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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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4 1 **Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with degenerative meniscus**
5
6 2 **lesions: a protocol for an individual participant data meta-analysis**
7

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59 37 Word count: 3223
60

1
2
3 38 **Abstract**

4
5 39 **Introduction**

6
7
8 40 Arthroscopic partial meniscectomy (APM) after degenerative meniscus tears is one of the most frequently
9
10 41 performed surgeries in orthopedics. Although several randomized controlled trials (RCTs) have been published
11
12 42 that showed no clear benefit compared to sham treatment or non-surgical treatment, the incidence of APM
13
14 43 remains high. The common perception by most orthopedic surgeons is that there are subgroups of patients
15
16 44 that *do* need APM to improve, and they argue that each study sample of the existing trials is not representative
17
18 45 for the day-to-day patients in the clinic. Therefore, the objective of this individual participant data meta-
19
20 46 analysis (IPDMA) is to assess whether there are subgroups of patients with degenerative meniscus lesions who
21
22 47 benefit from APM in comparison with non-surgical or sham treatment.
23
24

25 48 **Methods and Analysis**

26
27 49 An existing systematic review will be updated to identify all RCTs worldwide that evaluated APM compared to
28
29 50 sham- or non-surgical treatment in patients with knee symptoms and degenerative meniscus tears. Time and
30
31 51 effort will be spent in contacting principal investigators of the original trials and encourage them to collaborate
32
33 52 in this project by sharing their trial data. All individual participant data will be validated for missing data,
34
35 53 internal data consistency, randomization integrity and censoring patterns. After validation, all datasets will be
36
37 54 combined and analyzed using a one- and two-staged approach. The most important outcome will be the
38
39 55 difference between APM and control groups in knee pain, function and quality of life 2 years after the
40
41 56 intervention. Other outcomes of interest will include the difference in adverse events and mental health.
42
43

44 57 **Ethics and dissemination**

45
46
47 58 This IPDMA will provide the evidence base to update and tailor diagnostic and treatment protocols as well as
48
49 59 (international) guidelines for patients for whom orthopedic surgeons consider APM. The results will be
50
51 60 submitted for publication in a peer-reviewed journal.

52
53 61 **Registration**

54
55 62 Prospero registration number: CRD42017067240

56
57 63 **Keywords**

1
2
3 64 Arthroscopic surgery; Meniscectomy; Osteoarthritis; Individual Participant Data Meta-Analysis; IPDMA
4

5 65 **Article Summary**
6

7 66 **Strengths and limitations of this study**
8

- 9 67 • To our knowledge, this is the first study that combines the individual participant data of RCTs
10 performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery.
11 68
12
13 69 • The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of
14 existing studies is combined to achieve large patient numbers.
15 70
16
17 71 • Trial data might not be available, not accessible or sharing is not possible due to a stringent informed
18 consent that only enables the use of the data for the original study. This might limit the amount of
19 72 trials we can include.
20
21 73
22
23 74 • We are dependent on the outcomes that have been used in the included studies. These can differ
24 between studies.
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77 **Background**

78 Arthroscopic partial meniscectomy (APM) is a well-established surgical procedure intended to treat symptoms
79 believed to be caused by degenerative meniscus lesions. [1–3] Degenerative lesions are typically observed in
80 middle-aged and older people, and are caused by chronic degenerative processes. [4,5] Over the past decade,
81 evidence has accumulated that questions both the rationale for, and the effectiveness of APM for degenerative
82 meniscus lesions. [6,7] Additionally, concerns have been expressed on the harms associated with the
83 procedure [7–9] and the potential detrimental effect of the procedure on the progression of osteoarthritis.
84 [10–12] Still, the number of surgical procedures performed in the treatment of degenerative meniscus lesions
85 remains high. [13–17]

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

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

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

103

104

105 **Methods**

106 The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis
107 protocols (PRISMA-P) statement and is registered in PROSPERO with registration number: CRD42017067240.

108 [25] The first part of the method section describes a regular systematic review to identify eligible papers and
109 invite the study authors to collaborate and contribute data. The second part describes the analysis with the
110 individual participant data.

111 **Patient and Public Involvement**

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

116 **Part 1: Identifying eligible papers & data collection**

117 **Eligibility criteria**

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

127 **Identification and selection of eligible trials**

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

1
2
3 131 by Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina) to remove duplicates, and
4
5 132 randomly allocate references to two independent reviewers responsible for screening and selection. The two
6
7 133 reviewers will independently screen all titles and abstracts of identified reports for eligibility. Full-text copies of
8
9 134 all publications regarded as potentially eligible for inclusion, or where there is any uncertainty, will
10
11 135 subsequently be assessed. Trials will be included when they meet the eligibility criteria. Any discrepancies
12
13 136 between reviewers will be resolved by discussion, and if necessary, a third reviewer will be consulted. In
14
15 137 addition, the reference lists of included studies will be reviewed to identify additional eligible trials. The
16
17 138 electronic database search will be supplemented by searching for additional eligible trials in the World Health
18
19 139 Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, which contains the trial
20
21 140 registration datasets provided by several registries. This portal includes 16 national and international primary
22
23 141 registries, including ClinicalTrials.gov, ANZCTR, JPRN, and ISRCTN. The corresponding authors of eligible trials
24
25 142 will be invited to collaborate in the current IPDMA by sharing their data.

27 28 143 **Collection of individual participant data**

29 30 144 **Data collection and transfer**

31
32
33 145 Time and effort will be spent in tracing and encouraging original investigators to share their trial data. If no
34
35 146 reply is received on a first invitation, additional inquiries will be sent, including inquiries sent to alternative
36
37 147 email addresses identified for the corresponding author, inquiries sent to listed co-authors, and to the
38
39 148 institution of the corresponding author listed in the original publication. The principal investigators of the
40
41 149 original trials collaborating in the current project will be encouraged to actively participate in the IPDMA and
42
43 150 discuss and finalize the definitions and outcomes to be assessed and the analytical processes proposed. Where
44
45 151 possible, a face-to-face collaborator meeting will be scheduled, at which key decisions, including the project
46
47 152 design, analysis plan, and interpretation of findings will be discussed. Before sharing of the de-identified data,
48
49 153 we will sign a data sharing agreement with those principal investigators of the original trials that are interested
50
51 154 in collaboration, in which we will arrange that the research data will be used for the declared purposes and the
52
53 155 data will be stored on secured servers located in the Netherlands.

54 55 56 156 **Data check and risk of bias**

1
2
3 157 All received data will first be validated to match the results of the original publication. Statistical tests will be
4
5 158 repeated and analyzed in R (R Foundation for Statistical Computing, Vienna, Austria). The trial data provided by
6
7 159 original investigators will be checked for consistency, plausibility, integrity of randomization, and
8
9 160 reproducibility of published trial results. The aims of checking data are to increase the probability that data
10
11 161 supplied are accurate, and to confirm that trials were appropriately randomized. Inconsistencies will be
12
13 162 discussed and resolved with the individual investigators. All checked and de-identified data of randomized
14
15 163 participants will be entered into a pooled database, and every trial will be assigned a trial number. Data will
16
17 164 include characteristics relating to the participants (age, gender, body mass index (BMI)); radiographic
18
19 165 information on knee osteoarthritis; onset, duration, and severity of symptoms; generic and disease-specific
20
21 166 health-related quality-of-life); non-surgical or sham procedure; trial (sample size, setting, allocation
22
23 167 concealment); and outcome measures of interest. For eligible trials of which original data is not available the
24
25 168 aggregated data from trial reports will be collected.

27 169 Checking the IPD directly can provide more reliable investigations of key potential biases, some of
28
29 170 which might be reduced or alleviated in the process. The risk of bias in included trials will be independently
30
31 171 assessed by checking the IPD directly. Randomization and allocation concealment will be assessed by checking
32
33 172 if both treatment arms are balanced in every study.[26] The advantage of an IPDMA is that we can also include
34
35 173 outcomes not reported by the original journal article, possibly reducing outcome reporting bias by checking all
36
37 174 relevant outcomes at the same time. In order to avoid ecological bias, the within-trial information will be
38
39 175 examined for individual predictors of treatment effect, separately from the across-trial information.[27]
40
41 176 The potential for publication bias and small study effects will be examined, in the context of visual inspection,
42
43 177 using a contour-enhanced funnel plot.[28,29] To avoid availability bias, aggregated data from studies lacking
44
45 178 individual participant data will be used to consider their potential impact.

48 179 **Missing data**

50
51 180 The final IPDMA dataset will have a multilevel (i.e. clustered) structure, where the individual trials are the levels
52
53 181 (i.e. clusters). A foreseen feature of this dataset will be that some variables will be systematically missing, that
54
55 182 is missing for all individuals in one or more trials. Next to systematically missing variables, we may also
56
57 183 encounter sporadically missing variables, that is missing for some but not all individuals in one or more trials.

1
2
3 184 In order to optimally use the available participant data, reduce bias, and to increase statistical efficiency,
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5 185 incomplete data will be imputed using imputation methods that handle both systematically and sporadically
6
7 186 missing covariates in a two-level structure using hierarchical multiple imputations by chained equations (MICE).
8
9 187 [30–33]

11 188 **Outcomes variables**

13
14 189 The most important outcomes according to surgeons and patients is treatment effect, determined as the
15
16 190 difference between the intervention (surgery) and control group (non-surgical treatment) in knee pain,
17
18 191 function and quality of life 2 years after the intervention. The preferred outcome measure instrument will be
19
20 192 the Knee injury and Osteoarthritis Outcome Scale (KOOS). The KOOS is an instrument developed with the
21
22 193 purpose of evaluating short-term and long-term symptoms and function in subjects with a knee injury and
23
24 194 osteoarthritis. The KOOS consists of 5 subscales: pain, other symptoms, function in daily living, function in sport
25
26 195 and recreation, and knee-related quality of life and a composite score can be calculated (referred to as the
27
28 196 KOOS5). The KOOS has been validated for several orthopedic interventions such as anterior cruciate ligament
29
30 197 reconstruction, meniscectomy and total knee replacement. [34] The score of the KOOS pain subscales will be
31
32 198 compared between the intervention and control group across the included studies. Other measurement
33
34 199 instrument targeted at quantifying pain will be standardized and combined in one single pain outcome. The
35
36 200 functional outcome will be measured by using the KOOS function subscale or equivalent outcome aimed to
37
38 201 measure function. The health quality of life will be measured by using the EuroQol-5 dimensions (EQ5D)
39
40 202 questionnaire or the 36-Item Short Form Survey (SF-36).

41
42 203 Other outcomes of interest will include the difference between intervention and control group in adverse
43
44 204 events (defined as deep venous thrombosis, pulmonary thromboembolism, venous thromboembolism,
45
46 205 infection, and death) associated with the intervention from baseline to 2 years after intervention; difference in
47
48 206 mental health; difference in risk for future knee replacement surgery between groups (feasibility will depend
49
50 207 on whether the follow up of the trials will be long enough to capture the events), and the effect of follow-up
51
52 208 time after the intervention on the treatment effect.

55 209 **Part 2: Analysis**

58 210 **Treatment effect**

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3 211 The IPDMA will be used to assess the general effectiveness of APM in comparison with non-surgical or sham
4
5 212 treatments in patients with knee symptoms and degenerative meniscal lesions. For this part, we will apply both
6
7 213 a two-stage and one-stage approach.[35] In the two-stage approach, we will perform regression analyses for
8
9 214 each study to obtain effect estimates separately. Thereafter these are pooled in a random effects model (to
10
11 215 account for heterogeneity) like a regular meta-analysis. The random effects models in the two-stage will be
12
13 216 analyzed using the restricted maximum likelihood (REML) approach with the Hartung-Knapp-Sidik-Jonkman
14
15 217 method for continuous outcomes to account for uncertainty due to heterogeneity.[36] The two-stage approach
16
17 218 is ideal for assessing pooled treatment effect and detect heterogeneity. However, it is difficult to detect non-
18
19 219 linear trends or account for correlating covariates.

20
21 220 In the one-stage approach, the IPD from all studies will be analyzed simultaneously by adopting a
22
23 221 single statistical model (random effects model) that fully accounts for heterogeneity across studies whilst
24
25 222 accounting for the clustering of participants within studies. The one-stage approach is more flexible and more
26
27 223 exact compared to the two-stage but can face computational difficulties. Therefore, the results from the one-
28
29 224 stage will be compared to the results of the two-stage and differences will be investigated. The random effects
30
31 225 models in the one-stage will be analyzed using the REML approach with the Kenward-Rogers approach for
32
33 226 continuous outcome and the maximum likelihood method (ML) with quadrature for binary or survival
34
35 227 outcomes.[35,37,38] Heterogeneity will be addressed by I^2 and τ^2 , reflecting the heterogeneity between
36
37 228 studies. To reflect the variation of the treatment effect in a different setting, 95% prediction intervals will be
38
39 229 reported to provide more information on the expected effect in future patients.[39]

40
41 230 A key advantage of a one-stage approach is the flexibility in terms of the models that may be fitted
42
43 231 compared to a two-stage approach. One-stage models allow for the inclusion of multiple covariates in a single
44
45 232 model, multiple random-effects on different parameters, correlation between covariates and the separation of
46
47 233 within and across-trials information. It is this flexibility that is essential to the primary objective of this IPDMA.
48
49 234 [40]

50 51 52 235 **Heterogeneity in treatment effect (subgroups)**

53
54
55 236 To investigate which patients may benefit from (partial) meniscectomy we will assess whether the treatment
56
57 237 effect is modified by baseline patient characteristics. First, relevant baseline patient characteristics will be
58
59 238 identified. Modern regression procedures with penalization of estimated regression coefficients will be applied
60

1
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3 239 for the selection of those characteristics that are independent predictors of the treatment effect.[41,42] A full
4
5 240 list of the baseline patient characteristics that will be taken into consideration are listed in Additional file 2.
6
7 241 Second, it will be assessed whether these identified independent baseline predictors, (individually or in
8
9 242 combinations) modify the treatment effect. Effect modification will be assessed with a random effects model.
10
11 243 In this model, a dummy for the particular study will be the random effect and APM (yes vs. no), the potential
12
13 244 effect modifier, and an interaction term (APM * potential effect modifier) will be included as fixed variables
14
15 245 and the treatment effect as dependent variables.[33] The illustrated approach will allow assessment of effect
16
17 246 modification without overfitting the data and reducing the risk of type I errors.

18
19 247 In addition, we want to ensure that patient characteristics deemed to be of high clinical relevance in day-
20
21 248 to-day clinical practice are ultimately evaluated for effect modification. For this purpose, alongside the
22
23 249 procedure described above, we will also assess a set of predefined patient characteristics deemed to be of high
24
25 250 clinical relevance for effect modification. To define these characteristics the IPDMA collaborators will be asked
26
27 251 to provide a top-3 of characteristics that they regard as most clinically relevant. Subsequently, it will be
28
29 252 assessed whether the overall top-3 of these predefined patient characteristics modify the treatment effect.
30
31 253 Predefining these characteristics will be performed before actual analysis of the data.

32 33 34 254 **Sensitivity analysis**

35
36 255 To analyze the robustness of the results from the IPDMA, several sensitivity analyses will be performed. First,
37
38 256 to evaluate the impact of including aggregated data of published trials (of which the IPD was not available in
39
40 257 the meta-analysis), analyses will be performed in which we either only include studies with IPD available or
41
42 258 only studies of which only aggregated data was available.

43
44 259 Second, to determine the effect of imputation of missing values on the study outcome, analyses will be
45
46 260 performed in which we impute either only systematic missing variables, only sporadically missing variables
47
48 261 (within trials) or not impute at all.

49 50 51 262 **Publication considerations**

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53
54 263 The draft version of the final manuscript will be circulated among the collaborators for further discussion prior
55
56 264 to submission for publication. The authors of the IPDMA paper(s) will be the project team managing the

1
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3 265 IPDMA, followed by the collaborators, whom are the principal investigators that collaborated in the current
4
5 266 project by sharing their trial data and commenting upon the results and draft of the papers.
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7 267

10 268 **Discussion**

11
12 269 In the last decade, several RCTs found no or very little benefit of APM compared to non-operative or sham
13
14 270 treatment in patients with degenerative meniscus tears. [43–52] These findings started a discussion on the
15
16 271 effectiveness of the surgery and the methodology used in those RCTs by both orthopedic surgeons and other
17
18 272 health care professionals.[19–23,53] The published studies were not able to adequately tease out whether or
19
20 273 not there are subgroups that do additionally benefit from APM. This has resulted in a deadlock: APM is
21
22 274 continued to be performed, despite Level I evidence that discourage the treatment.[13]

23
24 275 The proposed IPDMA provides the opportunity to evaluate the relationship between potential
25
26 276 clinically-relevant baseline characteristics and the effectiveness of the APM of all patients that have been
27
28 277 included in the trials, and to possibly detect subgroups that may benefit from APM. IPDMA is the gold standard
29
30 278 of systematic review and meta-analysis that provides more power and is less prone to bias compared to meta-
31
32 279 analysis on aggregated data. To our knowledge, this is the first study that combines the individual participant
33
34 280 data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the
35
36 281 surgery. The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of
37
38 282 existing studies is combined to achieve large patient numbers. This prevents additional trials and patient
39
40 283 involvement. Moreover, combining individual patient data enables us to analyze the effects of within-study and
41
42 284 between-study moderators of effect sizes, even though the original studies were too small to analyze such
43
44 285 samples.

45
46 286 Although IPDMA is the best method to detect possible subgroups, performing an IPDMA also comes
47
48 287 with several challenges. First, all individual patient data from the eligible trials have to be collected. This time-
49
50 288 intensive task often requires us to contact the principal investigators multiple times to invite them to
51
52 289 collaborate. Unfortunately, data is sometimes not available, not accessible or sharing is not possible due to a
53
54 290 stringent informed consent that only enables the use of the data for the original study. While there are guiding
55
56 291 principles for open data management and sharing (Findable, Accessible, Interoperable and Reusable data
57
58 292 principles (FAIR principles)) these often conflict with the rules of the informed consent or national legislations,
59
60

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

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

310

311 **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

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

312

313 Declarations**314 Ethics approval and consent to participate**

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

317 Consent for publication

318 Not applicable

319 Availability of data and material

320 Following the ICMJE's data sharing statement policy, de-identified individual participant data will be made
321 available at the end of the research project, including the study protocol, beginning 9 months and ending 36
322 months following article publication. The data will be shared with investigators whose proposed use of the data
323 has been approved by a review committee to be identified for this purpose. Proposals may be submitted up to
324 36 months following article publication. After 36 months the data will be available in our University's data
325 warehouse without investigator support other than deposited metadata.

326 Competing interests

327 The authors declare that they have no competing interest

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331 Authors' contributions

332 SW, MR, JR, and GH drafted the manuscript. All authors read, reviewed and approved the manuscript before
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10 337 **References**
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8 475 **Additional files:**

9
10 476 File name: Additional file 1

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12 477 File format: Additional_file_1.doc

13
14 478 Title: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic
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16 479 meniscectomy to sham surgery or non-surgical techniques.

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18 480 Description: The systematic search strategy in Medline (PubMed), Embase, CENTRAL, CINAHL, Web of Science
19
20 481 and WHO trial register to detect randomized controlled trials that compared (partial) arthroscopic
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22 482 meniscectomy to sham surgery or non-surgical techniques.
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26 484 File name: Additional file 2

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28 485 File format: Additional_file_2.doc

29
30 486 Title: Potential clinically relevant baseline characteristics

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32 487 Description: A list of all identified potential clinically relevant baseline characteristics divided into 5 categories:
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34 488 General characteristics, patient history, meniscus information, symptoms and quality of life.
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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
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	65, 99
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6 - 36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	315-317
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	315-317
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Additional file 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	143-174
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	241-248
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	156-165
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031864.R1
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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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4 1 **Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with degenerative meniscus**
5
6 2 **lesions: a protocol for an individual participant data meta-analysis**
7

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58

59 37 Word count: 3223
60

1
2
3 38 **Abstract**

4
5 39 **Introduction**

6
7
8 40 Arthroscopic partial meniscectomy (APM) after degenerative meniscus tears is one of the most frequently
9
10 41 performed surgeries in orthopedics. Although several randomized controlled trials (RCTs) have been published
11
12 42 that showed no clear benefit compared to sham treatment or non-surgical treatment, the incidence of APM
13
14 43 remains high. The common perception by most orthopedic surgeons is that there are subgroups of patients
15
16 44 that *do* need APM to improve, and they argue that each study sample of the existing trials is not representative
17
18 45 for the day-to-day patients in the clinic. Therefore, the objective of this individual participant data meta-
19
20 46 analysis (IPDMA) is to assess whether there are subgroups of patients with degenerative meniscus lesions who
21
22 47 benefit from APM in comparison with non-surgical or sham treatment.

23
24
25 48 **Methods and Analysis**

26
27 49 An existing systematic review will be updated to identify all RCTs worldwide that evaluated APM compared to
28
29 50 sham- or non-surgical treatment in patients with knee symptoms and degenerative meniscus tears. Time and
30
31 51 effort will be spent in contacting principal investigators of the original trials and encourage them to collaborate
32
33 52 in this project by sharing their trial data. All individual participant data will be validated for missing data,
34
35 53 internal data consistency, randomization integrity and censoring patterns. After validation, all datasets will be
36
37 54 combined and analyzed using a one- and two-staged approach. The most important outcome will be the
38
39 55 difference between APM and control groups in knee pain, function and quality of life 2 years after the
40
41 56 intervention. Other outcomes of interest will include the difference in adverse events and mental health.

42
43
44 57 **Ethics and dissemination**

45
46
47 58 This IPDMA will provide the evidence base to update and tailor diagnostic and treatment protocols as well as
48
49 59 (international) guidelines for patients for whom orthopedic surgeons consider APM. The results will be
50
51 60 submitted for publication in a peer-reviewed journal.

52
53 61 **Registration**

54
55 62 Prospero registration number: CRD42017067240

56
57 63 **Keywords**

58
59
60 64 Arthroscopic surgery; Meniscectomy; Osteoarthritis; Individual Participant Data Meta-Analysis; IPDMA

1
2
3 65 **Article Summary**
4

5 66 **Strengths and limitations of this study**
6

- 7 67 • To our knowledge, this is the first study that combines the individual participant data of RCTs
8
9 68 performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery.
10
11 69 • The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of
12
13 70 existing studies is combined to achieve large patient numbers.
14
15 71 • Trial data might not be available, not accessible or sharing is not possible due to a stringent informed
16
17 72 consent that only enables the use of the data for the original study. This might limit the amount of
18
19 73 trials we can include.
20
21 74 • We are dependent on the outcomes that have been used in the included studies. These can differ
22
23 75 between studies.
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77 **Background**

78 Arthroscopic partial meniscectomy (APM) is a regularly performed surgical procedure intended to treat
79 symptoms believed to be caused by degenerative meniscus lesions. [1–3] Degenerative lesions are typically
80 observed in middle-aged and older people, and are caused by chronic degenerative processes. [4,5] Over the
81 past decade, evidence has accumulated that questions both the rationale for, and the effectiveness of APM for
82 degenerative meniscus lesions. [6,7] Additionally, concerns have been expressed on the harms associated with
83 the procedure [7–9] and the potential detrimental effect of the procedure on the progression of osteoarthritis.
84 [10–12] Still, the number of surgical procedures performed in the treatment of degenerative meniscus lesions
85 remains high. [13–17]

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

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

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

103

104

105 **Methods**

106 The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis
107 protocols (PRISMA-P) statement and is registered in PROSPERO with registration number: CRD42017067240.

108 [25] The first part of the method section describes a regular systematic review to identify eligible papers and
109 invite the study authors to collaborate and contribute data. The second part describes the analysis with the
110 individual participant data.

111 **Patient and Public Involvement**

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

116 **Part 1: Identifying eligible papers & data collection**

117 **Eligibility criteria**

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

127 **Identification and selection of eligible trials**

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

1
2
3 132 randomly allocate references to two independent reviewers responsible for screening and selection. The two
4
5 133 reviewers will independently screen all titles and abstracts of identified reports for eligibility. Full-text copies of
6
7 134 all publications regarded as potentially eligible for inclusion, or where there is any uncertainty, will
8
9 135 subsequently be assessed. Trials will be included when they meet the eligibility criteria. Any discrepancies
10
11 136 between reviewers will be resolved by discussion, and if necessary, a third reviewer will be consulted. In
12
13 137 addition, the reference lists of included studies will be reviewed to identify additional eligible trials. The
14
15 138 electronic database search will be supplemented by searching for additional eligible trials in the World Health
16
17 139 Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, which contains the trial
18
19 140 registration datasets provided by several registries. This portal includes 16 national and international primary
20
21 141 registries, including ClinicalTrials.gov, ANZCTR, JPRN, and ISRCTN. The corresponding authors of eligible trials
22
23 142 will be invited to collaborate in the current IPDMA by sharing their data.

24 25 26 143 **Collection of individual participant data**

27 28 144 **Data collection and transfer**

29
30
31 145 Time and effort will be spent in tracing and encouraging original investigators to share their trial data. If no
32
33 146 reply is received on a first invitation, additional inquiries will be sent, including inquiries sent to alternative
34
35 147 email addresses identified for the corresponding author, inquiries sent to listed co-authors, and to the
36
37 148 institution of the corresponding author listed in the original publication. The principal investigators of the
38
39 149 original trials collaborating in the current project will be encouraged to actively participate in the IPDMA and
40
41 150 discuss and finalize the definitions and outcomes to be assessed and the analytical processes proposed. Where
42
43 151 possible, a face-to-face collaborator meeting will be scheduled, at which key decisions, including the project
44
45 152 design, analysis plan, and interpretation of findings will be discussed. Before sharing of the de-identified data,
46
47 153 we will sign a data sharing agreement with those principal investigators of the original trials that are interested
48
49 154 in collaboration, in which we will arrange that the research data will be used for the declared purposes and the
50
51 155 data will be stored on secured servers located in the Netherlands.

52 53 54 156 **Data check and risk of bias**

55
56 157 All received data will first be validated to match the results of the original publication. Statistical tests will be
57
58 158 repeated and analyzed in R (R Foundation for Statistical Computing, Vienna, Austria). The trial data provided by
59
60

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3 159 original investigators will be checked for consistency, plausibility, integrity of randomization, and
4
5 160 reproducibility of published trial results. The aims of checking data are to increase the probability that data
6
7 161 supplied are accurate, and to confirm that trials were appropriately randomized. Inconsistencies will be
8
9 162 discussed and resolved with the individual investigators. All checked and de-identified data of randomized
10
11 163 participants will be entered into a pooled database, and every trial will be assigned a trial number. Data will
12
13 164 include characteristics relating to the participants (age, gender, body mass index (BMI)); radiographic
14
15 165 information on knee osteoarthritis; onset, duration, and severity of symptoms; generic and disease-specific
16
17 166 health-related quality-of-life); non-surgical or sham procedure; trial (sample size, setting, allocation
18
19 167 concealment); and outcome measures of interest. For eligible trials of which original data is not available the
20
21 168 aggregated data from trial reports will be collected.

22
23 169 Checking the IPD directly can provide more reliable investigations of key potential biases, some of
24
25 170 which might be reduced or alleviated in the process. The risk of bias in included trials will be independently
26
27 171 assessed by checking the IPD directly. Randomization and allocation concealment will be assessed by checking
28
29 172 if both treatment arms are balanced in every study.[26] The advantage of an IPDMA is that we can also include
30
31 173 outcomes not reported by the original journal article, possibly reducing outcome reporting bias by checking all
32
33 174 relevant outcomes at the same time. In order to avoid ecological bias, the within-trial information will be
34
35 175 examined for individual predictors of treatment effect, separately from the across-trial information.[27]
36
37 176 The potential for publication bias and small study effects will be examined, in the context of visual inspection,
38
39 177 using a contour-enhanced funnel plot.[28,29] To avoid availability bias, aggregated data from studies lacking
40
41 178 individual participant data will be used to consider their potential impact.

42 43 44 179 **Missing data**

45
46 180 The final IPDMA dataset will have a multilevel (i.e. clustered) structure, where the individual trials are the levels
47
48 181 (i.e. clusters). A foreseen feature of this dataset will be that some variables will be systematically missing, that
49
50 182 is missing for all individuals in one or more trials. Next to systematically missing variables, we may also
51
52 183 encounter sporadically missing variables, that is missing for some but not all individuals in one or more trials.

53
54
55 184 In order to optimally use the available participant data, reduce bias, and to increase statistical efficiency,
56
57 185 incomplete data will be imputed using imputation methods that handle both systematically and sporadically
58
59
60

186 missing covariates in a two-level structure using hierarchical multiple imputations by chained equations (MICE).
187 [30–33]

188 **Outcomes variables**

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

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

209 **Part 2: Analysis**

210 **Treatment effect**

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

1
2
3 213 a two-stage and one-stage approach.[35] In the two-stage approach, we will perform regression analyses for
4
5 214 each study to obtain effect estimates separately. Thereafter these are pooled in a random effects model (to
6
7 215 account for heterogeneity) like a regular meta-analysis. The random effects models in the two-stage will be
8
9 216 analyzed using the restricted maximum likelihood (REML) approach with the Hartung-Knapp-Sidik-Jonkman
10
11 217 method for continuous outcomes to account for uncertainty due to heterogeneity.[36] The two-stage approach
12
13 218 is ideal for assessing pooled treatment effect and detect heterogeneity. However, it is difficult to detect non-
14
15 219 linear trends or account for correlating covariates.

17 220 In the one-stage approach, the IPD from all studies will be analyzed simultaneously by adopting a
18
19 221 single statistical model (random effects model) that fully accounts for heterogeneity across studies whilst
20
21 222 accounting for the clustering of participants within studies. The one-stage approach is more flexible and more
22
23 223 exact compared to the two-stage but can face computational difficulties. Therefore, the results from the one-
24
25 224 stage will be compared to the results of the two-stage and differences will be investigated. The random effects
26
27 225 models in the one-stage will be analyzed using the REML approach with the Kenward-Rogers approach for
28
29 226 continuous outcome and the maximum likelihood method (ML) with quadrature for binary or survival
30
31 227 outcomes.[35,37,38] Heterogeneity will be addressed by I^2 and τ^2 , reflecting the heterogeneity between
32
33 228 studies. To reflect the variation of the treatment effect in a different setting, 95% prediction intervals will be
34
35 229 reported to provide more information on the expected effect in future patients.[39]

37 230 A key advantage of a one-stage approach is the flexibility in terms of the models that may be fitted
38
39 231 compared to a two-stage approach. One-stage models allow for the inclusion of multiple covariates in a single
40
41 232 model, multiple random-effects on different parameters, correlation between covariates and the separation of
42
43 233 within and across-trials information. It is this flexibility that is essential to the primary objective of this IPDMA.
44
45 234 [40]

235 **Heterogeneity in treatment effect (subgroups)**

51 236 To investigate which patients may benefit from (partial) meniscectomy we will assess whether the treatment
52
53 237 effect is modified by baseline patient characteristics. First, relevant baseline patient characteristics will be
54
55 238 identified. Modern regression procedures with penalization of estimated regression coefficients will be applied
56
57 239 for the selection of those characteristics that are independent predictors of the treatment effect.[41,42] A full
58
59 240 list of the baseline patient characteristics that will be taken into consideration are listed in Additional file 2.
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3 241 Second, it will be assessed whether these identified independent baseline predictors, (individually or in
4
5 242 combinations) modify the treatment effect. Effect modification will be assessed with a random effects model.
6
7 243 In this model, a dummy for the particular study will be the random effect and APM (yes vs. no), the potential
8
9 244 effect modifier, and an interaction term (APM * potential effect modifier) will be included as fixed variables
10
11 245 and the treatment effect as dependent variables.[33] The illustrated approach will allow assessment of effect
12
13 246 modification without overfitting the data and reducing the risk of type I errors.

15 247 In addition, we want to ensure that patient characteristics deemed to be of high clinical relevance in day-
16
17 248 to-day clinical practice are ultimately evaluated for effect modification. For this purpose, alongside the
18
19 249 procedure described above, we will also assess a set of predefined patient characteristics deemed to be of high
20
21 250 clinical relevance for effect modification. To define these characteristics the IPDMA collaborators will be asked
22
23 251 to provide a top-3 of characteristics that they regard as most clinically relevant. Subsequently, it will be
24
25 252 assessed whether the overall top-3 of these predefined patient characteristics modify the treatment effect.
26
27 253 Predefining these characteristics will be performed before actual analysis of the data.

254 **Sensitivity analysis**

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32
33 255 To analyze the robustness of the results from the IPDMA, several sensitivity analyses will be performed. First,
34
35 256 to evaluate the impact of including aggregated data of published trials (of which the IPD was not available in
36
37 257 the meta-analysis), analyses will be performed in which we either only include studies with IPD available or
38
39 258 only studies of which only aggregated data was available. Second, to determine the effect of imputation of
40
41 259 missing values on the study outcome, analyses will be performed in which we impute either only systematic
42
43 260 missing variables, only sporadically missing variables (within trials) or not impute at all. Third, we will study
44
45 261 whether the persistence of complains is a relevant subgrouping variable.

46
47 262 All analyses will be performed according to the intention-to-treat principle.

49 263 **Publication considerations**

51
52 264 The draft version of the final manuscript will be circulated among the collaborators for further discussion prior
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54 265 to submission for publication. The authors of the IPDMA paper(s) will be the project team managing the
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56 266 IPDMA, followed by the collaborators, whom are the principal investigators that collaborated in the current
57
58 267 project by sharing their trial data and commenting upon the results and draft of the papers.
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3 268 **Study status**
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6 269 Currently, we are contacting the original investigators of the included trials and encourage them to share the
7
8 270 trial data. We aim to start the analyses at the end of 2019 and publish our results in 2020/2021.
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13 272 **Discussion**
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15 273 In the last decade, several RCTs found no or very little benefit of APM compared to non-operative or sham
16
17 274 treatment in patients with MRI confirmed degenerative meniscus tears,[43–52] although there is circumstantial
18
19 275 evidence that it is effective in middle-aged patients with degenerative meniscal symptoms.[53] These findings
20
21 276 started a discussion on the effectiveness of the surgery and the methodology used in those RCTs by both
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23 277 orthopedic surgeons and other health care professionals.[19–23,54] The published studies were not able to
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25 278 adequately tease out whether or not there are subgroups that do additionally benefit from APM. This has
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27 279 resulted in a deadlock: APM is continued to be performed, despite Level I evidence that discourage the
28
29 280 treatment.[13]

30
31 281 The proposed IPDMA provides the opportunity to evaluate the relationship between potential
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33 282 clinically-relevant baseline characteristics and the effectiveness of the APM of all patients that have been
34
35 283 included in the trials, and to possibly detect subgroups that may benefit from APM. IPDMA is the gold standard
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37 284 of systematic review and meta-analysis that provides more power and is less prone to bias compared to meta-
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39 285 analysis on aggregated data. To our knowledge, this is the first study that combines the individual participant
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41 286 data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the
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43 287 surgery. The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of
44
45 288 existing studies is combined to achieve large patient numbers. This prevents additional trials and patient
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47 289 involvement. Moreover, combining individual patient data enables us to analyze the effects of within-study and
48
49 290 between-study moderators of effect sizes, even though the original studies were too small to analyze such
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51 291 samples.
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53
54 292 Although IPDMA is the best method to detect possible subgroups, performing an IPDMA also comes
55
56 293 with several challenges. First, all individual patient data from the eligible trials have to be collected. This time-
57
58 294 intensive task often requires us to contact the principal investigators multiple times to invite them to
59
60 295 collaborate. Unfortunately, data is sometimes not available, not accessible or sharing is not possible due to a

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3 296 stringent informed consent that only enables the use of the data for the original study. While there are guiding
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5 297 principles for open data management and sharing (Findable, Accessible, Interoperable and Reusable data
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7 298 principles (FAIR principles)) these often conflict with the rules of the informed consent or national legislations,
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9 299 creating a tension between privacy and reuse of (anonymous) medical data.[55] This might limit number of
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11 300 studies that can be included in this IPDMA. Second, there are multiple ways to measure knee pain, knee
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13 301 function or general quality of life. Every researcher can or will use their own set of outcome parameters,
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15 302 dependent on the experience of the researcher with a certain questionnaire/scoring system, preference or the
16
17 303 time-dependent academic insights of the optimal questionnaire/scoring system (especially if studies have been
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19 304 published in different time periods, i.e. different research paradigm). As a result, we are dependent on the
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21 305 outcomes that have been used in the included studies in the IPDMA and cause systematic missing variables in
22
23 306 the final pooled dataset of an IPDMA. These missing variables pose a methodological challenge, because they
24
25 307 require advanced imputation that preserve the hierarchical structure of the data followed by the one-stage
26
27 308 meta-analysis.[56]

29 309 In conclusion, the aim of this project is to identify potential subgroups of patients with degenerative
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31 310 meniscus lesions who may benefit from APM. It will provide the evidence base to update and tailor diagnostic
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33 311 and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons
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35 312 consider APM. Identifying potential subgroups can improve the quality of life of patients who *do* truly benefit
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37 313 from the treatment, and can perhaps be implemented with a clinical decision aid. In case we do not find a
38
39 314 subgroup that has additional benefits from the treatment, it can help to reduce the number of APMs, and thus
40
41 315 less risk of, e.g. complications.[9,57]

316

317 **List of abbreviations**

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

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2		
3	MICE	Multiple imputations by chained equations
4	KOOS	Knee injury and Osteoarthritis Outcome Scale
5	EQ5D	EuroQol-5 dimensions questionnaire
6	SF-36	36-Item Short Form Survey
7	REML	Restricted maximum likelihood
8	ML	Maximum likelihood
9	FAIR	Findable, Accessible, Interoperable and Reusable data principles

14 318

16 319 **Declarations**19 320 **Ethics approval and consent to participate**

21 321 All principal investigators provided written confirmation that all participants included in the original trials had
22 322 given informed consent.

26 323 **Consent for publication**

28 324 Not applicable

31 325 **Availability of data and material**

33 326 Following the ICMJE's data sharing statement policy, de-identified individual participant data will be made
34 327 available at the end of the research project, including the study protocol, beginning 9 months and ending 36
35 328 months following article publication. The data will be shared with investigators whose proposed use of the data
36 329 has been approved by a review committee to be identified for this purpose. Proposals may be submitted up to
37 330 36 months following article publication. After 36 months the data will be available in our University's data
38 331 warehouse without investigator support other than deposited metadata.

46 332 **Competing interests**

48 333 The authors declare that they have no competing interest

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58 337 **Authors' contributions**

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2
3 338 JR, GH, and MR conceived the idea for the review, with inputs from HØ, MR, ER, KH, VG, RP, and ME. SW, MR,
4
5 339 JR and GH designed and drafted the protocol. All authors (SW, MR, JR, HØ, MR, ER, KH, VG, RP, ME, and GH)
6
7 340 contributed to subsequent revisions and approved the protocol prior to its submission. GH is the guarantor.
8
9

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12 342 None
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6 483 **Additional files:**

7
8 484 File name: Additional file 1
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10 485 File format: Additional_file_1.doc
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12 486 Title: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic
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14 487 meniscectomy to sham surgery or non-surgical techniques.
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16 488 Description: The systematic search strategy in Medline (PubMed), Embase, CENTRAL, CINAHL, Web of Science
17
18 489 and WHO trial register to detect randomized controlled trials that compared (partial) arthroscopic
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20 490 meniscectomy to sham surgery or non-surgical techniques.
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22 491

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24 492 File name: Additional file 2
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26 493 File format: Additional_file_2.doc
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28 494 Title: Potential clinically relevant baseline characteristics
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30 495 Description: A list of all identified potential clinically relevant baseline characteristics divided into 5 categories:
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32 496 General characteristics, patient history, meniscus information, symptoms and quality of life.
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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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	65, 99
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6 - 36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	315-317
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	315-317
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Additional file 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	143-174
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	196-240

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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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	241-248
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	156-165
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031864.R2
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Complete List of Authors:	Wijn, Stan; Radboudumc, Department of Operating Rooms Rovers, Maroeska; The Radboud University, Nijmegen Medical Centre, Rongen, Jan; Radboudumc, Operating rooms Østerås, Håvard; Norges Teknisk-Naturvitenskapelige Universitet Fakultet for Medisin og Helsevitenskap, Neuromedicine and Movement Science Risberg, May Arna; Norwegian School of Sport Sciences, Department of Sports Medicine; Oslo universitetssykehus Ullevål, Division of Orthopedic Surgery, Department of Reserach Roos, Ewa; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Sports Science and Clinical Biomechanics Hare, Kristoffer; Region Zealand, Department of Orthopedics, Slagelse Medical Hospital van de Graaf, VA; Spaarne Gasthuis, Department of Orthopaedic Surgery, Joint Research Poolman, Rudolf; Onze Lieve Vrouwe Gasthuis, Orthopaedic Surgery Englund, Martin; Lund University, Dept of Orthopedics Hannink, Gerjon; Radboudumc, Department of Operating Rooms
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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4 1 **Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with MRI confirmed**
5
6 2 **degenerative meniscus lesions: a protocol for an individual participant data meta-analysis**
7

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58

59 37 Word count: 3886
60

1
2
3 38 **Abstract**

4
5 39 **Introduction**

6
7
8 40 Arthroscopic partial meniscectomy (APM) after degenerative meniscus tears is one of the most frequently
9
10 41 performed surgeries in orthopedics. Although several randomized controlled trials (RCTs) have been published
11
12 42 that showed no clear benefit compared to sham treatment or non-surgical treatment, the incidence of APM
13
14 43 remains high. The common perception by most orthopedic surgeons is that there are subgroups of patients
15
16 44 that *do* need APM to improve, and they argue that each study sample of the existing trials is not representative
17
18 45 for the day-to-day patients in the clinic. Therefore, the objective of this individual participant data meta-
19
20 46 analysis (IPDMA) is to assess whether there are subgroups of patients with degenerative meniscus lesions who
21
22 47 benefit from APM in comparison with non-surgical or sham treatment.

23
24
25 48 **Methods and Analysis**

26
27 49 An existing systematic review will be updated to identify all RCTs worldwide that evaluated APM compared to
28
29 50 sham- or non-surgical treatment in patients with knee symptoms and degenerative meniscus tears. Time and
30
31 51 effort will be spent in contacting principal investigators of the original trials and encourage them to collaborate
32
33 52 in this project by sharing their trial data. All individual participant data will be validated for missing data,
34
35 53 internal data consistency, randomization integrity and censoring patterns. After validation, all datasets will be
36
37 54 combined and analyzed using a one- and two-staged approach. The most important outcome will be the
38
39 55 difference between APM and control groups in knee pain, function and quality of life 2 years after the
40
41 56 intervention. Other outcomes of interest will include the difference in adverse events and mental health.

42
43
44 57 **Ethics and dissemination**

45
46 58 All trial data will be anonymized before it is shared with the authors. The data will be encrypted and stored on
47
48 59 secure server located in the Netherlands. No major ethical concerns remain. This IPDMA will provide the
49
50 60 evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for
51
52 61 patients for whom orthopedic surgeons consider APM. The results will be submitted for publication in a peer-
53
54 62 reviewed journal.

55
56
57 63 **Registration**

58
59 64 Prospero registration number: CRD42017067240
60

1
2
3 65 **Keywords**
4

5 66 Arthroscopic surgery; Meniscectomy; Osteoarthritis; Individual Participant Data Meta-Analysis; IPDMA
6

7 67 **Article Summary**
8

9 68 **Strengths and limitations of this study**
10

- 11 69 • To our knowledge, this is the first study that combines the individual participant data of RCTs
12 performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery.
13
14 70
15
16 71 • The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of
17 existing studies is combined to achieve large patient numbers.
18 72
19
20 73 • Trial data might not be available, not accessible or sharing is not possible due to a stringent informed
21 consent that only enables the use of the data for the original study. This might limit the amount of
22 74 trials we can include.
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24 75
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26 76 • We are dependent on the outcomes that have been used in the included studies. These can differ
27 between studies.
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79 **Background**

80 Arthroscopic partial meniscectomy (APM) is a regularly performed surgical procedure intended to treat
81 symptoms believed to be caused by degenerative meniscus lesions. [1–3] Degenerative lesions are typically
82 observed in middle-aged and older people, and are caused by chronic degenerative processes. [4,5] Over the
83 past decade, evidence has accumulated that questions both the rationale for, and the effectiveness of APM for
84 degenerative meniscus lesions. [6,7] Additionally, concerns have been expressed on the harms associated with
85 the procedure [7–9] and the potential detrimental effect of the procedure on the progression of osteoarthritis.
86 [10–12] Still, the number of surgical procedures performed in the treatment of degenerative meniscus lesions
87 remains high. [13–17]

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

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

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

105

106

107 **Methods**

108 The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis
109 protocols (PRISMA-P) statement and is registered in PROSPERO with registration number: CRD42017067240.

110 [25] The first part of the method section describes a regular systematic review to identify eligible papers and
111 invite the study authors to collaborate and contribute data. The second part describes the analysis with the
112 individual participant data.

113 **Patient and Public Involvement**

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

118 **Part 1: Identifying eligible papers & data collection**

119 **Eligibility criteria**

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

129 **Identification and selection of eligible trials**

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

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3 134 randomly allocate references to two independent reviewers responsible for screening and selection. The two
4
5 135 reviewers will independently screen all titles and abstracts of identified reports for eligibility. Full-text copies of
6
7 136 all publications regarded as potentially eligible for inclusion, or where there is any uncertainty, will
8
9 137 subsequently be assessed. Trials will be included when they meet the eligibility criteria. Any discrepancies
10
11 138 between reviewers will be resolved by discussion, and if necessary, a third reviewer will be consulted. In
12
13 139 addition, the reference lists of included studies will be reviewed to identify additional eligible trials. The
14
15 140 electronic database search will be supplemented by searching for additional eligible trials in the World Health
16
17 141 Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, which contains the trial
18
19 142 registration datasets provided by several registries. This portal includes 16 national and international primary
20
21 143 registries, including ClinicalTrials.gov, ANZCTR, JPRN, and ISRCTN. The corresponding authors of eligible trials
22
23 144 will be invited to collaborate in the current IPDMA by sharing their data.

25 26 145 **Collection of individual participant data**

27 28 146 **Data collection and transfer**

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30
31 147 Time and effort will be spent in tracing and encouraging original investigators to share their trial data. If no
32
33 148 reply is received on a first invitation, additional inquiries will be sent, including inquiries sent to alternative
34
35 149 email addresses identified for the corresponding author, inquiries sent to listed co-authors, and to the
36
37 150 institution of the corresponding author listed in the original publication. The principal investigators of the
38
39 151 original trials collaborating in the current project will be encouraged to actively participate in the IPDMA and
40
41 152 discuss and finalize the definitions and outcomes to be assessed and the analytical processes proposed. Where
42
43 153 possible, a face-to-face collaborator meeting will be scheduled, at which key decisions, including the project
44
45 154 design, analysis plan, and interpretation of findings will be discussed. Before sharing of the de-identified data,
46
47 155 we will sign a data sharing agreement with those principal investigators of the original trials that are interested
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49 156 in collaboration, in which we will arrange that the research data will be used for the declared purposes and the
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51 157 data will be stored on secured servers located in the Netherlands.

52 53 54 158 **Data check and risk of bias**

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56 159 All received data will first be validated to match the results of the original publication. Statistical tests will be
57
58 160 repeated and analyzed in R (R Foundation for Statistical Computing, Vienna, Austria). The trial data provided by
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3 161 original investigators will be checked for consistency, plausibility, integrity of randomization, and
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5 162 reproducibility of published trial results. The aims of checking data are to increase the probability that data
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7 163 supplied are accurate, and to confirm that trials were appropriately randomized. Inconsistencies will be
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9 164 discussed and resolved with the individual investigators. All checked and de-identified data of randomized
10
11 165 participants will be entered into a pooled database, and every trial will be assigned a trial number. Data will
12
13 166 include characteristics relating to the participants (age, gender, body mass index (BMI)); radiographic
14
15 167 information on knee osteoarthritis; onset, duration, and severity of symptoms; generic and disease-specific
16
17 168 health-related quality-of-life); non-surgical or sham procedure; trial (sample size, setting, allocation
18
19 169 concealment); and outcome measures of interest. For eligible trials of which original data is not available the
20
21 170 aggregated data from trial reports will be collected.

22
23 171 Checking the IPD directly can provide more reliable investigations of key potential biases, some of
24
25 172 which might be reduced or alleviated in the process. The risk of bias in included trials will be independently
26
27 173 assessed by checking the IPD directly. Randomization and allocation concealment will be assessed by checking
28
29 174 if both treatment arms are balanced in every study.[26] The advantage of an IPDMA is that we can also include
30
31 175 outcomes not reported by the original journal article, possibly reducing outcome reporting bias by checking all
32
33 176 relevant outcomes at the same time. In order to avoid ecological bias, the within-trial information will be
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35 177 examined for individual predictors of treatment effect, separately from the across-trial information.[27]

36
37 178 The potential for publication bias and small study effects will be examined, in the context of visual
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39 179 inspection, using a contour-enhanced funnel plot.[28,29] To avoid availability bias, aggregated data from
40
41 180 studies lacking individual participant data will be used to consider their potential impact. To enable to
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43 181 assessment of heterogeneity between the included trials, the following characteristics of the included RCTs will
44
45 182 be compared and described in a table: 1) selection of participants, 2) inclusion- and exclusion criteria, 3)
46
47 183 description of clinical path prior to inclusion, 4) number of participants that declined participation, 5) diagnostic
48
49 184 characteristics, 6) work characteristics, 7) socioeconomic characteristics, 8) intervention and control treatment,
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51 185 9) cross-over, 10) other health care services during follow-up, and 11) outcome measures.

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56 187 **Missing data**
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3 188 The final IPDMA dataset will have a multilevel (i.e. clustered) structure, where the individual trials are the levels
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5 189 (i.e. clusters). A foreseen feature of this dataset will be that some variables will be systematically missing, that
6
7 190 is missing for all individuals in one or more trials. Next to systematically missing variables, we may also
8
9 191 encounter sporadically missing variables, that is missing for some but not all individuals in one or more trials.

10
11 192 In order to optimally use the available participant data, reduce bias, and to increase statistical efficiency,
12
13 193 incomplete data will be imputed using imputation methods that handle both systematically and sporadically
14
15 194 missing covariates in a two-level structure using hierarchical multiple imputations by chained equations (MICE).
16
17 195 [30–33]

196 **Outcomes variables**

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

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

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3 215 on whether the follow up of the trials will be long enough to capture the events), and the effect of follow-up
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5 216 time after the intervention on the treatment effect.
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8 217 **Part 2: Analysis**

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10 218 **Treatment effect**

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13 219 The IPDMA will be used to assess the general effectiveness of APM in comparison with non-surgical or sham
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15 220 treatments in patients with knee symptoms and degenerative meniscal lesions. For this part, we will apply both
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17 221 a two-stage and one-stage approach.[35] In the two-stage approach, we will perform regression analyses for
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19 222 each study to obtain effect estimates separately. Thereafter these are pooled in a random effects model (to
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21 223 account for heterogeneity) like a regular meta-analysis. The random effects models in the two-stage will be
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23 224 analyzed using the restricted maximum likelihood (REML) approach with the Hartung-Knapp-Sidik-Jonkman
24
25 225 method for continuous outcomes to account for uncertainty due to heterogeneity.[36] The two-stage approach
26
27 226 is ideal for assessing pooled treatment effect and detect heterogeneity. However, it is difficult to detect non-
28
29 227 linear trends or account for correlating covariates.

30
31 228 In the one-stage approach, the IPD from all studies will be analyzed simultaneously by adopting a
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33 229 single statistical model (random effects model) that fully accounts for heterogeneity across studies whilst
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35 230 accounting for the clustering of participants within studies. The one-stage approach is more flexible and more
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37 231 exact compared to the two-stage but can face computational difficulties. Therefore, the results from the one-
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39 232 stage will be compared to the results of the two-stage and differences will be investigated. The random effects
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41 233 models in the one-stage will be analyzed using the REML approach with the Kenward-Rogers approach for
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43 234 continuous outcome and the maximum likelihood method (ML) with quadrature for binary or survival
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45 235 outcomes.[35,37,38] Heterogeneity will be addressed by I^2 and τ^2 , reflecting the heterogeneity between
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47 236 studies. To reflect the variation of the treatment effect in a different setting, 95% prediction intervals will be
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49 237 reported to provide more information on the expected effect in future patients.[39]

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51 238 A key advantage of a one-stage approach is the flexibility in terms of the models that may be fitted
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53 239 compared to a two-stage approach. One-stage models allow for the inclusion of multiple covariates in a single
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55 240 model, multiple random-effects on different parameters, correlation between covariates and the separation of
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57 241 within and across-trials information. It is this flexibility that is essential to the primary objective of this IPDMA.
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59 242 [40]
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243 **Heterogeneity in treatment effect (subgroups)**

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

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

262 **Sensitivity analysis**

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

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

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3 271 **Publication considerations**
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5 272 The draft version of the final manuscript will be circulated among the collaborators for further discussion prior
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7 273 to submission for publication. The authors of the IPDMA paper(s) will be the project team managing the
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9 274 IPDMA, followed by the collaborators, whom are the principal investigators that collaborated in the current
10
11 275 project by sharing their trial data and commenting upon the results and draft of the papers.
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15 276 **Study status**
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18 277 Currently, we are collecting the data and are contacting the original investigators of the included trials and
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20 278 encourage them to share the trial data. We have already received a part of the data and are still waiting on the
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22 279 data of a few trials. We expect to end data collection in Q1 2020. After validation of the data, we will start with
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24 280 the analyses. Our aim is to publish our results in 2020/2021.
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28 282 **Discussion**
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31 283 In the last decade, several RCTs found no or very little benefit of APM compared to non-operative or sham
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33 284 treatment in patients with MRI confirmed degenerative meniscus tears,[43–52] although there is some
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35 285 evidence that it is effective in middle-aged patients with degenerative meniscal symptoms.[53] These findings
36
37 286 started a discussion on the effectiveness of the surgery and the methodology used in those RCTs by both
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39 287 orthopedic surgeons and other health care professionals.[19–23,54] The published studies were not able to
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41 288 adequately tease out whether or not there are subgroups that do additionally benefit from APM. This has
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43 289 resulted in a deadlock: APM is continued to be performed, despite Level I evidence that discourage the
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45 290 treatment.[13]

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47 291 The proposed IPDMA provides the opportunity to evaluate the relationship between potential
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49 292 clinically-relevant baseline characteristics and the effectiveness of the APM of all patients that have been
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51 293 included in the trials, and to possibly detect subgroups that may benefit from APM. IPDMA is the gold standard
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53 294 of systematic review and meta-analysis that provides more power and is less prone to bias compared to meta-
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55 295 analysis on aggregated data. To our knowledge, this is the first study that combines the individual participant
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57 296 data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the
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59 297 surgery. The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of
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3 298 existing studies is combined to achieve large patient numbers. This prevents additional trials and patient
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5 299 involvement. Moreover, combining individual patient data enables us to analyze the effects of within-study and
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7 300 between-study moderators of effect sizes, even though the original studies were too small to analyze such
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9 301 samples.

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11 302 Although IPDMA is the best method to detect possible subgroups, performing an IPDMA also comes
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13 303 with several challenges. First, all individual patient data from the eligible trials have to be collected. This time-
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15 304 intensive task often requires us to contact the principal investigators multiple times to invite them to
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17 305 collaborate. Unfortunately, data is sometimes not available, not accessible or sharing is not possible due to a
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19 306 stringent informed consent that only enables the use of the data for the original study. While there are guiding
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21 307 principles for open data management and sharing (Findable, Accessible, Interoperable and Reusable data
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23 308 principles (FAIR principles)) these often conflict with the rules of the informed consent or national legislations,
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25 309 creating a tension between privacy and reuse of (anonymous) medical data.[55] This might limit number of
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27 310 studies that can be included in this IPDMA. Second, there are multiple ways to measure knee pain, knee
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29 311 function or general quality of life. Every researcher can or will use their own set of outcome parameters,
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31 312 dependent on the experience of the researcher with a certain questionnaire/scoring system, preference or the
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33 313 time-dependent academic insights of the optimal questionnaire/scoring system (especially if studies have been
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35 314 published in different time periods, i.e. different research paradigm). As a result, we are dependent on the
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37 315 outcomes that have been used in the included studies in the IPDMA and cause systematic missing variables in
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39 316 the final pooled dataset of an IPDMA. These missing variables pose a methodological challenge, because they
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41 317 require advanced imputation that preserve the hierarchical structure of the data followed by the one-stage
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43 318 meta-analysis.[56]

44
45 319 In conclusion, the aim of this project is to identify potential subgroups of patients with degenerative
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47 320 meniscus lesions who may benefit from APM. It will provide the evidence base to update and tailor diagnostic
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49 321 and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons
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51 322 consider APM. Identifying potential subgroups can improve the quality of life of patients who *do* truly benefit
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53 323 from the treatment, and can perhaps be implemented with a clinical decision aid. In case we do not find a
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55 324 subgroup that has additional benefits from the treatment, it can help to reduce the number of APMs, and thus
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57 325 less risk of, e.g. complications.[9,57]
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3 327 **List of abbreviations**
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5	APM	Arthroscopic partial meniscectomy
6	RCT	Randomized controlled trial
7	IPDMA	Individual participant data meta-analysis
8	PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols
9	CENTRAL	Cochrane Central Register of Controlled Trials
10	EROS	Early Review Organizing Software
11	WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
12	BMI	Body mass index
13	MICE	Multiple imputations by chained equations
14	KOOS	Knee injury and Osteoarthritis Outcome Scale
15	EQ5D	EuroQol-5 dimensions questionnaire
16	SF-36	36-Item Short Form Survey
17	REML	Restricted maximum likelihood
18	ML	Maximum likelihood
19	FAIR	Findable, Accessible, Interoperable and Reusable data principles

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32 329 **Declarations**
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34 330 **Ethics approval and consent to participate**
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37 331 All principal investigators provided written confirmation that all participants included in the original trials had
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39 332 given informed consent.

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41 333 **Consent for publication**
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44 334 Not applicable
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46 335 **Availability of data and material**
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48
49 336 Following the ICMJE's data sharing statement policy, de-identified individual participant data will be made
50
51 337 available at the end of the research project, including the study protocol, beginning 9 months and ending 36
52
53 338 months following article publication. The data will be shared with investigators whose proposed use of the data
54
55 339 has been approved by a review committee to be identified for this purpose. Proposals may be submitted up to
56
57 340 36 months following article publication. After 36 months the data will be available in our University's data
58
59 341 warehouse without investigator support other than deposited metadata.
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3 342 **Competing interests**
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5 343 The authors declare that they have no competing interest
6
7

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9

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11
12 346 University Medical Center, Nijmegen, The Netherlands.
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14

15 347 **Authors' contributions**
16

17 348 JR, GH, and MR conceived the idea for the review, with inputs from HØ, MR, ER, KH, VG, RP, and ME. SW, MR,
18
19 349 JR and GH designed and drafted the protocol. All authors (SW, MR, JR, HØ, MR, ER, KH, VG, RP, ME, and GH)
20
21 350 contributed to subsequent revisions and approved the protocol prior to its submission. GH is the guarantor.
22
23

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26 352 None
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31 354 **References**
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18
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21
22 493 **Additional files:**

23
24 494 File name: Additional file 1

25
26 495 File format: Additional_file_1.doc

27
28 496 Title: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic
29
30 497 meniscectomy to sham surgery or non-surgical techniques.

31
32 498 Description: The systematic search strategy in Medline (PubMed), Embase, CENTRAL, CINAHL, Web of Science
33
34 499 and WHO trial register to detect randomized controlled trials that compared (partial) arthroscopic
35
36 500 meniscectomy to sham surgery or non-surgical techniques.

37
38
39 501

40
41 502 File name: Additional file 2

42
43 503 File format: Additional_file_2.doc

44
45 504 Title: Potential clinically relevant baseline characteristics

46
47 505 Description: A list of all identified potential clinically relevant baseline characteristics divided into 5 categories:

48
49 506 General characteristics, patient history, meniscus information, symptoms and quality of life.
50
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60

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	64, 109
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6 - 36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	344-346
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	344-346
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Additional file 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	159-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	262-270
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	178-185
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031864.R3
Article Type:	Protocol
Date Submitted by the Author:	22-Jan-2020
Complete List of Authors:	Wijn, Stan; Radboudumc, Department of Operating Rooms Rovers, Maroeska; The Radboud University, Nijmegen Medical Centre, Rongen, Jan; Radboudumc, Operating rooms Østerås, Håvard; Norges Teknisk-Naturvitenskapelige Universitet Fakultet for Medisin og Helsevitenskap, Neuromedicine and Movement Science Risberg, May Arna; Norwegian School of Sport Sciences, Department of Sports Medicine; Oslo universitetssykehus Ullevål, Division of Orthopedic Surgery, Department of Reserach Roos, Ewa; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Sports Science and Clinical Biomechanics Hare, Kristoffer; Region Zealand, Department of Orthopedics, Slagelse Medical Hospital van de Graaf, VA; Spaarne Gasthuis, Department of Orthopaedic Surgery, Joint Research Poolman, Rudolf; Onze Lieve Vrouwe Gasthuis, Orthopaedic Surgery Englund, Martin; Lund University, Dept of Orthopedics Hannink, Gerjon; Radboudumc, Department of Operating Rooms
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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4 1 **Arthroscopic meniscectomy versus non-surgical or sham treatment in patients with MRI confirmed**
5
6 2 **degenerative meniscus lesions: a protocol for an individual participant data meta-analysis**
7

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58

59 37 Word count: 3886
60

1
2
3 38 **Abstract**

4
5 39 **Introduction**

6
7
8 40 Arthroscopic partial meniscectomy (APM) after degenerative meniscus tears is one of the most frequently
9
10 41 performed surgeries in orthopedics. Although several randomized controlled trials (RCTs) have been published
11
12 42 that showed no clear benefit compared to sham treatment or non-surgical treatment, the incidence of APM
13
14 43 remains high. The common perception by most orthopedic surgeons is that there are subgroups of patients
15
16 44 that *do* need APM to improve, and they argue that each study sample of the existing trials is not representative
17
18 45 for the day-to-day patients in the clinic. Therefore, the objective of this individual participant data meta-
19
20 46 analysis (IPDMA) is to assess whether there are subgroups of patients with degenerative meniscus lesions who
21
22 47 benefit from APM in comparison with non-surgical or sham treatment.

23
24
25 48 **Methods and Analysis**

26
27 49 An existing systematic review will be updated to identify all RCTs worldwide that evaluated APM compared to
28
29 50 sham- or non-surgical treatment in patients with knee symptoms and degenerative meniscus tears. Time and
30
31 51 effort will be spent in contacting principal investigators of the original trials and encourage them to collaborate
32
33 52 in this project by sharing their trial data. All individual participant data will be validated for missing data,
34
35 53 internal data consistency, randomization integrity and censoring patterns. After validation, all datasets will be
36
37 54 combined and analyzed using a one- and two-staged approach. The most important outcome will be the
38
39 55 difference between APM and control groups in knee pain, function and quality of life 2 years after the
40
41 56 intervention. Other outcomes of interest will include the difference in adverse events and mental health.

42
43
44 57 **Ethics and dissemination**

45
46 58 All trial data will be anonymized before it is shared with the authors. The data will be encrypted and stored on
47
48 59 a secure server located in the Netherlands. No major ethical concerns remain. This IPDMA will provide the
49
50 60 evidence base to update and tailor diagnostic and treatment protocols as well as (international) guidelines for
51
52 61 patients for whom orthopedic surgeons consider APM. The results will be submitted for publication in a peer-
53
54 62 reviewed journal.

55
56
57 63 **Registration**

58
59 64 Prospero registration number: CRD42017067240
60

1
2
3 65 **Keywords**
4

5
6 66 Arthroscopic surgery; Meniscectomy; Osteoarthritis; Individual Participant Data Meta-Analysis; IPDMA
7

8 67 **Article Summary**
9

10 68 **Strengths and limitations of this study**

- 11
12 69 • To our knowledge, this is the first study that combines the individual participant data of RCTs
13
14 70 performed on APM, maximizing the capability to detect subgroups that may benefit from the surgery.
15
16 71 • The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of
17
18 72 existing studies is combined to achieve large patient numbers.
19
20 73 • Trial data might not be available, not accessible or sharing is not possible due to a stringent informed
21
22 74 consent that only enables the use of the data for the original study. This might limit the amount of
23
24 75 trials we can include.
25
26 76 • We are dependent on the outcomes that have been used in the included studies. These can differ
27
28 77 between studies.
29
30
31 78

79 **Background**

80 Arthroscopic partial meniscectomy (APM) is a regularly performed surgical procedure intended to treat
81 symptoms believed to be caused by degenerative meniscus lesions. [1–3] Degenerative lesions are typically
82 observed in middle-aged and older people, and are caused by chronic degenerative processes. [4,5] Over the
83 past decade, evidence has accumulated that questions both the rationale for, and the effectiveness of APM for
84 degenerative meniscus lesions. [6,7] Additionally, concerns have been expressed on the harms associated with
85 the procedure [7–9] and the potential detrimental effect of the procedure on the progression of osteoarthritis.
86 [10–12] Still, the number of surgical procedures performed in the treatment of degenerative meniscus lesions
87 remains high. [13–17]

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

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

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

105

106

107 **Methods**

108 The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis
109 protocols (PRISMA-P) statement and is registered in PROSPERO with registration number: CRD42017067240.

110 [25] The first part of the method section describes a regular systematic review to identify eligible papers and
111 invite the study authors to collaborate and contribute data. The second part describes the analysis with the
112 individual participant data.

113 **Patient and Public Involvement**

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

118 **Part 1: Identifying eligible papers & data collection**

119 **Eligibility criteria**

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

129 **Identification and selection of eligible trials**

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

1
2
3 134 randomly allocate references to two independent reviewers responsible for screening and selection. The two
4
5 135 reviewers will independently screen all titles and abstracts of identified reports for eligibility. Full-text copies of
6
7 136 all publications regarded as potentially eligible for inclusion, or where there is any uncertainty, will
8
9 137 subsequently be assessed. Trials will be included when they meet the eligibility criteria. Any discrepancies
10
11 138 between reviewers will be resolved by discussion, and if necessary, a third reviewer will be consulted. In
12
13 139 addition, the reference lists of included studies will be reviewed to identify additional eligible trials. The
14
15 140 electronic database search will be supplemented by searching for additional eligible trials in the World Health
16
17 141 Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, which contains the trial
18
19 142 registration datasets provided by several registries. This portal includes 16 national and international primary
20
21 143 registries, including ClinicalTrials.gov, ANZCTR, JPRN, and ISRCTN. The corresponding authors of eligible trials
22
23 144 will be invited to collaborate in the current IPDMA by sharing their data.

25 26 145 **Collection of individual participant data**

27 28 146 **Data collection and transfer**

29
30
31 147 Time and effort will be spent in tracing and encouraging original investigators to share their trial data. If no
32
33 148 reply is received on a first invitation, additional inquiries will be sent, including inquiries sent to alternative
34
35 149 email addresses identified for the corresponding author, inquiries sent to listed co-authors, and to the
36
37 150 institution of the corresponding author listed in the original publication. The principal investigators of the
38
39 151 original trials collaborating in the current project will be encouraged to actively participate in the IPDMA and
40
41 152 discuss and finalize the definitions and outcomes to be assessed and the analytical processes proposed. Where
42
43 153 possible, a face-to-face collaborator meeting will be scheduled, at which key decisions, including the project
44
45 154 design, analysis plan, and interpretation of findings will be discussed. Before sharing of the de-identified data,
46
47 155 we will sign a data sharing agreement with those principal investigators of the original trials that are interested
48
49 156 in collaboration, in which we will arrange that the research data will be used for the declared purposes and the
50
51 157 data will be stored on secured servers located in the Netherlands.

52 53 54 158 **Data check and risk of bias**

55
56 159 All received data will first be validated to match the results of the original publication. Statistical tests will be
57
58 160 repeated and analyzed in R (R Foundation for Statistical Computing, Vienna, Austria). The trial data provided by
59
60

1
2
3 161 original investigators will be checked for consistency, plausibility, integrity of randomization, and
4
5 162 reproducibility of published trial results. The aims of checking data are to increase the probability that data
6
7 163 supplied are accurate, and to confirm that trials were appropriately randomized. Inconsistencies will be
8
9 164 discussed and resolved with the individual investigators. All checked and de-identified data of randomized
10
11 165 participants will be entered into a pooled database, and every trial will be assigned a trial number. Data will
12
13 166 include characteristics relating to the participants (age, gender, body mass index (BMI)); radiographic
14
15 167 information on knee osteoarthritis; onset, duration, and severity of symptoms; generic and disease-specific
16
17 168 health-related quality-of-life); non-surgical or sham procedure; trial (sample size, setting, allocation
18
19 169 concealment); and outcome measures of interest. For eligible trials of which original data is not available the
20
21 170 aggregated data from trial reports will be collected.

22
23 171 Checking the IPD directly can provide more reliable investigations of key potential biases, some of
24
25 172 which might be reduced or alleviated in the process. The risk of bias in included trials will be independently
26
27 173 assessed by checking the IPD directly. Randomization and allocation concealment will be assessed by checking
28
29 174 if both treatment arms are balanced in every study.[26] The advantage of an IPDMA is that we can also include
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31 175 outcomes not reported by the original journal article, possibly reducing outcome reporting bias by checking all
32
33 176 relevant outcomes at the same time. In order to avoid ecological bias, the within-trial information will be
34
35 177 examined for individual predictors of treatment effect, separately from the across-trial information.[27]

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37 178 The potential for publication bias and small study effects will be examined, in the context of visual
38
39 179 inspection, using a contour-enhanced funnel plot.[28,29] To avoid availability bias, aggregated data from
40
41 180 studies lacking individual participant data will be used to consider their potential impact.

42
43 181 To enable to assessment of homogeneity/heterogeneity between the included trials, the following
44
45 182 characteristics of the included RCTs will be compared and described in a table: 1) selection of participants, 2)
46
47 183 previous (conservative) treatment(s) before randomization, 2) inclusion- and exclusion criteria, 3) description
48
49 184 of clinical path prior to inclusion, 4) number of participants that declined participation, 5) diagnostic
50
51 185 characteristics, including traumatic or non-traumatic injury and presence or absence of osteoarthritis, 6) work
52
53 186 characteristics, 7) socioeconomic characteristics, 8) intervention and control treatment, 9) cross-over, 10)
54
55 187 adherence to the intervention in both treatment arms, 11) other health care services during follow-up, and 12)
56
57 188 outcome measures. These study characteristics will be used to assess which trials can enter the meta-analysis
58
59 189 and to determine the generalizability of the results.

190 **Missing data**

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

195 In order to optimally use the available participant data, reduce bias, and to increase statistical efficiency,
196 incomplete data will be imputed using imputation methods that handle both systematically and sporadically
197 missing covariates in a two-level structure using hierarchical multiple imputations by chained equations (MICE).
198 [30–33]

199 **Outcomes variables**

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

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

1
2
3 218 on whether the follow up of the trials will be long enough to capture the events), and the effect of follow-up
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5 219 time after the intervention on the treatment effect.
6

7 220 **Part 2: Analysis**

8 221 **Treatment effect**

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12 222 The IPDMA will be used to assess the general effectiveness of APM in comparison with non-surgical or sham
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14 223 treatments in patients with knee symptoms and degenerative meniscal lesions. For this part, we will apply both
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16 224 a two-stage and one-stage approach.[35] In the two-stage approach, we will perform regression analyses for
17
18 225 each study to obtain effect estimates separately. Thereafter these are pooled in a random effects model (to
19
20 226 account for heterogeneity) like a regular meta-analysis. The random effects models in the two-stage will be
21
22 227 analyzed using the restricted maximum likelihood (REML) approach with the Hartung-Knapp-Sidik-Jonkman
23
24 228 method for continuous outcomes to account for uncertainty due to heterogeneity.[36] The two-stage approach
25
26 229 is ideal for assessing pooled treatment effect and detect heterogeneity. However, it is difficult to detect non-
27
28 230 linear trends or account for correlating covariates.

29
30
31 231 In the one-stage approach, the IPD from all studies will be analyzed simultaneously by adopting a
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33 232 single statistical model (random effects model) that fully accounts for heterogeneity across studies whilst
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35 233 accounting for the clustering of participants within studies. The one-stage approach is more flexible and more
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37 234 exact compared to the two-stage but can face computational difficulties. Therefore, the results from the one-
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39 235 stage will be compared to the results of the two-stage and differences will be investigated. The random effects
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41 236 models in the one-stage will be analyzed using the REML approach with the Kenward-Rogers approach for
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43 237 continuous outcome and the maximum likelihood method (ML) with quadrature for binary or survival
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45 238 outcomes.[35,37,38] Heterogeneity will be addressed by I^2 and τ^2 , reflecting the heterogeneity between
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47 239 studies. To reflect the variation of the treatment effect in a different setting, 95% prediction intervals will be
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49 240 reported to provide more information on the expected effect in future patients.[39]

50
51 241 A key advantage of a one-stage approach is the flexibility in terms of the models that may be fitted
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53 242 compared to a two-stage approach. One-stage models allow for the inclusion of multiple covariates in a single
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55 243 model, multiple random-effects on different parameters, correlation between covariates and the separation of
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57 244 within and across-trials information. It is this flexibility that is essential to the primary objective of this IPDMA.
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59 245 [40]
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246 **Heterogeneity in treatment effect (subgroups)**

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

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

265 **Sensitivity analysis**

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

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

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3 274 **Publication considerations**
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6 275 The draft version of the final manuscript will be circulated among the collaborators for further discussion prior
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8 276 to submission for publication. The authors of the IPDMA paper(s) will be the project team managing the
9
10 277 IPDMA, followed by the collaborators, whom are the principal investigators that collaborated in the current
11
12 278 project by sharing their trial data and commenting upon the results and draft of the papers.
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15 279 **Study status**
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18 280 Currently, we are collecting the data and are contacting the original investigators of the included trials and
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20 281 encourage them to share the trial data. We have already received a part of the data and are still waiting on the
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22 282 data of a few trials. We expect to end data collection in Q1 2020. After validation of the data, we will start with
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24 283 the analyses. Our aim is to publish our results in 2020/2021.
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28 285 **Discussion**
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31 286 In the last decade, several RCTs found no or very little benefit of APM compared to non-operative or sham
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33 287 treatment in patients with MRI confirmed degenerative meniscus tears,[43–52] although there is some
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35 288 evidence that it is effective in middle-aged patients with degenerative meniscal symptoms.[53] These findings
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37 289 started a discussion on the effectiveness of the surgery and the methodology used in those RCTs by both
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39 290 orthopedic surgeons and other health care professionals.[19–23,54] The published studies were not able to
40
41 291 adequately tease out whether or not there are subgroups that do additionally benefit from APM. This has
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43 292 resulted in a deadlock: APM is continued to be performed, despite Level I evidence that discourage the
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45 293 treatment.[13]

46
47 294 The proposed IPDMA provides the opportunity to evaluate the relationship between potential
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49 295 clinically-relevant baseline characteristics and the effectiveness of the APM of all patients that have been
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51 296 included in the trials, and to possibly detect subgroups that may benefit from APM. IPDMA is the gold standard
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53 297 of systematic review and meta-analysis that provides more power and is less prone to bias compared to meta-
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55 298 analysis on aggregated data. To our knowledge, this is the first study that combines the individual participant
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57 299 data of RCTs performed on APM, maximizing the capability to detect subgroups that may benefit from the
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59 300 surgery. The main advantage of an IPDMA is that no large-scale RCT is required, but instead the power of
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3 301 existing studies is combined to achieve large patient numbers. This prevents additional trials and patient
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5 302 involvement. Moreover, combining individual patient data enables us to analyze the effects of within-study and
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7 303 between-study moderators of effect sizes, even though the original studies were too small to analyze such
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9 304 samples.

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11 305 Although IPDMA is the best method to detect possible subgroups, performing an IPDMA also comes
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13 306 with several challenges. First, all individual patient data from the eligible trials have to be collected. This time-
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15 307 intensive task often requires us to contact the principal investigators multiple times to invite them to
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17 308 collaborate. Unfortunately, data is sometimes not available, not accessible or sharing is not possible due to a
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19 309 stringent informed consent that only enables the use of the data for the original study. While there are guiding
20
21 310 principles for open data management and sharing (Findable, Accessible, Interoperable and Reusable data
22
23 311 principles (FAIR principles)) these often conflict with the rules of the informed consent or national legislations,
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25 312 creating a tension between privacy and reuse of (anonymous) medical data.[55] This might limit number of
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27 313 studies that can be included in this IPDMA. Second, there are multiple ways to measure knee pain, knee
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29 314 function or general quality of life. Every researcher can or will use their own set of outcome parameters,
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31 315 dependent on the experience of the researcher with a certain questionnaire/scoring system, preference or the
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33 316 time-dependent academic insights of the optimal questionnaire/scoring system (especially if studies have been
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35 317 published in different time periods, i.e. different research paradigm). As a result, we are dependent on the
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37 318 outcomes that have been used in the included studies in the IPDMA and cause systematic missing variables in
38
39 319 the final pooled dataset of an IPDMA. These missing variables pose a methodological challenge, because they
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41 320 require advanced imputation that preserve the hierarchical structure of the data followed by the one-stage
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43 321 meta-analysis.[56]

44
45 322 In conclusion, the aim of this project is to identify potential subgroups of patients with degenerative
46
47 323 meniscus lesions who may benefit from APM. It will provide the evidence base to update and tailor diagnostic
48
49 324 and treatment protocols as well as (international) guidelines for patients for whom orthopedic surgeons
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51 325 consider APM. Identifying potential subgroups can improve the quality of life of patients who *do* truly benefit
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53 326 from the treatment, and can perhaps be implemented with a clinical decision aid. In case we do not find a
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55 327 subgroup that has additional benefits from the treatment, it can help to reduce the number of APMs, and thus
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57 328 less risk of, e.g. complications.[9,57]

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1
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3 330 **List of abbreviations**
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5	APM	Arthroscopic partial meniscectomy
6	RCT	Randomized controlled trial
7	IPDMA	Individual participant data meta-analysis
8	PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols
9	CENTRAL	Cochrane Central Register of Controlled Trials
10	EROS	Early Review Organizing Software
11	WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
12	BMI	Body mass index
13	MICE	Multiple imputations by chained equations
14	KOOS	Knee injury and Osteoarthritis Outcome Scale
15	EQ5D	EuroQol-5 dimensions questionnaire
16	SF-36	36-Item Short Form Survey
17	REML	Restricted maximum likelihood
18	ML	Maximum likelihood
19	FAIR	Findable, Accessible, Interoperable and Reusable data principles

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32 332 **Declarations**
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34 333 **Ethics approval and consent to participate**
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37 334 All principal investigators provided written confirmation that all participants included in the original trials had
38
39 335 given informed consent.

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41 336 **Consent for publication**
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43
44 337 Not applicable
45

46 338 **Availability of data and material**
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48
49 339 Following the ICMJE's data sharing statement policy, de-identified individual participant data will be made
50
51 340 available at the end of the research project, including the study protocol, beginning 9 months and ending 36
52
53 341 months following article publication. The data will be shared with investigators whose proposed use of the data
54
55 342 has been approved by a review committee to be identified for this purpose. Proposals may be submitted up to
56
57 343 36 months following article publication. After 36 months the data will be available in our University's data
58
59 344 warehouse without investigator support other than deposited metadata.
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2
3 345 **Competing interests**
4

5 346 The authors declare that they have no competing interest
6
7

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9

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11
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14

15 350 **Authors' contributions**
16

17
18 351 JR, GH, and MR conceived the idea for the review, with inputs from HØ, MR, ER, KH, VG, RP, and ME. SW, MR,
19
20 352 JR and GH designed and drafted the protocol. All authors (SW, MR, JR, HØ, MR, ER, KH, VG, RP, ME, and GH)
21
22 353 contributed to subsequent revisions and approved the protocol prior to its submission. GH is the guarantor.
23

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25

26
27 355 None
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31 357 **References**
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21
22 496 **Additional files:**

23
24 497 File name: Additional file 1

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26 498 File format: Additional_file_1.doc

27
28 499 Title: Systematic search of literature to detect randomized controlled trials that compared (partial) arthroscopic
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30 500 meniscectomy to sham surgery or non-surgical techniques.

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32 501 Description: The systematic search strategy in Medline (PubMed), Embase, CENTRAL, CINAHL, Web of Science
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34 502 and WHO trial register to detect randomized controlled trials that compared (partial) arthroscopic
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36 503 meniscectomy to sham surgery or non-surgical techniques.

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41 505 File name: Additional file 2

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43 506 File format: Additional_file_2.doc

44
45 507 Title: Potential clinically relevant baseline characteristics

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47 508 Description: A list of all identified potential clinically relevant baseline characteristics divided into 5 categories:

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49 509 General characteristics, patient history, meniscus information, symptoms and quality of life.
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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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	64, 109
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6 - 36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	344-346
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	344-346
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Additional file 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	159-185
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	262-270
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	178-185
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	