or 4 or 5 or 6	Arthroscopic debridement:ti,ab,kw (Word variations have been searched)	TI "Arthroscopic lavage" OR AB "Arthroscopic lavage"	menisci, tibial AND injury	
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	randomized controlled trial/	arthroscopic meniscectomy:ti,ab,kw (Word variations have been searched	TI "Arthroscopic debridement" OR AB "Arthroscopic debridement"	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	
9	"Randomized" [TIAB]	randomized.ti,ab,kw.	1 or 4 or 5 or 6 or 7 or 8	TI "arthroscopic meniscectomy" OR AB "arthroscopic meniscectomy"	randomized	
10	"Randomized controlled trial"[Publication Type]	randomized.ti,ab,kw.		1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	randomised	
11	"randomized controlled trials as topic"[Mesh]	random allocation.mp.		TI "Randomized" OR AB "Randomized"	random allocation	
12	"Random allocation"[Mesh]	randomized.mp.		MH "Randomized Controlled Trials" OR TI "Randomized Controlled Trials" OR AB "Randomized Controlled Trials"	control group	
13	"Control group"[TIAB]	"randomized controlled trial (topic)"/		MH "Random Assignment" OR AB "Random Assignment" OR TI "Random Assignment"	cross-over stud*	
14	"Control groups"[Mesh]	control group.mp.		AB "Random Allocation" OR TI "Random Allocation"	randomized controlled trial	
15	"Cross-over studies"[TIAB]	control group/		(MH "Control Group") OR (AB "Control Group") OR (TI "Control Group")	9 OR 10 OR 11 OR 12 OR 13 OR 14	
16	"Cross-over study"[TIAB]	crossover procedure/		(MH "Crossover Design") AND (AB "Crossover Design") AND (TI "Crossover Design")	8 AND 15	
17	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16		11 OR 12 OR 13 OR 14 OR 15 OR 16		
18	8 AND 17	7 and 17		10 AND 17		

Additional file 2. Potential clinically relevant baseline characteristics

Category	Characteristics
General characteristics	
	Age
	Gender
	Weight, height (BMI)
Patient history	
	History of medication for knee symptoms
	History of serious knee injury
	History of knee surgery
	Family history of knee OA / of knee replacement surgery
	History of osteoarthritis
Meniscus information	
	Medial/lateral meniscus
	Radiographic severity of knee OA
	MRI meniscus extrusion
	MRI meniscus tear type/degeneration
	Onset of symptoms (e.g. gradual, after event, suddenly)
	Duration of symptoms
	Grading of work and sporting activities
Symptoms	
	Signs and symptoms during specific physical examination test
	Knee locking symptoms / mechanical symptoms
	Knee-related daily function
	Knee pain
	Knee stiffness
	Knee-related quality of life
	Knee swelling
Quality of life	
	Generic quality of life (EQ-5D / SF36)
	Mental health score

Additional file 1: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

	Medline (Pubmed)	Embase	Cochrane Database of registered trial (CENTRAL)	Cumulative Index to Nursing and Allied Health Literature (CINAHL)	Web of Science (Thomson Reuter)	WHO trial register
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4	"Arthroscopic lavage"[TIAB]	Degenerative meniscal tear.ti,ab,kw.	2 and 3	2 AND 3	arthroscopic lavage	1 OR 2 OR 3
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13	"Control group"[TIAB]	"randomized controlled trial (topic)"/		MH "Random Assignment" OR AB "Random Assignment" OR TI "Random Assignment"	cross-over stud*	
14	"Control groups"[Mesh]	control group.mp.		AB "Random Allocation" OR TI "Random Allocation"	randomized controlled trial	
15	"Cross-over studies"[TIAB]	control group/		(MH "Control Group") OR (AB "Control Group") OR (TI "Control Group")	9 OR 10 OR 11 OR 12 OR 13 OR 14	
16	"Cross-over study"[TIAB]	crossover procedure/		(MH "Crossover Design") AND (AB "Crossover Design") AND (TI "Crossover Design")	8 AND 15	
17	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16		11 OR 12 OR 13 OR 14 OR 15 OR 16		
18	8 AND 17	7 and 17		10 AND 17		

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Meniscus information	
	Medial/lateral meniscus
	Radiographic severity of knee OA
	MRI meniscus extrusion
	MRI meniscus tear type / degeneration
	Onset of symptoms (e.g. gradual, after event, suddenly)
	Duration of symptoms
	Grading of work and sporting activities
Symptoms	
	Signs and symptoms during specific physical examination test
	Knee locking symptoms / mechanical symptoms
	Knee related daily function
	Knee pain
	Knee stiffness
	Knee related quality of life
	Knee swelling
Quality of life	
	Generic quality of life (EQ-5D / SF36)
	Mental health score

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	65, 99
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	6 - 36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	318 - 320
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	315-317
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	315-317
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	75-93

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	94-95
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	104-113
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	114-130
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Additional file 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	144-155
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	130-142
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	130-142
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	175-195 + Additional file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	175-195 + Additional file 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	143-174
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	196-240

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	241-248
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	156-165
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	

BMJ Open

Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with degenerative meniscus lesions: a protocol for an individual participant data meta-analysis

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Arthroscopic surgery, Meniscectomy, Osteoarthritis, Individual Participant Data Meta-Analysis, IPDMA

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Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with degenerative meniscus lesions: a protocol for an individual participant data meta-analysis

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Word count: 3223

Abstract

Introduction

Arthroscopic partial meniscectomy (APM) after degenerative meniscus tears is one of the most frequently performed surgeries in orthopedics. Although several randomized controlled trials (RCTs) have been published that showed no clear benefit compared to sham treatment or non-surgical treatment, the incidence of APM remains high. The common perception by most orthopedic surgeons is that there are subgroups of patients that *do* need APM to improve, and they argue that each study sample of the existing trials is not representative for the day-to-day patients in the clinic. Therefore, the objective of this individual participant data meta-analysis (IPDMA) is to assess whether there are subgroups of patients with degenerative meniscus lesions who benefit from APM in comparison with non-surgical or sham treatment.

Methods and Analysis

An existing systematic review will be updated to identify all RCTs worldwide that evaluated APM compared to sham- or non-surgical treatment in patients with knee symptoms and degenerative meniscus tears. Time and effort will be spent in contacting principal investigators of the original trials and encourage them to collaborate in this project by sharing their trial data. All individual participant data will be validated for missing data, internal data consistency, randomization integrity and censoring patterns. After validation, all datasets will be combined and analyzed using a one- and two-staged approach. The most important outcome will be the difference between APM and control groups in knee pain, function and quality of life 2 years after the intervention. Other outcomes of interest will include the difference in adverse events and mental health.

Ethics and dissemination

This IPDMA will provide the evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons consider APM. The results will be submitted for publication in a peer-reviewed journal.

Registration

Prospero registration number: CRD42017067240

Keywords

Arthroscopic surgery; Meniscectomy; Osteoarthritis; Individual Participant Data Meta-Analysis; IPDMA

Article Summary

Strengths and limitations of this study

- To our knowledge, this is the first study that combines the individual participant data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery.
- The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of existing studies is combined to achieve large patient numbers.
- Trial data might not be available, not accessible or sharing is not possible due to a stringent informed consent that only enables the use of the data for the original study. This might limit the amount of trials we can include.
- We are dependent on the outcomes that have been used in the included studies. These can differ between studies.

Background

Arthroscopic partial meniscectomy (APM) is a regularly performed surgical procedure intended to treat symptoms believed to be caused by degenerative meniscus lesions. [1–3] Degenerative lesions are typically observed in middle-aged and older people, and are caused by chronic degenerative processes. [4,5] Over the past decade, evidence has accumulated that questions both the rationale for, and the effectiveness of APM for degenerative meniscus lesions. [6,7] Additionally, concerns have been expressed on the harms associated with the procedure [7–9] and the potential detrimental effect of the procedure on the progression of osteoarthritis. [10–12] Still, the number of surgical procedures performed in the treatment of degenerative meniscus lesions remains high. [13–17]

Orthopedic surgeons have expressed concerns about the generalizability of the trial results and point out that the study samples are not representative of the subjects they select for surgery in their day-to-day clinical practice.[18–24] The common perception by most surgeons is that there are subgroups of patients that *do* need the procedure to improve.[8] Hence, applying the mean effects of randomized controlled trials (RCTs) to individual patients in day-to-day practice runs against the intuitive approach of doctors to use the specific characteristics of a particular patient to tailor management accordingly. Unfortunately, the identification of subgroups of patients that may/may not benefit from the procedure has been problematic, as the individual trials performed so far were too small to perform valid and reliable subgroup analyses.

An individual participant data meta-analysis (IPDMA), i.e. a meta-analysis on the original individual participant data of previously performed trials, has been described as the gold standard of systematic review and meta-analysis. An IPDMA offers the unique opportunity to recode, and re-analyze all original trial data, and evaluate the effectiveness of surgical treatment of degenerative meniscus lesions and to identify potential subgroups more likely to benefit from the intervention. Identifying these subgroups can assist physicians to make personalized treatment decisions and thereby improving the overall quality of life of patients that are currently selected for APM.

Therefore, the objective of this IPDMA is to assess whether there are subgroups of patients with degenerative meniscus lesions who benefit from APM in comparison with non-surgical or sham treatment.

Methods

The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) statement and is registered in PROSPERO with registration number: CRD42017067240. [25] The first part of the method section describes a regular systematic review to identify eligible papers and invite the study authors to collaborate and contribute data. The second part describes the analysis with the individual participant data.

Patient and Public Involvement

Patients and members of the public were not involved in development of the protocol. A panel of patient representatives will provide detailed input regarding outcomes and the interpretation of the results from this IPDMA.

Part 1: Identifying eligible papers & data collection

Eligibility criteria

This IPDMA will include RCTs that evaluated the effectiveness of (partial) meniscectomy compared to non-surgical or sham treatments in persons with MRI-verified degenerative meniscus lesions. Degenerative meniscus lesions are typically observed in middle-aged and older people and may be the result of early degenerative knee disease. Persistent knee symptoms may encompass knee pain, limitation of function, and mechanical symptoms such as the sensation of catching or locking of the knee. Non-surgical or sham treatments may include, but are not limited to, sham surgery, pain and/or anti-inflammatory medication, exercise programs, and/or watchful waiting. Trials that included persons with traumatic meniscal lesions, defined as being the result of a specific traumatic incident will be excluded. There will be no restrictions on publication date, type of setting, length of follow up, or language.

Identification and selection of eligible trials

The search strategy described by Thorlund et al. [7] will be adopted to systematically search for eligible trials in Medline, Embase, CINAHL, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). (Additional file 1) The identified studies will be exported to EROS (Early Review Organizing Software, developed by Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina) to remove duplicates, and

randomly allocate references to two independent reviewers responsible for screening and selection. The two reviewers will independently screen all titles and abstracts of identified reports for eligibility. Full-text copies of all publications regarded as potentially eligible for inclusion, or where there is any uncertainty, will subsequently be assessed. Trials will be included when they meet the eligibility criteria. Any discrepancies between reviewers will be resolved by discussion, and if necessary, a third reviewer will be consulted. In addition, the reference lists of included studies will be reviewed to identify additional eligible trials. The electronic database search will be supplemented by searching for additional eligible trials in the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, which contains the trial registration datasets provided by several registries. This portal includes 16 national and international primary registries, including ClinicalTrials.gov, ANZCTR, JPRN, and ISRCTN. The corresponding authors of eligible trials will be invited to collaborate in the current IPDMA by sharing their data.

Collection of individual participant data

Data collection and transfer

Time and effort will be spent in tracing and encouraging original investigators to share their trial data. If no reply is received on a first invitation, additional inquiries will be sent, including inquiries sent to alternative email addresses identified for the corresponding author, inquiries sent to listed co-authors, and to the institution of the corresponding author listed in the original publication. The principal investigators of the original trials collaborating in the current project will be encouraged to actively participate in the IPDMA and discuss and finalize the definitions and outcomes to be assessed and the analytical processes proposed. Where possible, a face-to-face collaborator meeting will be scheduled, at which key decisions, including the project design, analysis plan, and interpretation of findings will be discussed. Before sharing of the de-identified data, we will sign a data sharing agreement with those principal investigators of the original trials that are interested in collaboration, in which we will arrange that the research data will be used for the declared purposes and the data will be stored on secured servers located in the Netherlands.

Data check and risk of bias

All received data will first be validated to match the results of the original publication. Statistical tests will be repeated and analyzed in R (R Foundation for Statistical Computing, Vienna, Austria). The trial data provided by

original investigators will be checked for consistency, plausibility, integrity of randomization, and reproducibility of published trial results. The aims of checking data are to increase the probability that data supplied are accurate, and to confirm that trials were appropriately randomized. Inconsistencies will be discussed and resolved with the individual investigators. All checked and de-identified data of randomized participants will be entered into a pooled database, and every trial will be assigned a trial number. Data will include characteristics relating to the participants (age, gender, body mass index (BMI)); radiographic information on knee osteoarthritis; onset, duration, and severity of symptoms; generic and disease-specific health-related quality-of-life); non-surgical or sham procedure; trial (sample size, setting, allocation concealment); and outcome measures of interest. For eligible trials of which original data is not available the aggregated data from trial reports will be collected.

Checking the IPD directly can provide more reliable investigations of key potential biases, some of which might be reduced or alleviated in the process. The risk of bias in included trials will be independently assessed by checking the IPD directly. Randomization and allocation concealment will be assessed by checking if both treatment arms are balanced in every study.[26] The advantage of an IPDMA is that we can also include outcomes not reported by the original journal article, possibly reducing outcome reporting bias by checking all relevant outcomes at the same time. In order to avoid ecological bias, the within-trial information will be examined for individual predictors of treatment effect, separately from the across-trial information.[27] The potential for publication bias and small study effects will be examined, in the context of visual inspection, using a contour-enhanced funnel plot.[28,29] To avoid availability bias, aggregated data from studies lacking individual participant data will be used to consider their potential impact.

Missing data

The final IPDMA dataset will have a multilevel (i.e. clustered) structure, where the individual trials are the levels (i.e. clusters). A foreseen feature of this dataset will be that some variables will be systematically missing, that is missing for all individuals in one or more trials. Next to systematically missing variables, we may also encounter sporadically missing variables, that is missing for some but not all individuals in one or more trials.

In order to optimally use the available participant data, reduce bias, and to increase statistical efficiency, incomplete data will be imputed using imputation methods that handle both systematically and sporadically

missing covariates in a two-level structure using hierarchical multiple imputations by chained equations (MICE). [30–33]

Outcomes variables

The most important outcomes according to surgeons and patients is treatment effect, determined as the difference between the intervention (surgery) and control group (non-surgical treatment) in knee pain, function and quality of life 2 years after the intervention. The preferred outcome measure instrument will be the Knee injury and Osteoarthritis Outcome Scale (KOOS). The KOOS is an instrument developed with the purpose of evaluating short-term and long-term symptoms and function in subjects with a knee injury and osteoarthritis. The KOOS consists of 5 subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee-related quality of life and a composite score can be calculated (referred to as the KOOS5). The KOOS has been validated for several orthopedic interventions such as anterior cruciate ligament reconstruction, meniscectomy and total knee replacement. [34] The score of the KOOS pain subscales will be compared between the intervention and control group across the included studies. Other measurement instrument targeted at quantifying pain will be standardized and combined in one single pain outcome. The functional outcome will be measured by using the KOOS function subscale or equivalent outcome aimed to measure function. The health quality of life will be measured by using the EuroQol-5 dimensions (EQ5D) questionnaire or the 36-Item Short Form Survey (SF-36).

Other outcomes of interest will include the difference between intervention and control group in adverse events (defined as deep venous thrombosis, pulmonary thromboembolism, venous thromboembolism, infection, and death) associated with the intervention from baseline to 2 years after intervention; difference in mental health; difference in risk for future knee replacement surgery between groups (feasibility will depend on whether the follow up of the trials will be long enough to capture the events), and the effect of follow-up time after the intervention on the treatment effect.

Part 2: Analysis

Treatment effect

The IPDMA will be used to assess the general effectiveness of APM in comparison with non-surgical or sham treatments in patients with knee symptoms and degenerative meniscal lesions. For this part, we will apply both

a two-stage and one-stage approach.[35] In the two-stage approach, we will perform regression analyses for each study to obtain effect estimates separately. Thereafter these are pooled in a random effects model (to account for heterogeneity) like a regular meta-analysis. The random effects models in the two-stage will be analyzed using the restricted maximum likelihood (REML) approach with the Hartung-Knapp-Sidik-Jonkman method for continuous outcomes to account for uncertainty due to heterogeneity.[36] The two-stage approach is ideal for assessing pooled treatment effect and detect heterogeneity. However, it is difficult to detect non-linear trends or account for correlating covariates.

In the one-stage approach, the IPD from all studies will be analyzed simultaneously by adopting a single statistical model (random effects model) that fully accounts for heterogeneity across studies whilst accounting for the clustering of participants within studies. The one-stage approach is more flexible and more exact compared to the two-stage but can face computational difficulties. Therefore, the results from the one-stage will be compared to the results of the two-stage and differences will be investigated. The random effects models in the one-stage will be analyzed using the REML approach with the Kenward-Rogers approach for continuous outcome and the maximum likelihood method (ML) with quadrature for binary or survival outcomes.[35,37,38] Heterogeneity will be addressed by I^2 and τ^2, reflecting the heterogeneity between studies. To reflect the variation of the treatment effect in a different setting, 95% prediction intervals will be reported to provide more information on the expected effect in future patients.[39]

A key advantage of a one-stage approach is the flexibility in terms of the models that may be fitted compared to a two-stage approach. One-stage models allow for the inclusion of multiple covariates in a single model, multiple random-effects on different parameters, correlation between covariates and the separation of within and across-trials information. It is this flexibility that is essential to the primary objective of this IPDMA. [40]

Heterogeneity in treatment effect (subgroups)

To investigate which patients may benefit from (partial) meniscectomy we will assess whether the treatment effect is modified by baseline patient characteristics. First, relevant baseline patient characteristics will be identified. Modern regression procedures with penalization of estimated regression coefficients will be applied for the selection of those characteristics that are independent predictors of the treatment effect.[41,42] A full list of the baseline patient characteristics that will be taken into consideration are listed in Additional file 2.

Second, it will be assessed whether these identified independent baseline predictors, (individually or in combinations) modify the treatment effect. Effect modification will be assessed with a random effects model. In this model, a dummy for the particular study will be the random effect and APM (yes vs. no), the potential effect modifier, and an interaction term (APM * potential effect modifier) will be included as fixed variables and the treatment effect as dependent variables.[33] The illustrated approach will allow assessment of effect modification without overfitting the data and reducing the risk of type I errors.

In addition, we want to ensure that patient characteristics deemed to be of high clinical relevance in day-to-day clinical practice are ultimately evaluated for effect modification. For this purpose, alongside the procedure described above, we will also assess a set of predefined patient characteristics deemed to be of high clinical relevance for effect modification. To define these characteristics the IPDMA collaborators will be asked to provide a top-3 of characteristics that they regard as most clinically relevant. Subsequently, it will be assessed whether the overall top-3 of these predefined patient characteristics modify the treatment effect. Predefining these characteristics will be performed before actual analysis of the data.

Sensitivity analysis

To analyze the robustness of the results from the IPDMA, several sensitivity analyses will be performed. First, to evaluate the impact of including aggregated data of published trials (of which the IPD was not available in the meta-analysis), analyses will be performed in which we either only include studies with IPD available or only studies of which only aggregated data was available. Second, to determine the effect of imputation of missing values on the study outcome, analyses will be performed in which we impute either only systematic missing variables, only sporadically missing variables (within trials) or not impute at all. Third, we will study whether the persistence of complains is a relevant subgrouping variable.

All analyses will be performed according to the intention-to-treat principle.

Publication considerations

The draft version of the final manuscript will be circulated among the collaborators for further discussion prior to submission for publication. The authors of the IPDMA paper(s) will be the project team managing the IPDMA, followed by the collaborators, whom are the principal investigators that collaborated in the current project by sharing their trial data and commenting upon the results and draft of the papers.

Study status

Currently, we are contacting the original investigators of the included trials and encourage them to share the trial data. We aim to start the analyses at the end of 2019 and publish our results in 2020/2021.

Discussion

In the last decade, several RCTs found no or very little benefit of APM compared to non-operative or sham treatment in patients with MRI confirmed degenerative meniscus tears,[43–52] although there is circumstantial evidence that it is effective in middle-aged patients with degenerative meniscal symptoms.[53] These findings started a discussion on the effectiveness of the surgery and the methodology used in those RCTs by both orthopedic surgeons and other health care professionals.[19–23,54] The published studies were not able to adequately tease out whether or not there are subgroups that do additionally benefit from APM. This has resulted in a deadlock: APM is continued to be performed, despite Level I evidence that discourage the treatment.[13]

The proposed IPDMA provides the opportunity to evaluate the relationship between potential clinically-relevant baseline characteristics and the effectiveness of the APM of all patients that have been included in the trials, and to possibly detect subgroups that may benefit from APM. IPDMA is the gold standard of systematic review and meta-analysis that provides more power and is less prone to bias compared to meta-analysis on aggregated data. To our knowledge, this is the first study that combines the individual participant data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery. The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of existing studies is combined to achieve large patient numbers. This prevents additional trials and patient involvement. Moreover, combining individual patient data enables us to analyze the effects of within-study and between-study moderators of effect sizes, even though the original studies were too small to analyze such samples.

Although IPDMA is the best method to detect possible subgroups, performing an IPDMA also comes with several challenges. First, all individual patient data from the eligible trials have to be collected. This time-intensive task often requires us to contact the principal investigators multiple times to invite them to collaborate. Unfortunately, data is sometimes not available, not accessible or sharing is not possible due to a

stringent informed consent that only enables the use of the data for the original study. While there are guiding principles for open data management and sharing (Findable, Accessible, Interoperable and Reusable data principles (FAIR principles)) these often conflict with the rules of the informed consent or national legislations, creating a tension between privacy and reuse of (anonymous) medical data.[55] This might limit number of studies that can be included in this IPDMA. Second, there are multiple ways to measure knee pain, knee function or general quality of life. Every researcher can or will use their own set of outcome parameters, dependent on the experience of the researcher with a certain questionnaire/scoring system, preference or the time-dependent academic insights of the optimal questionnaire/scoring system (especially if studies have been published in different time periods, i.e. different research paradigm). As a result, we are dependent on the outcomes that have been used in the included studies in the IPDMA and cause systematic missing variables in the final pooled dataset of an IPDMA. These missing variables pose a methodological challenge, because they require advanced imputation that preserve the hierarchical structure of the data followed by the one-stage meta-analysis.[56]

In conclusion, the aim of this project is to identify potential subgroups of patients with degenerative meniscus lesions who may benefit from APM. It will provide the evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons consider APM. Identifying potential subgroups can improve the quality of life of patients who *do* truly benefit from the treatment, and can perhaps be implemented with a clinical decision aid. In case we do not find a subgroup that has additional benefits from the treatment, it can help to reduce the number of APMs, and thus less risk of, e.g. complications.[9,57]

List of abbreviations

APM	Arthroscopic partial meniscectomy
RCT	Randomized controlled trial
IPDMA	Individual participant data meta-analysis
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols
CENTRAL	Cochrane Central Register of Controlled Trials
EROS	Early Review Organizing Software
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
BMI	Body mass index

MICE	Multiple imputations by chained equations
KOOS	Knee injury and Osteoarthritis Outcome Scale
EQ5D	EuroQol-5 dimensions questionnaire
SF-36	36-Item Short Form Survey
REML	Restricted maximum likelihood
ML	Maximum likelihood
FAIR	Findable, Accessible, Interoperable and Reusable data principles

Declarations

Ethics approval and consent to participate

All principal investigators provided written confirmation that all participants included in the original trials had given informed consent.

Consent for publication

Not applicable

Availability of data and material

Following the ICMJE's data sharing statement policy, de-identified individual participant data will be made available at the end of the research project, including the study protocol, beginning 9 months and ending 36 months following article publication. The data will be shared with investigators whose proposed use of the data has been approved by a review committee to be identified for this purpose. Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse without investigator support other than deposited metadata.

Competing interests

The authors declare that they have no competing interest

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Authors' contributions

JR, GH, and MR conceived the idea for the review, with inputs from HØ, MR, ER, KH, VG, RP, and ME. SW, MR, JR and GH designed and drafted the protocol. All authors (SW, MR, JR, HØ, MR, ER, KH, VG, RP, ME, and GH) contributed to subsequent revisions and approved the protocol prior to its submission. GH is the guarantor.

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Additional files:

File name: Additional file 1

File format: Additional_file_1.doc

Title: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

Description: The systematic search strategy in Medline (PubMed), Embase, CENTRAL, CINAHL, Web of Science and WHO trial register to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

File name: Additional file 2

File format: Additional_file_2.doc

Title: Potential clinically relevant baseline characteristics

Description: A list of all identified potential clinically relevant baseline characteristics divided into 5 categories: General characteristics, patient history, meniscus information, symptoms and quality of life.

Additional file 1: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

	Medline (Pubmed)	Embase	Cochrane Database of registered trial (CENTRAL)	Cumulative Index to Nursing and Allied Health Literature (CINAHL)	Web of Science (Thomson Reuter)	WHO trial register
1	"Menisci, Tibial/surgery"[Mesh]	Arthroscopic meniscectomy.ti,ab,kw.	MeSH descriptor: [Menisci, Tibial] explode all trees and with qualifier(s): [Injuries – IN, Surgery – SU]	TI "Degenerative meniscal tear" OR AB "Degenerative meniscal tear"	arthroscopy AND knee	"Menisc*" in the title
2	"Menisci, Tibial/injuries"[Mesh]	Arthroscopic debridement.ti,ab,kw.	MeSH descriptor: [Arthroscopy] explode all trees	MH "Arthroscopy" OR "arthroscopy"	arthroscopic meniscectomy	"Menisc*" in the condition
3	"Degenerative meniscal tear" [TIAB]	Arthroscopic lavage.ti,ab,kw.	MeSH descriptor: [Knee] explode all trees	MH "knee" OR AB "knee" OR TI "knee"	arthroscopic debridement	"Menisc*" in the intervention
4	"Arthroscopic lavage"[TIAB]	Degenerative meniscal tear.ti,ab,kw.	2 and 3	2 AND 3	arthroscopic lavage	1 OR 2 OR 3
5	"Arthroscopic debridement"[TIAB]	knee meniscus/ or meniscus tibial.mp	Degenerative meniscal tear:ti,ab,kw (Word variations have been searched)	MH "Meniscal Injuries" OR AB "meniscal Injuries" OR TI "meniscal Injuries"	degenerative meniscal tear	
6	"arthroscopic meniscectomy"[TIAB]	exp knee arthroscopy/	Arthroscopic lavage:ti,ab,kw (Word variations have been searched)	MH "Menisci, Tibial" OR AB "tibial meniscus" OR TI "tibial meniscus"	menisci, tibial AND surgery	
7	"Arthroscopy"[TIAB] AND "Knee"[TIAB]	1 or 2 or 3 or 4 or 5 or 6	Arthroscopic debridement:ti,ab,kw (Word variations have been searched)	TI "Arthroscopic lavage" OR AB "Arthroscopic lavage"	menisci, tibial AND injury	
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	randomized controlled trial/	arthroscopic meniscectomy:ti,ab,kw (Word variations have been searched	TI "Arthroscopic debridement" OR AB "Arthroscopic debridement"	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	
9	"Randomized" [TIAB]	randomized.ti,ab,kw.	1 or 4 or 5 or 6 or 7 or 8	TI "arthroscopic meniscectomy" OR AB "arthroscopic meniscectomy"	randomized	
10	"Randomized controlled trial"[Publication Type]	randomized.ti,ab,kw.		1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	randomised	
11	"randomized controlled trials as topic"[Mesh]	random allocation.mp.		TI "Randomized" OR AB "Randomized"	random allocation	
12	"Random allocation"[Mesh]	randomized.mp.		MH "Randomized Controlled Trials" OR TI "Randomized Controlled Trials" OR AB "Randomized Controlled Trials"	control group	
13	"Control group"[TIAB]	"randomized controlled trial (topic)"/		MH "Random Assignment" OR AB "Random Assignment" OR TI "Random Assignment"	cross-over stud*	
14	"Control groups"[Mesh]	control group.mp.		AB "Random Allocation" OR TI "Random Allocation"	randomized controlled trial	
15	"Cross-over studies"[TIAB]	control group/		(MH "Control Group") OR (AB "Control Group") OR (TI "Control Group")	9 OR 10 OR 11 OR 12 OR 13 OR 14	
16	"Cross-over study"[TIAB]	crossover procedure/		(MH "Crossover Design") AND (AB "Crossover Design") AND (TI "Crossover Design")	8 AND 15	
17	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16		11 OR 12 OR 13 OR 14 OR 15 OR 16		
18	8 AND 17	7 and 17		10 AND 17		

Additional file 2. Potential clinically relevant baseline characteristics

Category	Characteristics
General characteristics	
	Age
	Gender
	Weight, height (BMI)
Patient history	
	History of medication for knee symptoms
	History of serious knee injury
	History of knee surgery
	Family history of knee OA / of knee replacement surgery
	History of osteoarthritis
Meniscus information	
	Medial/lateral meniscus
	Radiographic severity of knee OA
	MRI meniscus extrusion
	MRI meniscus tear type / degeneration
	Onset of symptoms (e.g. gradual, after event, suddenly)
	Duration of symptoms
	Grading of work and sporting activities
Symptoms	
	Signs and symptoms during specific physical examination test
	Knee locking symptoms / mechanical symptoms
	Knee related daily function
	Knee pain
	Knee stiffness
	Knee related quality of life
	Knee swelling
Quality of life	
	Generic quality of life (EQ-5D / SF36)
	Mental health score

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	65, 99
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	6 - 36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	318 - 320
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	315-317
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	315-317
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	75-93

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	94-95
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	104-113
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	114-130
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Additional file 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	144-155
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	130-142
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	130-142
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	175-195 + Additional file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	175-195 + Additional file 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	143-174
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	196-240

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	241-248
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	156-165
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	

BMJ Open

Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with MRI confirmed degenerative meniscus lesions: a protocol for an individual participant data meta-analysis

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Arthroscopic surgery, Meniscectomy, Osteoarthritis, Individual Participant Data Meta-Analysis, IPDMA

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Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with MRI confirmed degenerative meniscus lesions: a protocol for an individual participant data meta-analysis

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Word count: 3886

Abstract

Introduction

Arthroscopic partial meniscectomy (APM) after degenerative meniscus tears is one of the most frequently performed surgeries in orthopedics. Although several randomized controlled trials (RCTs) have been published that showed no clear benefit compared to sham treatment or non-surgical treatment, the incidence of APM remains high. The common perception by most orthopedic surgeons is that there are subgroups of patients that *do* need APM to improve, and they argue that each study sample of the existing trials is not representative for the day-to-day patients in the clinic. Therefore, the objective of this individual participant data meta-analysis (IPDMA) is to assess whether there are subgroups of patients with degenerative meniscus lesions who benefit from APM in comparison with non-surgical or sham treatment.

Methods and Analysis

An existing systematic review will be updated to identify all RCTs worldwide that evaluated APM compared to sham- or non-surgical treatment in patients with knee symptoms and degenerative meniscus tears. Time and effort will be spent in contacting principal investigators of the original trials and encourage them to collaborate in this project by sharing their trial data. All individual participant data will be validated for missing data, internal data consistency, randomization integrity and censoring patterns. After validation, all datasets will be combined and analyzed using a one- and two-staged approach. The most important outcome will be the difference between APM and control groups in knee pain, function and quality of life 2 years after the intervention. Other outcomes of interest will include the difference in adverse events and mental health.

Ethics and dissemination

All trial data will be anonymized before it is shared with the authors. The data will be encrypted and stored on secure server located in the Netherlands. No major ethical concerns remain. This IPDMA will provide the evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons consider APM. The results will be submitted for publication in a peer-reviewed journal.

Registration

Prospero registration number: CRD42017067240

Keywords

Arthroscopic surgery; Meniscectomy; Osteoarthritis; Individual Participant Data Meta-Analysis; IPDMA

Article Summary

Strengths and limitations of this study

- To our knowledge, this is the first study that combines the individual participant data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery.
- The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of existing studies is combined to achieve large patient numbers.
- Trial data might not be available, not accessible or sharing is not possible due to a stringent informed consent that only enables the use of the data for the original study. This might limit the amount of trials we can include.
- We are dependent on the outcomes that have been used in the included studies. These can differ between studies.

Background

Arthroscopic partial meniscectomy (APM) is a regularly performed surgical procedure intended to treat symptoms believed to be caused by degenerative meniscus lesions. [1–3] Degenerative lesions are typically observed in middle-aged and older people, and are caused by chronic degenerative processes. [4,5] Over the past decade, evidence has accumulated that questions both the rationale for, and the effectiveness of APM for degenerative meniscus lesions. [6,7] Additionally, concerns have been expressed on the harms associated with the procedure [7–9] and the potential detrimental effect of the procedure on the progression of osteoarthritis. [10–12] Still, the number of surgical procedures performed in the treatment of degenerative meniscus lesions remains high. [13–17]

Orthopedic surgeons have expressed concerns about the generalizability of the trial results and point out that the study samples are not representative of the subjects they select for surgery in their day-to-day clinical practice.[18–24] The common perception by most surgeons is that there are subgroups of patients that *do* need the procedure to improve.[8] Hence, applying the mean effects of randomized controlled trials (RCTs) to individual patients in day-to-day practice runs against the intuitive approach of doctors to use the specific characteristics of a particular patient to tailor management accordingly. Unfortunately, the identification of subgroups of patients that may/may not benefit from the procedure has been problematic, as the individual trials performed so far were too small to perform valid and reliable subgroup analyses.

An individual participant data meta-analysis (IPDMA), i.e. a meta-analysis on the original individual participant data of previously performed trials, has been described as the gold standard of systematic review and meta-analysis. An IPDMA offers the unique opportunity to recode, and re-analyze all original trial data, and evaluate the effectiveness of surgical treatment of degenerative meniscus lesions and to identify potential subgroups more likely to benefit from the intervention. Identifying these subgroups can assist physicians to make personalized treatment decisions and thereby improving the overall quality of life of patients that are currently selected for APM.

Therefore, the objective of this IPDMA is to assess whether there are subgroups of patients with degenerative meniscus lesions who benefit from APM in comparison with non-surgical or sham treatment.

Methods

The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) statement and is registered in PROSPERO with registration number: CRD42017067240. [25] The first part of the method section describes a regular systematic review to identify eligible papers and invite the study authors to collaborate and contribute data. The second part describes the analysis with the individual participant data.

Patient and Public Involvement

Patients and members of the public were not involved in development of the protocol. A panel of patient representatives will provide detailed input regarding outcomes and the interpretation of the results from this IPDMA.

Part 1: Identifying eligible papers & data collection

Eligibility criteria

This IPDMA will include RCTs that evaluated the effectiveness of (partial) meniscectomy compared to non-surgical or sham treatments in persons with MRI-verified degenerative meniscus lesions. Degenerative meniscus lesions are typically observed in middle-aged and older people and may be the result of early degenerative knee disease. Persistent knee symptoms may encompass knee pain, limitation of function, and mechanical symptoms such as the sensation of catching or locking of the knee. Non-surgical or sham treatments may include, but are not limited to, sham surgery, pain and/or anti-inflammatory medication, exercise programs, and/or watchful waiting. Trials that included persons with traumatic meniscal lesions, defined as being the result of a specific traumatic incident will be excluded. There will be no restrictions on publication date, type of setting, length of follow up, or language.

Identification and selection of eligible trials

The search strategy described by Thorlund et al. [7] will be adopted to systematically search for eligible trials in Medline, Embase, CINAHL, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). (Additional file 1) The identified studies will be exported to EROS (Early Review Organizing Software, developed by Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina) to remove duplicates, and

randomly allocate references to two independent reviewers responsible for screening and selection. The two reviewers will independently screen all titles and abstracts of identified reports for eligibility. Full-text copies of all publications regarded as potentially eligible for inclusion, or where there is any uncertainty, will subsequently be assessed. Trials will be included when they meet the eligibility criteria. Any discrepancies between reviewers will be resolved by discussion, and if necessary, a third reviewer will be consulted. In addition, the reference lists of included studies will be reviewed to identify additional eligible trials. The electronic database search will be supplemented by searching for additional eligible trials in the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, which contains the trial registration datasets provided by several registries. This portal includes 16 national and international primary registries, including ClinicalTrials.gov, ANZCTR, JPRN, and ISRCTN. The corresponding authors of eligible trials will be invited to collaborate in the current IPDMA by sharing their data.

Collection of individual participant data

Data collection and transfer

Time and effort will be spent in tracing and encouraging original investigators to share their trial data. If no reply is received on a first invitation, additional inquiries will be sent, including inquiries sent to alternative email addresses identified for the corresponding author, inquiries sent to listed co-authors, and to the institution of the corresponding author listed in the original publication. The principal investigators of the original trials collaborating in the current project will be encouraged to actively participate in the IPDMA and discuss and finalize the definitions and outcomes to be assessed and the analytical processes proposed. Where possible, a face-to-face collaborator meeting will be scheduled, at which key decisions, including the project design, analysis plan, and interpretation of findings will be discussed. Before sharing of the de-identified data, we will sign a data sharing agreement with those principal investigators of the original trials that are interested in collaboration, in which we will arrange that the research data will be used for the declared purposes and the data will be stored on secured servers located in the Netherlands.

Data check and risk of bias

All received data will first be validated to match the results of the original publication. Statistical tests will be repeated and analyzed in R (R Foundation for Statistical Computing, Vienna, Austria). The trial data provided by

original investigators will be checked for consistency, plausibility, integrity of randomization, and reproducibility of published trial results. The aims of checking data are to increase the probability that data supplied are accurate, and to confirm that trials were appropriately randomized. Inconsistencies will be discussed and resolved with the individual investigators. All checked and de-identified data of randomized participants will be entered into a pooled database, and every trial will be assigned a trial number. Data will include characteristics relating to the participants (age, gender, body mass index (BMI)); radiographic information on knee osteoarthritis; onset, duration, and severity of symptoms; generic and disease-specific health-related quality-of-life); non-surgical or sham procedure; trial (sample size, setting, allocation concealment); and outcome measures of interest. For eligible trials of which original data is not available the aggregated data from trial reports will be collected.

Checking the IPD directly can provide more reliable investigations of key potential biases, some of which might be reduced or alleviated in the process. The risk of bias in included trials will be independently assessed by checking the IPD directly. Randomization and allocation concealment will be assessed by checking if both treatment arms are balanced in every study.[26] The advantage of an IPDMA is that we can also include outcomes not reported by the original journal article, possibly reducing outcome reporting bias by checking all relevant outcomes at the same time. In order to avoid ecological bias, the within-trial information will be examined for individual predictors of treatment effect, separately from the across-trial information.[27]

The potential for publication bias and small study effects will be examined, in the context of visual inspection, using a contour-enhanced funnel plot.[28,29] To avoid availability bias, aggregated data from studies lacking individual participant data will be used to consider their potential impact. To enable to assessment of heterogeneity between the included trials, the following characteristics of the included RCTs will be compared and described in a table: 1) selection of participants, 2) inclusion- and exclusion criteria, 3) description of clinical path prior to inclusion, 4) number of participants that declined participation, 5) diagnostic characteristics, 6) work characteristics, 7) socioeconomic characteristics, 8) intervention and control treatment, 9) cross-over, 10) other health care services during follow-up, and 11) outcome measures.

Missing data

The final IPDMA dataset will have a multilevel (i.e. clustered) structure, where the individual trials are the levels (i.e. clusters). A foreseen feature of this dataset will be that some variables will be systematically missing, that is missing for all individuals in one or more trials. Next to systematically missing variables, we may also encounter sporadically missing variables, that is missing for some but not all individuals in one or more trials.

In order to optimally use the available participant data, reduce bias, and to increase statistical efficiency, incomplete data will be imputed using imputation methods that handle both systematically and sporadically missing covariates in a two-level structure using hierarchical multiple imputations by chained equations (MICE). [30–33]

Outcomes variables

The most important outcomes according to surgeons and patients is treatment effect, determined as the difference between the intervention (surgery) and control group (non-surgical treatment) in knee pain, function and quality of life 2 years after the intervention. The preferred outcome measure instrument will be the Knee injury and Osteoarthritis Outcome Scale (KOOS). The KOOS is an instrument developed with the purpose of evaluating short-term and long-term symptoms and function in subjects with a knee injury and osteoarthritis. The KOOS consists of 5 subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee-related quality of life and a composite score can be calculated (referred to as the KOOS5). The KOOS has been validated for several orthopedic interventions such as anterior cruciate ligament reconstruction, meniscectomy and total knee replacement. [34] The score of the KOOS pain subscales will be compared between the intervention and control group across the included studies. Other measurement instrument targeted at quantifying pain will be standardized and combined in one single pain outcome. The functional outcome will be measured by using the KOOS function subscale or equivalent outcome aimed to measure function. The health quality of life will be measured by using the EuroQol-5 dimensions (EQ5D) questionnaire or the 36-Item Short Form Survey (SF-36).

Other outcomes of interest will include the difference between intervention and control group in adverse events (defined as deep venous thrombosis, pulmonary thromboembolism, venous thromboembolism, infection, and death) associated with the intervention from baseline to 2 years after intervention; difference in mental health; difference in risk for future knee replacement surgery between groups (feasibility will depend

on whether the follow up of the trials will be long enough to capture the events), and the effect of follow-up time after the intervention on the treatment effect.

Part 2: Analysis

Treatment effect

The IPDMA will be used to assess the general effectiveness of APM in comparison with non-surgical or sham treatments in patients with knee symptoms and degenerative meniscal lesions. For this part, we will apply both a two-stage and one-stage approach.[35] In the two-stage approach, we will perform regression analyses for each study to obtain effect estimates separately. Thereafter these are pooled in a random effects model (to account for heterogeneity) like a regular meta-analysis. The random effects models in the two-stage will be analyzed using the restricted maximum likelihood (REML) approach with the Hartung-Knapp-Sidik-Jonkman method for continuous outcomes to account for uncertainty due to heterogeneity.[36] The two-stage approach is ideal for assessing pooled treatment effect and detect heterogeneity. However, it is difficult to detect non-linear trends or account for correlating covariates.

In the one-stage approach, the IPD from all studies will be analyzed simultaneously by adopting a single statistical model (random effects model) that fully accounts for heterogeneity across studies whilst accounting for the clustering of participants within studies. The one-stage approach is more flexible and more exact compared to the two-stage but can face computational difficulties. Therefore, the results from the one-stage will be compared to the results of the two-stage and differences will be investigated. The random effects models in the one-stage will be analyzed using the REML approach with the Kenward-Rogers approach for continuous outcome and the maximum likelihood method (ML) with quadrature for binary or survival outcomes.[35,37,38] Heterogeneity will be addressed by I^2 and τ^2, reflecting the heterogeneity between studies. To reflect the variation of the treatment effect in a different setting, 95% prediction intervals will be reported to provide more information on the expected effect in future patients.[39]

A key advantage of a one-stage approach is the flexibility in terms of the models that may be fitted compared to a two-stage approach. One-stage models allow for the inclusion of multiple covariates in a single model, multiple random-effects on different parameters, correlation between covariates and the separation of within and across-trials information. It is this flexibility that is essential to the primary objective of this IPDMA. [40]

Heterogeneity in treatment effect (subgroups)

To investigate which patients may benefit from (partial) meniscectomy we will assess whether the treatment effect is modified by baseline patient characteristics. First, relevant baseline patient characteristics will be identified. Modern regression procedures with penalization of estimated regression coefficients will be applied for the selection of those characteristics that are independent predictors of the treatment effect.[41,42] A full list of the baseline patient characteristics that will be taken into consideration are listed in Additional file 2. Second, it will be assessed whether these identified independent baseline predictors, (individually or in combinations) modify the treatment effect. Effect modification will be assessed with a random effects model. In this model, a dummy for the particular study will be the random effect and APM (yes vs. no), the potential effect modifier, and an interaction term (APM * potential effect modifier) will be included as fixed variables and the treatment effect as dependent variables.[33] The illustrated approach will allow assessment of effect modification without overfitting the data and reducing the risk of type I errors.

In addition, we want to ensure that patient characteristics deemed to be of high clinical relevance in day-to-day clinical practice are ultimately evaluated for effect modification. For this purpose, alongside the procedure described above, we will also assess a set of predefined patient characteristics deemed to be of high clinical relevance for effect modification. To define these characteristics the IPDMA collaborators will be asked to provide a top-3 of characteristics that they regard as most clinically relevant. Subsequently, it will be assessed whether the overall top-3 of these predefined patient characteristics modify the treatment effect. Predefining these characteristics will be performed before actual analysis of the data.

Sensitivity analysis

To analyze the robustness of the results from the IPDMA, several sensitivity analyses will be performed. First, to evaluate the impact of including aggregated data of published trials (of which the IPD was not available in the meta-analysis), analyses will be performed in which we either only include studies with IPD available or only studies of which only aggregated data was available. Second, to determine the effect of imputation of missing values on the study outcome, analyses will be performed in which we impute either only systematic missing variables, only sporadically missing variables (within trials) or not impute at all. Third, we will study whether the persistence of complains is a relevant subgrouping variable.

All analyses will be performed according to the intention-to-treat principle.

Publication considerations

The draft version of the final manuscript will be circulated among the collaborators for further discussion prior to submission for publication. The authors of the IPDMA paper(s) will be the project team managing the IPDMA, followed by the collaborators, whom are the principal investigators that collaborated in the current project by sharing their trial data and commenting upon the results and draft of the papers.

Study status

Currently, we are collecting the data and are contacting the original investigators of the included trials and encourage them to share the trial data. We have already received a part of the data and are still waiting on the data of a few trials. We expect to end data collection in Q1 2020. After validation of the data, we will start with the analyses. Our aim is to publish our results in 2020/2021.

Discussion

In the last decade, several RCTs found no or very little benefit of APM compared to non-operative or sham treatment in patients with MRI confirmed degenerative meniscus tears,[43–52] although there is some evidence that it is effective in middle-aged patients with degenerative meniscal symptoms.[53] These findings started a discussion on the effectiveness of the surgery and the methodology used in those RCTs by both orthopedic surgeons and other health care professionals.[19–23,54] The published studies were not able to adequately tease out whether or not there are subgroups that do additionally benefit from APM. This has resulted in a deadlock: APM is continued to be performed, despite Level I evidence that discourage the treatment.[13]

The proposed IPDMA provides the opportunity to evaluate the relationship between potential clinically-relevant baseline characteristics and the effectiveness of the APM of all patients that have been included in the trials, and to possibly detect subgroups that may benefit from APM. IPDMA is the gold standard of systematic review and meta-analysis that provides more power and is less prone to bias compared to meta-analysis on aggregated data. To our knowledge, this is the first study that combines the individual participant data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery. The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of

existing studies is combined to achieve large patient numbers. This prevents additional trials and patient involvement. Moreover, combining individual patient data enables us to analyze the effects of within-study and between-study moderators of effect sizes, even though the original studies were too small to analyze such samples.

Although IPDMA is the best method to detect possible subgroups, performing an IPDMA also comes with several challenges. First, all individual patient data from the eligible trials have to be collected. This time-intensive task often requires us to contact the principal investigators multiple times to invite them to collaborate. Unfortunately, data is sometimes not available, not accessible or sharing is not possible due to a stringent informed consent that only enables the use of the data for the original study. While there are guiding principles for open data management and sharing (Findable, Accessible, Interoperable and Reusable data principles (FAIR principles)) these often conflict with the rules of the informed consent or national legislations, creating a tension between privacy and reuse of (anonymous) medical data.[55] This might limit number of studies that can be included in this IPDMA. Second, there are multiple ways to measure knee pain, knee function or general quality of life. Every researcher can or will use their own set of outcome parameters, dependent on the experience of the researcher with a certain questionnaire/scoring system, preference or the time-dependent academic insights of the optimal questionnaire/scoring system (especially if studies have been published in different time periods, i.e. different research paradigm). As a result, we are dependent on the outcomes that have been used in the included studies in the IPDMA and cause systematic missing variables in the final pooled dataset of an IPDMA. These missing variables pose a methodological challenge, because they require advanced imputation that preserve the hierarchical structure of the data followed by the one-stage meta-analysis.[56]

In conclusion, the aim of this project is to identify potential subgroups of patients with degenerative meniscus lesions who may benefit from APM. It will provide the evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons consider APM. Identifying potential subgroups can improve the quality of life of patients who *do* truly benefit from the treatment, and can perhaps be implemented with a clinical decision aid. In case we do not find a subgroup that has additional benefits from the treatment, it can help to reduce the number of APMs, and thus less risk of, e.g. complications.[9,57]

List of abbreviations

APM	Arthroscopic partial meniscectomy
RCT	Randomized controlled trial
IPDMA	Individual participant data meta-analysis
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols
CENTRAL	Cochrane Central Register of Controlled Trials
EROS	Early Review Organizing Software
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
BMI	Body mass index
MICE	Multiple imputations by chained equations
KOOS	Knee injury and Osteoarthritis Outcome Scale
EQ5D	EuroQol-5 dimensions questionnaire
SF-36	36-Item Short Form Survey
REML	Restricted maximum likelihood
ML	Maximum likelihood
FAIR	Findable, Accessible, Interoperable and Reusable data principles

Declarations

Ethics approval and consent to participate

All principal investigators provided written confirmation that all participants included in the original trials had given informed consent.

Consent for publication

Not applicable

Availability of data and material

Following the ICMJE's data sharing statement policy, de-identified individual participant data will be made available at the end of the research project, including the study protocol, beginning 9 months and ending 36 months following article publication. The data will be shared with investigators whose proposed use of the data has been approved by a review committee to be identified for this purpose. Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse without investigator support other than deposited metadata.

Competing interests

The authors declare that they have no competing interest

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Authors' contributions

JR, GH, and MR conceived the idea for the review, with inputs from HØ, MR, ER, KH, VG, RP, and ME. SW, MR, JR and GH designed and drafted the protocol. All authors (SW, MR, JR, HØ, MR, ER, KH, VG, RP, ME, and GH) contributed to subsequent revisions and approved the protocol prior to its submission. GH is the guarantor.

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Additional files:

File name: Additional file 1

File format: Additional_file_1.doc

Title: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

Description: The systematic search strategy in Medline (PubMed), Embase, CENTRAL, CINAHL, Web of Science and WHO trial register to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

File name: Additional file 2

File format: Additional_file_2.doc

Title: Potential clinically relevant baseline characteristics

Description: A list of all identified potential clinically relevant baseline characteristics divided into 5 categories: General characteristics, patient history, meniscus information, symptoms and quality of life.

Additional file 1: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

	Medline (Pubmed)	Embase	Cochrane Database of registered trial (CENTRAL)	Cumulative Index to Nursing and Allied Health Literature (CINAHL)	Web of Science (Thomson Reuter)	WHO trial register
1	"Menisci, Tibial/surgery"[Mesh]	Arthroscopic meniscectomy.ti,ab,kw.	MeSH descriptor: [Menisci, Tibial] explode all trees and with qualifier(s): [Injuries – IN, Surgery – SU]	TI "Degenerative meniscal tear" OR AB "Degenerative meniscal tear"	arthroscopy AND knee	"Menisc*" in the title
2	"Menisci, Tibial/injuries"[Mesh]	Arthroscopic debridement.ti,ab,kw.	MeSH descriptor: [Arthroscopy] explode all trees	MH "Arthroscopy" OR "arthroscopy"	arthroscopic meniscectomy	"Menisc*" in the condition
3	"Degenerative meniscal tear" [TIAB]	Arthroscopic lavage.ti,ab,kw.	MeSH descriptor: [Knee] explode all trees	MH "knee" OR AB "knee" OR TI "knee"	arthroscopic debridement	"Menisc*" in the intervention
4	"Arthroscopic lavage"[TIAB]	Degenerative meniscal tear.ti,ab,kw.	2 and 3	2 AND 3	arthroscopic lavage	1 OR 2 OR 3
5	"Arthroscopic debridement"[TIAB]	knee meniscus/ or meniscus tibial.mp	Degenerative meniscal tear:ti,ab,kw (Word variations have been searched)	MH "Meniscal Injuries" OR AB "meniscal Injuries" OR TI "meniscal Injuries"	degenerative meniscal tear	
6	"arthroscopic meniscectomy"[TIAB]	exp knee arthroscopy/	Arthroscopic lavage:ti,ab,kw (Word variations have been searched)	MH "Menisci, Tibial" OR AB "tibial meniscus" OR TI "tibial meniscus"	menisci, tibial AND surgery	
7	"Arthroscopy"[TIAB] AND "Knee"[TIAB]	1 or 2 or 3 or 4 or 5 or 6	Arthroscopic debridement:ti,ab,kw (Word variations have been searched)	TI "Arthroscopic lavage" OR AB "Arthroscopic lavage"	menisci, tibial AND injury	
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	randomized controlled trial/	arthroscopic meniscectomy:ti,ab,kw (Word variations have been searched	TI "Arthroscopic debridement" OR AB "Arthroscopic debridement"	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	
9	"Randomized" [TIAB]	randomized.ti,ab,kw.	1 or 4 or 5 or 6 or 7 or 8	TI "arthroscopic meniscectomy" OR AB "arthroscopic meniscectomy"	randomized	
10	"Randomized controlled trial"[Publication Type]	randomized.ti,ab,kw.		1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	randomised	
11	"randomized controlled trials as topic"[Mesh]	random allocation.mp.		TI "Randomized" OR AB "Randomized"	random allocation	
12	"Random allocation"[Mesh]	randomized.mp.		MH "Randomized Controlled Trials" OR TI "Randomized Controlled Trials" OR AB "Randomized Controlled Trials"	control group	
13	"Control group"[TIAB]	"randomized controlled trial (topic)"/		MH "Random Assignment" OR AB "Random Assignment" OR TI "Random Assignment"	cross-over stud*	
14	"Control groups"[Mesh]	control group.mp.		AB "Random Allocation" OR TI "Random Allocation"	randomized controlled trial	
15	"Cross-over studies"[TIAB]	control group/		(MH "Control Group") OR (AB "Control Group") OR (TI "Control Group")	9 OR 10 OR 11 OR 12 OR 13 OR 14	
16	"Cross-over study"[TIAB]	crossover procedure/		(MH "Crossover Design") AND (AB "Crossover Design") AND (TI "Crossover Design")	8 AND 15	
17	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16		11 OR 12 OR 13 OR 14 OR 15 OR 16		
18	8 AND 17	7 and 17		10 AND 17		

Additional file 2. Potential clinically relevant baseline characteristics

Category	Characteristics
General characteristics	
	Age
	Gender
	Weight, height (BMI)
Patient history	
	History of medication for knee symptoms
	History of serious knee injury
	History of knee surgery
	Family history of knee OA / of knee replacement surgery
	History of osteoarthritis
Meniscus information	
	Medial/lateral meniscus
	Radiographic severity of knee OA
	MRI meniscus extrusion
	MRI meniscus tear type / degeneration
	Onset of symptoms (e.g. gradual, after event, suddenly)
	Duration of symptoms
	Grading of work and sporting activities
Symptoms	
	Signs and symptoms during specific physical examination test
	Knee locking symptoms / mechanical symptoms
	Knee related daily function
	Knee pain
	Knee stiffness
	Knee related quality of life
	Knee swelling
Quality of life	
	Generic quality of life (EQ-5D / SF36)
	Mental health score

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	64, 109
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	6 - 36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	347 - 350
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	344-346
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	344-346
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	79-102

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	103-104
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	119-1128
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	129-1144
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Additional file 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	145-157
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	130-144
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	130-144
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	159-170 + Additional file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	159-170 + Additional file 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	159-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	219-261

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	262-270
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	178-185
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	

BMJ Open

Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with MRI confirmed degenerative meniscus lesions: a protocol for an individual participant data meta-analysis

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Arthroscopic surgery, Meniscectomy, Osteoarthritis, Individual Participant Data Meta-Analysis, IPDMA

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Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with MRI confirmed degenerative meniscus lesions: a protocol for an individual participant data meta-analysis

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Word count: 3886

Abstract

Introduction

Arthroscopic partial meniscectomy (APM) after degenerative meniscus tears is one of the most frequently performed surgeries in orthopedics. Although several randomized controlled trials (RCTs) have been published that showed no clear benefit compared to sham treatment or non-surgical treatment, the incidence of APM remains high. The common perception by most orthopedic surgeons is that there are subgroups of patients that *do* need APM to improve, and they argue that each study sample of the existing trials is not representative for the day-to-day patients in the clinic. Therefore, the objective of this individual participant data meta-analysis (IPDMA) is to assess whether there are subgroups of patients with degenerative meniscus lesions who benefit from APM in comparison with non-surgical or sham treatment.

Methods and Analysis

An existing systematic review will be updated to identify all RCTs worldwide that evaluated APM compared to sham- or non-surgical treatment in patients with knee symptoms and degenerative meniscus tears. Time and effort will be spent in contacting principal investigators of the original trials and encourage them to collaborate in this project by sharing their trial data. All individual participant data will be validated for missing data, internal data consistency, randomization integrity and censoring patterns. After validation, all datasets will be combined and analyzed using a one- and two-staged approach. The most important outcome will be the difference between APM and control groups in knee pain, function and quality of life 2 years after the intervention. Other outcomes of interest will include the difference in adverse events and mental health.

Ethics and dissemination

All trial data will be anonymized before it is shared with the authors. The data will be encrypted and stored on a secure server located in the Netherlands. No major ethical concerns remain. This IPDMA will provide the evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons consider APM. The results will be submitted for publication in a peer-reviewed journal.

Registration

Prospero registration number: CRD42017067240

Keywords

Arthroscopic surgery; Meniscectomy; Osteoarthritis; Individual Participant Data Meta-Analysis; IPDMA

Article Summary

Strengths and limitations of this study

- To our knowledge, this is the first study that combines the individual participant data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery.
- The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of existing studies is combined to achieve large patient numbers.
- Trial data might not be available, not accessible or sharing is not possible due to a stringent informed consent that only enables the use of the data for the original study. This might limit the amount of trials we can include.
- We are dependent on the outcomes that have been used in the included studies. These can differ between studies.

Background

Arthroscopic partial meniscectomy (APM) is a regularly performed surgical procedure intended to treat symptoms believed to be caused by degenerative meniscus lesions. [1–3] Degenerative lesions are typically observed in middle-aged and older people, and are caused by chronic degenerative processes. [4,5] Over the past decade, evidence has accumulated that questions both the rationale for, and the effectiveness of APM for degenerative meniscus lesions. [6,7] Additionally, concerns have been expressed on the harms associated with the procedure [7–9] and the potential detrimental effect of the procedure on the progression of osteoarthritis. [10–12] Still, the number of surgical procedures performed in the treatment of degenerative meniscus lesions remains high. [13–17]

Orthopedic surgeons have expressed concerns about the generalizability of the trial results and point out that the study samples are not representative of the subjects they select for surgery in their day-to-day clinical practice.[18–24] The common perception by most surgeons is that there are subgroups of patients that *do* need the procedure to improve.[8] Hence, applying the mean effects of randomized controlled trials (RCTs) to individual patients in day-to-day practice runs against the intuitive approach of doctors to use the specific characteristics of a particular patient to tailor management accordingly. Unfortunately, the identification of subgroups of patients that may/may not benefit from the procedure has been problematic, as the individual trials performed so far were too small to perform valid and reliable subgroup analyses.

An individual participant data meta-analysis (IPDMA), i.e. a meta-analysis on the original individual participant data of previously performed trials, has been described as the gold standard of systematic review and meta-analysis. An IPDMA offers the unique opportunity to recode, and re-analyze all original trial data, and evaluate the effectiveness of surgical treatment of degenerative meniscus lesions and to identify potential subgroups more likely to benefit from the intervention. Identifying these subgroups can assist physicians to make personalized treatment decisions and thereby improving the overall quality of life of patients that are currently selected for APM.

Therefore, the objective of this IPDMA is to assess whether there are subgroups of patients with degenerative meniscus lesions who benefit from APM in comparison with non-surgical or sham treatment.

Methods

The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) statement and is registered in PROSPERO with registration number: CRD42017067240. [25] The first part of the method section describes a regular systematic review to identify eligible papers and invite the study authors to collaborate and contribute data. The second part describes the analysis with the individual participant data.

Patient and Public Involvement

Patients and members of the public were not involved in development of the protocol. A panel of patient representatives will provide detailed input regarding outcomes and the interpretation of the results from this IPDMA.

Part 1: Identifying eligible papers & data collection

Eligibility criteria

This IPDMA will include RCTs that evaluated the effectiveness of (partial) meniscectomy compared to non-surgical or sham treatments in persons with MRI-verified degenerative meniscus lesions. Degenerative meniscus lesions are typically observed in middle-aged and older people and may be the result of early degenerative knee disease. Persistent knee symptoms may encompass knee pain, limitation of function, and mechanical symptoms such as the sensation of catching or locking of the knee. Non-surgical or sham treatments may include, but are not limited to, sham surgery, pain and/or anti-inflammatory medication, exercise programs, and/or watchful waiting. Trials that included persons with traumatic meniscal lesions, defined as being the result of a specific traumatic incident will be excluded. There will be no restrictions on publication date, type of setting, length of follow up, or language.

Identification and selection of eligible trials

The search strategy described by Thorlund et al. [7] will be adopted to systematically search for eligible trials in Medline, Embase, CINAHL, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). (Additional file 1) The identified studies will be exported to EROS (Early Review Organizing Software, developed by Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina) to remove duplicates, and

randomly allocate references to two independent reviewers responsible for screening and selection. The two reviewers will independently screen all titles and abstracts of identified reports for eligibility. Full-text copies of all publications regarded as potentially eligible for inclusion, or where there is any uncertainty, will subsequently be assessed. Trials will be included when they meet the eligibility criteria. Any discrepancies between reviewers will be resolved by discussion, and if necessary, a third reviewer will be consulted. In addition, the reference lists of included studies will be reviewed to identify additional eligible trials. The electronic database search will be supplemented by searching for additional eligible trials in the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, which contains the trial registration datasets provided by several registries. This portal includes 16 national and international primary registries, including ClinicalTrials.gov, ANZCTR, JPRN, and ISRCTN. The corresponding authors of eligible trials will be invited to collaborate in the current IPDMA by sharing their data.

Collection of individual participant data

Data collection and transfer

Time and effort will be spent in tracing and encouraging original investigators to share their trial data. If no reply is received on a first invitation, additional inquiries will be sent, including inquiries sent to alternative email addresses identified for the corresponding author, inquiries sent to listed co-authors, and to the institution of the corresponding author listed in the original publication. The principal investigators of the original trials collaborating in the current project will be encouraged to actively participate in the IPDMA and discuss and finalize the definitions and outcomes to be assessed and the analytical processes proposed. Where possible, a face-to-face collaborator meeting will be scheduled, at which key decisions, including the project design, analysis plan, and interpretation of findings will be discussed. Before sharing of the de-identified data, we will sign a data sharing agreement with those principal investigators of the original trials that are interested in collaboration, in which we will arrange that the research data will be used for the declared purposes and the data will be stored on secured servers located in the Netherlands.

Data check and risk of bias

All received data will first be validated to match the results of the original publication. Statistical tests will be repeated and analyzed in R (R Foundation for Statistical Computing, Vienna, Austria). The trial data provided by

original investigators will be checked for consistency, plausibility, integrity of randomization, and reproducibility of published trial results. The aims of checking data are to increase the probability that data supplied are accurate, and to confirm that trials were appropriately randomized. Inconsistencies will be discussed and resolved with the individual investigators. All checked and de-identified data of randomized participants will be entered into a pooled database, and every trial will be assigned a trial number. Data will include characteristics relating to the participants (age, gender, body mass index (BMI)); radiographic information on knee osteoarthritis; onset, duration, and severity of symptoms; generic and disease-specific health-related quality-of-life); non-surgical or sham procedure; trial (sample size, setting, allocation concealment); and outcome measures of interest. For eligible trials of which original data is not available the aggregated data from trial reports will be collected.

Checking the IPD directly can provide more reliable investigations of key potential biases, some of which might be reduced or alleviated in the process. The risk of bias in included trials will be independently assessed by checking the IPD directly. Randomization and allocation concealment will be assessed by checking if both treatment arms are balanced in every study.[26] The advantage of an IPDMA is that we can also include outcomes not reported by the original journal article, possibly reducing outcome reporting bias by checking all relevant outcomes at the same time. In order to avoid ecological bias, the within-trial information will be examined for individual predictors of treatment effect, separately from the across-trial information.[27]

The potential for publication bias and small study effects will be examined, in the context of visual inspection, using a contour-enhanced funnel plot.[28,29] To avoid availability bias, aggregated data from studies lacking individual participant data will be used to consider their potential impact.

To enable to assessment of homogeneity/heterogeneity between the included trials, the following characteristics of the included RCTs will be compared and described in a table: 1) selection of participants, 2) previous (conservative) treatment(s) before randomization, 2) inclusion- and exclusion criteria, 3) description of clinical path prior to inclusion, 4) number of participants that declined participation, 5) diagnostic characteristics, including traumatic or non-traumatic injury and presence or absence of osteoarthrosis, 6) work characteristics, 7) socioeconomic characteristics, 8) intervention and control treatment, 9) cross-over, 10) adherence to the intervention in both treatment arms, 11) other health care services during follow-up, and 12) outcome measures. These study characteristics will be used to assess which trials can enter the meta-analysis and to determine the generalizability of the results.

Missing data

The final IPDMA dataset will have a multilevel (i.e. clustered) structure, where the individual trials are the levels (i.e. clusters). A foreseen feature of this dataset will be that some variables will be systematically missing, that is missing for all individuals in one or more trials. Next to systematically missing variables, we may also encounter sporadically missing variables, that is missing for some but not all individuals in one or more trials.

In order to optimally use the available participant data, reduce bias, and to increase statistical efficiency, incomplete data will be imputed using imputation methods that handle both systematically and sporadically missing covariates in a two-level structure using hierarchical multiple imputations by chained equations (MICE). [30–33]

Outcomes variables

The most important outcomes according to surgeons and patients is treatment effect, determined as the difference between the intervention (surgery) and control group (non-surgical treatment) in knee pain, function and quality of life 2 years after the intervention. The preferred outcome measure instrument will be the Knee injury and Osteoarthritis Outcome Scale (KOOS). The KOOS is an instrument developed with the purpose of evaluating short-term and long-term symptoms and function in subjects with a knee injury and osteoarthritis. The KOOS consists of 5 subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee-related quality of life and a composite score can be calculated (referred to as the KOOS5). The KOOS has been validated for several orthopedic interventions such as anterior cruciate ligament reconstruction, meniscectomy and total knee replacement. [34] The score of the KOOS pain subscales will be compared between the intervention and control group across the included studies. Other measurement instrument targeted at quantifying pain will be standardized and combined in one single pain outcome. The functional outcome will be measured by using the KOOS function subscale or equivalent outcome aimed to measure function. The health quality of life will be measured by using the EuroQol-5 dimensions (EQ5D) questionnaire or the 36-Item Short Form Survey (SF-36).

Other outcomes of interest will include the difference between intervention and control group in adverse events (defined as deep venous thrombosis, pulmonary thromboembolism, venous thromboembolism, infection, and death) associated with the intervention from baseline to 2 years after intervention; difference in mental health; difference in risk for future knee replacement surgery between groups (feasibility will depend

on whether the follow up of the trials will be long enough to capture the events), and the effect of follow-up time after the intervention on the treatment effect.

Part 2: Analysis

Treatment effect

The IPDMA will be used to assess the general effectiveness of APM in comparison with non-surgical or sham treatments in patients with knee symptoms and degenerative meniscal lesions. For this part, we will apply both a two-stage and one-stage approach.[35] In the two-stage approach, we will perform regression analyses for each study to obtain effect estimates separately. Thereafter these are pooled in a random effects model (to account for heterogeneity) like a regular meta-analysis. The random effects models in the two-stage will be analyzed using the restricted maximum likelihood (REML) approach with the Hartung-Knapp-Sidik-Jonkman method for continuous outcomes to account for uncertainty due to heterogeneity.[36] The two-stage approach is ideal for assessing pooled treatment effect and detect heterogeneity. However, it is difficult to detect non-linear trends or account for correlating covariates.

In the one-stage approach, the IPD from all studies will be analyzed simultaneously by adopting a single statistical model (random effects model) that fully accounts for heterogeneity across studies whilst accounting for the clustering of participants within studies. The one-stage approach is more flexible and more exact compared to the two-stage but can face computational difficulties. Therefore, the results from the one-stage will be compared to the results of the two-stage and differences will be investigated. The random effects models in the one-stage will be analyzed using the REML approach with the Kenward-Rogers approach for continuous outcome and the maximum likelihood method (ML) with quadrature for binary or survival outcomes.[35,37,38] Heterogeneity will be addressed by I^2 and τ^2, reflecting the heterogeneity between studies. To reflect the variation of the treatment effect in a different setting, 95% prediction intervals will be reported to provide more information on the expected effect in future patients.[39]

A key advantage of a one-stage approach is the flexibility in terms of the models that may be fitted compared to a two-stage approach. One-stage models allow for the inclusion of multiple covariates in a single model, multiple random-effects on different parameters, correlation between covariates and the separation of within and across-trials information. It is this flexibility that is essential to the primary objective of this IPDMA. [40]

Heterogeneity in treatment effect (subgroups)

To investigate which patients may benefit from (partial) meniscectomy we will assess whether the treatment effect is modified by baseline patient characteristics. First, relevant baseline patient characteristics will be identified. Modern regression procedures with penalization of estimated regression coefficients will be applied for the selection of those characteristics that are independent predictors of the treatment effect.[41,42] A full list of the baseline patient characteristics that will be taken into consideration are listed in Additional file 2. Second, it will be assessed whether these identified independent baseline predictors, (individually or in combinations) modify the treatment effect. Effect modification will be assessed with a random effects model. In this model, a dummy for the particular study will be the random effect and APM (yes vs. no), the potential effect modifier, and an interaction term (APM * potential effect modifier) will be included as fixed variables and the treatment effect as dependent variables.[33] The illustrated approach will allow assessment of effect modification without overfitting the data and reducing the risk of type I errors.

In addition, we want to ensure that patient characteristics deemed to be of high clinical relevance in day-to-day clinical practice are ultimately evaluated for effect modification. For this purpose, alongside the procedure described above, we will also assess a set of predefined patient characteristics deemed to be of high clinical relevance for effect modification. To define these characteristics the IPDMA collaborators will be asked to provide a top-3 of characteristics that they regard as most clinically relevant. Subsequently, it will be assessed whether the overall top-3 of these predefined patient characteristics modify the treatment effect. Predefining these characteristics will be performed before actual analysis of the data.

Sensitivity analysis

To analyze the robustness of the results from the IPDMA, several sensitivity analyses will be performed. First, to evaluate the impact of including aggregated data of published trials (of which the IPD was not available in the meta-analysis), analyses will be performed in which we either only include studies with IPD available or only studies of which only aggregated data was available. Second, to determine the effect of imputation of missing values on the study outcome, analyses will be performed in which we impute either only systematic missing variables, only sporadically missing variables (within trials) or not impute at all. Third, we will study whether the persistence of complains is a relevant subgrouping variable.

All analyses will be performed according to the intention-to-treat principle.

Publication considerations

The draft version of the final manuscript will be circulated among the collaborators for further discussion prior to submission for publication. The authors of the IPDMA paper(s) will be the project team managing the IPDMA, followed by the collaborators, whom are the principal investigators that collaborated in the current project by sharing their trial data and commenting upon the results and draft of the papers.

Study status

Currently, we are collecting the data and are contacting the original investigators of the included trials and encourage them to share the trial data. We have already received a part of the data and are still waiting on the data of a few trials. We expect to end data collection in Q1 2020. After validation of the data, we will start with the analyses. Our aim is to publish our results in 2020/2021.

Discussion

In the last decade, several RCTs found no or very little benefit of APM compared to non-operative or sham treatment in patients with MRI confirmed degenerative meniscus tears,[43–52] although there is some evidence that it is effective in middle-aged patients with degenerative meniscal symptoms.[53] These findings started a discussion on the effectiveness of the surgery and the methodology used in those RCTs by both orthopedic surgeons and other health care professionals.[19–23,54] The published studies were not able to adequately tease out whether or not there are subgroups that do additionally benefit from APM. This has resulted in a deadlock: APM is continued to be performed, despite Level I evidence that discourage the treatment.[13]

The proposed IPDMA provides the opportunity to evaluate the relationship between potential clinically-relevant baseline characteristics and the effectiveness of the APM of all patients that have been included in the trials, and to possibly detect subgroups that may benefit from APM. IPDMA is the gold standard of systematic review and meta-analysis that provides more power and is less prone to bias compared to meta-analysis on aggregated data. To our knowledge, this is the first study that combines the individual participant data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery. The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of

existing studies is combined to achieve large patient numbers. This prevents additional trials and patient involvement. Moreover, combining individual patient data enables us to analyze the effects of within-study and between-study moderators of effect sizes, even though the original studies were too small to analyze such samples.

Although IPDMA is the best method to detect possible subgroups, performing an IPDMA also comes with several challenges. First, all individual patient data from the eligible trials have to be collected. This time-intensive task often requires us to contact the principal investigators multiple times to invite them to collaborate. Unfortunately, data is sometimes not available, not accessible or sharing is not possible due to a stringent informed consent that only enables the use of the data for the original study. While there are guiding principles for open data management and sharing (Findable, Accessible, Interoperable and Reusable data principles (FAIR principles)) these often conflict with the rules of the informed consent or national legislations, creating a tension between privacy and reuse of (anonymous) medical data.[55] This might limit number of studies that can be included in this IPDMA. Second, there are multiple ways to measure knee pain, knee function or general quality of life. Every researcher can or will use their own set of outcome parameters, dependent on the experience of the researcher with a certain questionnaire/scoring system, preference or the time-dependent academic insights of the optimal questionnaire/scoring system (especially if studies have been published in different time periods, i.e. different research paradigm). As a result, we are dependent on the outcomes that have been used in the included studies in the IPDMA and cause systematic missing variables in the final pooled dataset of an IPDMA. These missing variables pose a methodological challenge, because they require advanced imputation that preserve the hierarchical structure of the data followed by the one-stage meta-analysis.[56]

In conclusion, the aim of this project is to identify potential subgroups of patients with degenerative meniscus lesions who may benefit from APM. It will provide the evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons consider APM. Identifying potential subgroups can improve the quality of life of patients who *do* truly benefit from the treatment, and can perhaps be implemented with a clinical decision aid. In case we do not find a subgroup that has additional benefits from the treatment, it can help to reduce the number of APMs, and thus less risk of, e.g. complications.[9,57]

List of abbreviations

APM	Arthroscopic partial meniscectomy
RCT	Randomized controlled trial
IPDMA	Individual participant data meta-analysis
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols
CENTRAL	Cochrane Central Register of Controlled Trials
EROS	Early Review Organizing Software
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
BMI	Body mass index
MICE	Multiple imputations by chained equations
KOOS	Knee injury and Osteoarthritis Outcome Scale
EQ5D	EuroQol-5 dimensions questionnaire
SF-36	36-Item Short Form Survey
REML	Restricted maximum likelihood
ML	Maximum likelihood
FAIR	Findable, Accessible, Interoperable and Reusable data principles

Declarations

Ethics approval and consent to participate

All principal investigators provided written confirmation that all participants included in the original trials had given informed consent.

Consent for publication

Not applicable

Availability of data and material

Following the ICMJE's data sharing statement policy, de-identified individual participant data will be made available at the end of the research project, including the study protocol, beginning 9 months and ending 36 months following article publication. The data will be shared with investigators whose proposed use of the data has been approved by a review committee to be identified for this purpose. Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse without investigator support other than deposited metadata.

Competing interests

The authors declare that they have no competing interest

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Authors' contributions

JR, GH, and MR conceived the idea for the review, with inputs from HØ, MR, ER, KH, VG, RP, and ME. SW, MR, JR and GH designed and drafted the protocol. All authors (SW, MR, JR, HØ, MR, ER, KH, VG, RP, ME, and GH) contributed to subsequent revisions and approved the protocol prior to its submission. GH is the guarantor.

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Additional files:

File name: Additional file 1

File format: Additional_file_1.doc

Title: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

Description: The systematic search strategy in Medline (PubMed), Embase, CENTRAL, CINAHL, Web of Science and WHO trial register to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

File name: Additional file 2

File format: Additional_file_2.doc

Title: Potential clinically relevant baseline characteristics

Description: A list of all identified potential clinically relevant baseline characteristics divided into 5 categories: General characteristics, patient history, meniscus information, symptoms and quality of life.

Additional file 1: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic meniscectomy to sham surgery or non-surgical techniques.

	Medline (Pubmed)	Embase	Cochrane Database of registered trial (CENTRAL)	Cumulative Index to Nursing and Allied Health Literature (CINAHL)	Web of Science (Thomson Reuter)	WHO trial register
1	"Menisci, Tibial/surgery"[Mesh]	Arthroscopic meniscectomy.ti,ab,kw.	MeSH descriptor: [Menisci, Tibial] explode all trees and with qualifier(s): [Injuries – IN, Surgery – SU]	TI "Degenerative meniscal tear" OR AB "Degenerative meniscal tear"	arthroscopy AND knee	"Menisc*" in the title
2	"Menisci, Tibial/injuries"[Mesh]	Arthroscopic debridement.ti,ab,kw.	MeSH descriptor: [Arthroscopy] explode all trees	MH "Arthroscopy" OR "arthroscopy"	arthroscopic meniscectomy	"Menisc*" in the condition
3	"Degenerative meniscal tear" [TIAB]	Arthroscopic lavage.ti,ab,kw.	MeSH descriptor: [Knee] explode all trees	MH "knee" OR AB "knee" OR TI "knee"	arthroscopic debridement	"Menisc*" in the intervention
4	"Arthroscopic lavage"[TIAB]	Degenerative meniscal tear.ti,ab,kw.	2 and 3	2 AND 3	arthroscopic lavage	1 OR 2 OR 3
5	"Arthroscopic debridement"[TIAB]	knee meniscus/ or meniscus tibial.mp	Degenerative meniscal tear:ti,ab,kw (Word variations have been searched)	MH "Meniscal Injuries" OR AB "meniscal Injuries" OR TI "meniscal Injuries"	degenerative meniscal tear	
6	"arthroscopic meniscectomy"[TIAB]	exp knee arthroscopy/	Arthroscopic lavage:ti,ab,kw (Word variations have been searched)	MH "Menisci, Tibial" OR AB "tibial meniscus" OR TI "tibial meniscus"	menisci, tibial AND surgery	
7	"Arthroscopy"[TIAB] AND "Knee"[TIAB]	1 or 2 or 3 or 4 or 5 or 6	Arthroscopic debridement:ti,ab,kw (Word variations have been searched)	TI "Arthroscopic lavage" OR AB "Arthroscopic lavage"	menisci, tibial AND injury	
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	randomized controlled trial/	arthroscopic meniscectomy:ti,ab,kw (Word variations have been searched	TI "Arthroscopic debridement" OR AB "Arthroscopic debridement"	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	
9	"Randomized" [TIAB]	randomized.ti,ab,kw.	1 or 4 or 5 or 6 or 7 or 8	TI "arthroscopic meniscectomy" OR AB "arthroscopic meniscectomy"	randomized	
10	"Randomized controlled trial"[Publication Type]	randomized.ti,ab,kw.		1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	randomised	
11	"randomized controlled trials as topic"[Mesh]	random allocation.mp.		TI "Randomized" OR AB "Randomized"	random allocation	
12	"Random allocation"[Mesh]	randomized.mp.		MH "Randomized Controlled Trials" OR TI "Randomized Controlled Trials" OR AB "Randomized Controlled Trials"	control group	
13	"Control group"[TIAB]	"randomized controlled trial (topic)"/		MH "Random Assignment" OR AB "Random Assignment" OR TI "Random Assignment"	cross-over stud*	
14	"Control groups"[Mesh]	control group.mp.		AB "Random Allocation" OR TI "Random Allocation"	randomized controlled trial	
15	"Cross-over studies"[TIAB]	control group/		(MH "Control Group") OR (AB "Control Group") OR (TI "Control Group")	9 OR 10 OR 11 OR 12 OR 13 OR 14	
16	"Cross-over study"[TIAB]	crossover procedure/		(MH "Crossover Design") AND (AB "Crossover Design") AND (TI "Crossover Design")	8 AND 15	
17	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16		11 OR 12 OR 13 OR 14 OR 15 OR 16		
18	8 AND 17	7 and 17		10 AND 17		

Additional file 2. Potential clinically relevant baseline characteristics

Category	Characteristics
General characteristics	
	Age
	Gender
	Weight, height (BMI)
Patient history	
	History of medication for knee symptoms
	History of serious knee injury
	History of knee surgery
	Family history of knee OA / of knee replacement surgery
	History of osteoarthritis
Meniscus information	
	Medial/lateral meniscus
	Radiographic severity of knee OA
	MRI meniscus extrusion
	MRI meniscus tear type / degeneration
	Onset of symptoms (e.g. gradual, after event, suddenly)
	Duration of symptoms
	Grading of work and sporting activities
Symptoms	
	Signs and symptoms during specific physical examination test
	Knee locking symptoms / mechanical symptoms
	Knee related daily function
	Knee pain
	Knee stiffness
	Knee related quality of life
	Knee swelling
Quality of life	
	Generic quality of life (EQ-5D / SF36)
	Mental health score

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	64, 109
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	6 - 36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	347 - 350
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	344-346
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	344-346
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	79-102

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	103-104
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	119-1128
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	129-1144
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Additional file 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	145-157
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	130-144
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	130-144
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	159-170 + Additional file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	159-170 + Additional file 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	159-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	219-261

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	262-270
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	178-185
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	