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TITLE: Evaluating the design and reporting of pragmatic trials in osteoarthritis research

RUNNING HEADER: Pragmatic trials in osteoarthritis research

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KEY WORDS: pragmatic trials, osteoarthritis, PRECIS, CONSORT, implementation

ABSTRACT

Objectives: Among challenges in health research is translating interventions from controlled experimental settings to clinical and community settings where chronic disease is managed daily. Pragmatic trials offer a method for testing interventions in real-world settings, but are seldom used in osteoarthritis research. We evaluate the literature on pragmatic trials in osteoarthritis research up to August 2016 in order to identify strengths and weaknesses in the design and reporting of these trials.

Methods: We used established guidelines to assess the degree to which 61 osteoarthritis studies complied with pragmatic trial design and reporting. We assessed design according to the pragmatic-explanatory continuum indicator summary (PRECIS), and reporting according to the pragmatic trials extension of the CONSORT (CONsolidated Standards of Reporting Trials) guidelines.

Results: None of the pragmatic trials met all 11 criteria evaluated, most of the trials met between 5 and 8 of the criteria. Criteria most often unmet pertained to practitioner expertise (by requiring specialists), and criteria most often met pertained to primary outcome analysis (by using intention-to-treat analysis).

Conclusion: Our results suggest a lack of highly pragmatic trials in osteoarthritis research. We identify this as a point of opportunity to improve research translation, since optimizing the design and reporting of pragmatic trials can facilitate implementation of evidence-based interventions for osteoarthritis care.

INTRODUCTION

The prevalence of osteoarthritis is expected to rise with population aging [1]. There is no cure for osteoarthritis, but there are strategies that can reduce progression and mitigate symptoms [2, 3]. The challenge lies in effective implementation of these interventions, particularly since there are demonstrated practice gaps in the delivery of osteoarthritis care [4]. Implementation research aims to reduce the gap between what is known to be clinically effective and what is actually delivered in clinical care [5]. Allen et al. provide an overview of the design and conduct of implementation trials of interventions for osteoarthritis [6]. The authors describe conceptual frameworks (e.g. knowledge-to-action), study designs (e.g. pragmatic trials), and evaluations (both process and formative) for implementation trials.

Pragmatic trials are particularly useful in implementation research, since they are designed to determine the generalizability of interventions to routine practice [6]. Whereas explanatory trials are used to test the *efficacy* of interventions in controlled settings, pragmatic trials are used to demonstrate the *effectiveness* of interventions in real-world settings [7, 8]. In theory, pragmatic trials test interventions that are evidence-based with flexibiity for application across multiple settings with large and heterogeneous populations, looking at stakeholder-related outcomes over longer periods of time [9, 10]. In practice, this may not always be the case.

The objective of this study is to evaluate the degree to which existing pragmatic trials in osteoarthritis research comply with guidelines for the design and reporting of pragmatic trials [11, 12]. We identify strengths and weaknesses of pragmatic trials in osteoarthritis research,

and suggest ways in which pragmatic trial guidelines can be applied to osteoarthritis research to achieve highly pragmatic trials. By optimizing pragmatic trial methodology in osteoarthritis research, we can facilitate implementation of evidence-based interventions in routine practice, and reduce care gaps.

METHODS

We searched PubMed and Web of Science using the terms “pragmatic AND trial AND osteoarthritis [All Fields]” to identify publications prior to August 2016. Our search identified 63 citations from PubMed and 93 citations from Web of Science, with 96 unique citations combined (**Supplementary Figure 1**). We included articles that explicitly stated that the study was “pragmatic” in the title (36%), abstract (59%), or methods/discussion (5%). We excluded articles that were not reports of primary research, were not available in full-text or English, and were not related to osteoarthritis. We excluded reports of trial results when reports of trial protocol for the same study were already included. For each study, we determined whether the intervention was clinician-based (oral drug, injections, acupuncture, surgery, or clinical pathways) or patient-based (diet, exercise, self-management programs, devices, topical therapies), and which joints were targeted (**Supplementary Table 1**).

We used the pragmatic-explanatory continuum indicator summary (PRECIS) [11] and the pragmatic trials extension of the CONSORT (CONsolidated Standards of Reporting Trials) [12] guidelines to determine the parameters of an ideal pragmatic trial in osteoarthritis research [13, 14]. Guidelines for optimal pragmatic trial design (PRECIS) and reporting (CONSORT) were consistent, with an additional guideline for reporting ‘Blinding’ in the CONSORT extension. We combined these guidelines into 11 criteria (**Table 1**) to evaluate each of the 61 studies reporting a pragmatic trial in osteoarthritis research. Determinations were made for each criterion using a simple binary system to indicate whether the study met pragmatic criteria (yes = 1) or not (no = 0), where a maximum score of 11 could be assigned per study (**Supplementary Table 2**). After

being trained to code [15], two independent raters (KL and KW) evaluated each study. Inter-rater agreement of coding for a random sample of studies (N=30) was determined to be 78%. A third reviewer (SAA) evaluated any discrepancies in coding (an average of 3 criteria per study).

RESULTS

None of the 61 pragmatic trials we evaluated met all 11 criteria described in **Table 1**. Most of the trials, for both clinician- and patient-based interventions, met 5 to 8 of the criteria (**Supplementary Figure 2**). Few trials were at either extreme, meeting 9 or more criteria, or 4 or less criteria (**Supplementary Figure 2**). Of note, 5% of studies met 9 or more criteria, suggesting that it is possible, but rare, to have highly pragmatic trials in osteoarthritis research.

The criteria that most studies failed to meet were practitioner expertise for both experimental and comparison interventions. This requires the intervention be applied by practitioners ordinarily involved with the care of patients [11]. For osteoarthritis patients, this typically includes general practitioners, pharmacists, family, and friends. Only 10% of studies met this criterion for the experimental intervention and only 34% for the comparison intervention (**Table 2**). The majority of studies required additional training of practitioners delivering the intervention, or included experts that would require special referral in many health care systems (e.g. physiotherapists, orthopaedic surgeons).

Only 41% of studies met pragmatic trial guidelines for participant eligibility criteria (**Table 2**). As described by Thorpe et al., trials with minimal inclusion and exclusion criteria are considered pragmatic [11]. The majority of trials we evaluated imposed specific participant eligibility criteria relating to the severity or type of osteoarthritis (inclusion criteria), and the presence of co-morbidities (exclusion criteria), and seldom explained why. For example, 61% of studies recruited participants with knee osteoarthritis (16% knee and hip, 5% hip, 5% did not specify a

joint, 8% generalized osteoarthritis, 3% hand, 2% shoulder), and many studies excluded participants who had undergone joint replacement or other surgical interventions. These design decisions may be appropriate for trials examining interventions for specific populations, but do not capture the osteoarthritis population with multiple morbidities due to advanced age, and with persistent symptoms in the same or additional joints after surgery.

We found 48% of studies met criteria for flexibility of the comparison intervention (**Table 2**), where pragmatic trials use the existing standard of care as the comparison intervention [11]. This number may be inflated since many studies did not report the standard of care, so we assumed no changes were made. Many studies did change the standard of care, for example by offering the comparison group information pamphlets. Lack of reporting was also evident for blinding procedures. Traditional single- or double-blinding may not always be possible for pragmatic trials [10], but only 43% of studies provided an explanation for the blinding decisions (**Table 2**).

Pragmatic trials avoid monitoring participant compliance with the intervention [11]; we found 54% of the studies met this criterion (**Table 2**). Several studies required participants to keep track of a behaviour using diaries or logs over extended periods of time. While compliance measures may help researchers explain effect sizes, they may also introduce an observer effect. Truly pragmatic trials accept non-compliance as a reality [13]. This relates to flexibility of the experimental intervention, for which 51% of studies met the criterion (**Table 2**). Pragmatic trials

have interventions that are not closely monitored, that are flexible in delivery, and that accommodate variation across settings [13].

Strengths of pragmatic trials in osteoarthritis research include the choice of primary trial outcome, where 82% of studies used outcomes that were minimally invasive and clinically meaningful to participants (e.g. pain, quality of life, function), and analysis of primary outcome, where 87% of studies used intention-to-treat analysis. We found 79% of studies did not monitor practitioner adherence to the study protocol, although this number may reflect a common practice to refrain from monitoring practitioners rather than a research effort to comply with pragmatic trial guidelines. We found 77% of studies met the criterion for minimizing follow-up intensity, although we allowed for up to 2 follow-ups, and considered any follow-up by phone or mail to be pragmatic (**Table 2**).

DISCUSSION

In osteoarthritis research, studies that self-identify as pragmatic trials fail to meet many criteria for the design and reporting of pragmatic trials. While the PRECIS tool [11] is not intended as a method for classifying trials, it is useful for evaluating the degree to which pragmatic trials meet design recommendations [13, 15]. Our results show that most trials have both pragmatic and explanatory elements, supporting the idea of a pragmatic-explanatory continuum in trial design [11, 13].

Ideally, pragmatic trials should maximize external validity, and this requires moving away from the controlled conditions of traditional explanatory trials. In the 'real-world', populations are heterogeneous with different stages of osteoarthritis, practitioners apply protocols variably, and patients may not fully comply with interventions, particularly since osteoarthritis is deprioritized in clinical settings [4]. Yet for scientific rigor, trials must have some inclusion/exclusion criteria, practitioners must follow protocol to some degree, an appropriate comparison group is needed, and some type of follow-up is required to measure change in outcomes. As a result, there is considerable tension for some pragmatic trials criteria, between minimizing bias and maximizing generalizability [10]. How these tensions are reconciled will depend on the research question and parameters of individual studies [7].

Going forward, improved reporting of design decisions can reveal whether trials are more pragmatic, more explanatory, or potentially negligent in a particular domain of trial design. We did not evaluate overall quality of the studies included, but only what was reported, making it

difficult to distinguish shortcomings in design versus reporting. Although 75% of the studies included were published after the CONSORT extension for pragmatic trials was available in 2008 [12], it appears that there are still deficiencies in reporting of pragmatic trials.

To clarify what may constitute a pragmatic trial in osteoarthritis research, we identified common design decisions that are consistent with guidelines (**Table 1**). The list in **Table 1** is not exhaustive and was formulated based on the pragmatic trials we evaluated, of which 41% were clinician-based interventions and 59% were patient-based interventions. Existing guidelines for pragmatic trials had to be flexibly applied for trials with clinician-based interventions to qualify as pragmatic. We found eligibility criteria were more specific, experimental and comparison interventions were less flexible, practitioner adherence to protocol was stricter, and follow-up intensity was more frequent – out of necessity for surgical and pharmacologic interventions. Therefore, if the trial design captured as closely as possible the way in which the intervention would ultimately be delivered in usual clinical care, we considered it pragmatic.

We excluded articles that were not related to osteoarthritis or declared as pragmatic trials, making our search specific, but not necessarily sensitive. Other studies may have incorporated elements of pragmatic trial design without declaring the trial type as pragmatic, or may have tested interventions for joint pain without declaring an osteoarthritis diagnosis. This may have resulted in under-counting of pragmatic trials in osteoarthritis in our literature search. Other articles may have inappropriately declared the trial type as pragmatic, causing our results to reflect poor design and reporting and an overall lack of highly pragmatic trials. The underlying

issue may be a lack of clarity and consensus in the field about what constitutes a pragmatic trial [7].

It remains unclear whether trials are not sufficiently pragmatic, or whether existing pragmatic trial guidelines are not appropriate. Ultimately, pragmatic trials test implementation of interventions in the real-world, and what constitutes 'real-world' will differ depending on the intervention type (in-home for many lifestyle interventions, hospital-based for surgical interventions), the end-users (patients, clinicians, policy-makers), and the social, political, and economic contexts in which the intervention will ultimately be delivered [16]. It is difficult to prove whether having more trials that are more pragmatic will improve implementation of evidence-based interventions [17]. Certainly without pragmatic trials and implementation research, practitioners may lack trial evidence that is amenable to their clinical context, and this may hinder their ability to operationalize clinical practice guidelines.

In conclusion, there is a lack of highly pragmatic trials in osteoarthritis research, as defined by current guidelines for the design [11] and reporting [12] of pragmatic trials. Understanding existing pragmatic trial guidelines and how they can be applied to osteoarthritis research may improve use of this method in implementation research. Further efforts are needed to achieve a common understanding among researchers about what constitutes a pragmatic trial.

KEY MESSAGES

- Only 61 self-identified pragmatic trials on osteoarthritis were published prior to August 2016.
- Existing pragmatic trials in osteoarthritis research show variable compliance with established guidelines.
- Most pragmatic trials met guidelines for 'Analysis of primary outcome', but not 'Practitioner expertise'.

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Author Contributions: SAA conceptualized the study, interpreted results, and wrote the manuscript. Data collection and analyses were performed by SAA, KL, and KW. Revision of the manuscript was performed by MK, JCM and DF. All authors approved the final manuscript.

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Disclosure Statement: The authors declare no conflicts of interest.

REFERENCES

1 Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol 2014.

2 Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64(4):465-74.

3 McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22(3):363-88.

4 Paskins Z, Sanders T, Croft PR, Hassell AB. The Identity Crisis of Osteoarthritis in General Practice: A Qualitative Study Using Video-Stimulated Recall. Ann Fam Med 2015;13(6):537-44.

5 Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci 2015;10:53.

6 Allen KD, Bierma-Zeinstra SM, Foster NE, Golightly YM, Hawker G. OARSI Clinical Trials Recommendations: Design and conduct of implementation trials of interventions for osteoarthritis. Osteoarthritis Cartilage 2015;23(5):826-38.

7 Price D, Bateman ED, Chisholm A, et al. Complementing the randomized controlled trial evidence base. Evolution not revolution. Ann Am Thorac Soc 2014;11 Suppl 2:S92-8.

8 Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. Clin Transl Gastroenterol 2014;5:e45.

9 Roland M, Torgerson DJ. What are pragmatic trials? BMJ 1998;316(7127):285.

10 Williams HC, Burden-Teh E, Nunn AJ. What is a pragmatic clinical trial? J Invest Dermatol 2015;135(6):e33.

11 Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol 2009;62(5):464-75.

12 Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008;337:a2390.

13 Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci 2011;13(2):217-24.

14 Tosh G, Soares-Weiser K, Adams CE. Pragmatic vs explanatory trials: the pragmascope tool to help measure differences in protocols of mental health randomized controlled trials. Dialogues Clin Neurosci 2011;13(2):209-15.

15 Gaglio B, Phillips SM, Heurtin-Roberts S, Sanchez MA, Glasgow RE. How pragmatic is it? Lessons learned using PRECIS and RE-AIM for determining pragmatic characteristics of research. Implement Sci 2014;9:96.

16 Glasgow RE. What does it mean to be pragmatic? Pragmatic methods, measures, and models to facilitate research translation. Health Educ Behav 2013;40(3):257-65.

17 Lau R, Stevenson F, Ong BN, et al. Achieving change in primary care--effectiveness of strategies for improving implementation of complex interventions: systematic review of reviews. BMJ Open 2015;5(12):e009993.

TABLE/FIGURE LEGENDS

Table 1. Summary of PRECIS (11) and CONSORT (12) guidelines, showing their overlap and application to pragmatic trials in osteoarthritis research.

Table 2. Evaluation of pragmatic trials in osteoarthritis research. Number (and percentage) of studies that met each criteria, separated by clinician- or patient-based intervention, and combined.

Supplementary Figure 1. Flowchart of literature search strategy.

Supplementary Figure 2. Distribution of summed scores for each pragmatic trial evaluated (N=61), with a maximum possible score of 11. Clinician-based intervention (black bars) = oral drug, injections, acupuncture, surgery, or clinical pathways. Patient-based intervention (grey bars) = diet, exercise, self-management programs, devices, topical therapies.

Supplementary Table 1. Summary of included studies.

Supplementary Table 2. Detailed evaluation of pragmatic trials in osteoarthritis research.

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ABSTRACT

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Methods: We used established guidelines to assess the degree to which 61 osteoarthritis studies complied with pragmatic trial design ~~[pragmatic-explanatory continuum indicator summary (PRECIS)]~~ and reporting. ~~[pragmatic trials extension of the CONSORT (CONsolidated Standards of Reporting Trials) guidelines].~~ We assessed design according to the pragmatic-explanatory continuum indicator summary (PRECIS), and reporting according to the pragmatic trials extension of the CONSORT (CONsolidated Standards of Reporting Trials) guidelines.

Results: None of the pragmatic trials met all 11 criteria evaluated, most of the trials met between 5 and 8 of the criteria. Criteria most often unmet pertained to practitioner expertise (by requiring specialists), and criteria most often met pertained to primary outcome analysis (by using intention-to-treat analysis).

Conclusion: Our results suggest a lack of highly pragmatic trials in osteoarthritis research. We identify this as a point of opportunity to improve research translation, since ~~;~~ optimizing the

design and reporting of pragmatic trials can facilitate implementation of evidence-based interventions for osteoarthritis care.

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INTRODUCTION

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Pragmatic trials are particularly useful in implementation research, since they are designed to determine the generalizability of interventions to routine practice [6]. Whereas explanatory trials are used to test the *efficacy* of interventions in controlled settings, pragmatic trials are used to demonstrate the *effectiveness* of interventions in real-world settings [7, 8]. In theory,

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METHODS

We searched PubMed and Web of Science using the terms "pragmatic AND trial AND osteoarthritis [All Fields]" to identify publications prior to August 2016. Our search identified 63 citations from PubMed and 93 citations from Web of Science, with 96 unique citations combined (**Supplementary Figure 1**). We included articles that explicitly stated that the study was "pragmatic" in the title (36%), abstract (59%), or methods/discussion (5%). We excluded articles that were not reports of primary research, were not available in full-text or English, and were not related to osteoarthritis. We excluded reports of trial results when reports of trial protocol for the same study were already included. For each study, we determined whether the

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RESULTS

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more criteria, or 4 or less criteria (~~Figure 1A~~Supplementary Figure 2). Of note, 5% of studies met 9 or more criteria, suggesting that it is possible, but rare, to have highly pragmatic trials in osteoarthritis research.

The criteria that most studies failed to meet were practitioner expertise for both experimental and comparison interventions. This requires the intervention be applied by practitioners ordinarily involved with the care of patients [11]. For osteoarthritis patients, this typically includes general practitioners, pharmacists, family, and friends. Only 10% of studies met this criterion for the experimental intervention and only 34% for the comparison intervention (~~Figure 1B~~Table 2). The majority of studies required additional training of practitioners delivering the intervention, or included experts that would require special referral in many health care systems (e.g. physiotherapists, orthopaedic surgeons).

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Strengths of pragmatic trials in osteoarthritis research include the choice of primary trial outcome, where 82% of studies used outcomes that were minimally invasive and clinically meaningful to participants (e.g. pain, quality of life, function), and analysis of primary outcome, where 87% of studies used intention-to-treat analysis. We found 79% of studies did not monitor practitioner adherence to the study protocol, although this number may reflect a common practice to refrain from monitoring practitioners rather than a research effort to comply with pragmatic trial guidelines. We found 77% of studies met the criterion for minimizing follow-up intensity, although we allowed for up to 2 follow-ups, and considered any follow-up by phone or mail to be pragmatic (~~Figure 1B~~Table 2).

DISCUSSION

In osteoarthritis research, studies that self-identify as pragmatic trials fail to meet many criteria for the design and reporting of pragmatic trials. While the PRECIS tool [11] is not intended as a method for classifying trials, it is useful for evaluating the degree to which pragmatic trials meet design recommendations [13, 15]. Our results show that most trials have both pragmatic and explanatory elements, supporting the idea of a pragmatic-explanatory continuum in trial design [11, 13].

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deprioritized in clinical settings [4]. Yet for scientific rigor, trials must have some inclusion/exclusion criteria, practitioners must follow protocol to some degree, an appropriate comparison group is needed, and some type of follow-up is required to measure change in outcomes. As a result, there is considerable tension for some pragmatic trials criteria, between minimizing bias and maximizing generalizability [10]. How these tensions are reconciled will depend on the research question and parameters of individual studies [7].

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To clarify what may constitute a pragmatic trial in osteoarthritis research, we identified common design decisions that are consistent with guidelines (**Table 1**). The list in **Table 1** is not exhaustive and was formulated based on the pragmatic trials we evaluated, of which 41% were ~~medical~~ clinician-based interventions and 59% were ~~lifestyle~~ patient-based interventions. Existing guidelines for pragmatic trials had to be flexibly applied for trials with ~~medical~~ clinician-based interventions to qualify as pragmatic. We found eligibility criteria were more specific, experimental and comparison interventions were less flexible, practitioner adherence to

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We excluded articles that were not related to osteoarthritis or declared as pragmatic trials, making our search specific, but not necessarily sensitive. ~~, since o~~Other studies may have incorporated elements of pragmatic trial design without declaring the trial type as pragmatic, or may have tested interventions for joint pain without declaring an osteoarthritis diagnosis. This may have resulted in under-counting of pragmatic trials in osteoarthritis in our literature search. Other articles may have inappropriately declared the trial type as pragmatic, causing our results to reflect poor design and reporting and an overall lack of highly pragmatic trials. The underlying issue may be a lack of clarity and consensus in the field about what constitutes a pragmatic trial [7].

It remains unclear whether trials are not sufficiently pragmatic, or whether existing pragmatic trial guidelines are not appropriate. Ultimately, pragmatic trials test implementation of interventions in the real-world, and what constitutes 'real-world' will differ depending on the intervention type (in-home for many lifestyle interventions, hospital-based for surgical interventions), the end-users (patients, clinicians, policy-makers), and the social, political, and economic contexts in which the intervention will ultimately be delivered [16]. It is difficult to prove whether having more trials that are more pragmatic will improve implementation of

evidence-based interventions [17]. Certainly without pragmatic trials and implementation research, practitioners may lack trial evidence that is amenable to their clinical context, and this may hinder their ability to operationalize clinical practice guidelines.

In conclusion, there is a lack of highly pragmatic trials in osteoarthritis research, as defined by current guidelines for the design [11] and reporting [12] of pragmatic trials. Understanding existing pragmatic trial guidelines and how they can be applied to osteoarthritis research may improve use of this method in implementation research. Further efforts are needed to achieve a common understanding among researchers about what constitutes a pragmatic trial.

KEY MESSAGES

- ~~Pragmatic trials facilitate implementation of health research, but are seldom used in osteoarthritis research.~~
- Only 61 self-identified pragmatic trials on osteoarthritis were published prior to August 2016.
- Existing pragmatic trials in osteoarthritis research show variable compliance with established guidelines.

- Most pragmatic trials met guidelines for 'Analysis of primary outcome', but not 'Practitioner expertise'.

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Author Contributions: SAA conceptualized the study, interpreted results, and wrote the manuscript. Data collection and analyses were performed by SAA, KL, and KW. Revision of the manuscript was performed by MK, JCM and DF. All authors approved the final manuscript.

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REFERENCES

1 Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol 2014.

2 Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64(4):465-74.

3 McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22(3):363-88.

4 Paskins Z, Sanders T, Croft PR, Hassell AB. The Identity Crisis of Osteoarthritis in General Practice: A Qualitative Study Using Video-Stimulated Recall. Ann Fam Med 2015;13(6):537-44.
5 Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci 2015;10:53.
6 Allen KD, Bierma-Zeinstra SM, Foster NE, Golightly YM, Hawker G. OARSI Clinical Trials Recommendations: Design and conduct of implementation trials of interventions for osteoarthritis. Osteoarthritis Cartilage 2015;23(5):826-38.
7 Price D, Bateman ED, Chisholm A, et al. Complementing the randomized controlled trial evidence base. Evolution not revolution. Ann Am Thorac Soc 2014;11 Suppl 2:S92-8.
8 Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. Clin Transl Gastroenterol 2014;5:e45.
9 Roland M, Torgerson DJ. What are pragmatic trials? BMJ 1998;316(7127):285.
10 Williams HC, Burden-Teh E, Nunn AJ. What is a pragmatic clinical trial? J Invest Dermatol 2015;135(6):e33.
11 Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol 2009;62(5):464-75.
12 Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008;337:a2390.
13 Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci 2011;13(2):217-24.
14 Tosh G, Soares-Weiser K, Adams CE. Pragmatic vs explanatory trials: the pragmascope tool to help measure differences in protocols of mental health randomized controlled trials. Dialogues Clin Neurosci 2011;13(2):209-15.
15 Gaglio B, Phillips SM, Heurtin-Roberts S, Sanchez MA, Glasgow RE. How pragmatic is it? Lessons learned using PRECIS and RE-AIM for determining pragmatic characteristics of research. Implement Sci 2014;9:96.
16 Glasgow RE. What does it mean to be pragmatic? Pragmatic methods, measures, and models to facilitate research translation. Health Educ Behav 2013;40(3):257-65.
17 Lau R, Stevenson F, Ong BN, et al. Achieving change in primary care--effectiveness of strategies for improving implementation of complex interventions: systematic review of reviews. BMJ Open 2015;5(12):e009993.

TABLE/FIGURE LEGENDS

Table 1. Summary of PRECIS (1~~0~~) and CONSORT (1~~1~~) guidelines, showing their overlap and application to pragmatic trials in osteoarthritis research.

~~Figure~~ Table ~~2~~1. Evaluation of pragmatic trials in osteoarthritis research. ~~A) Distribution of summed scores for each pragmatic trial evaluated (N=61), with a maximum possible score of 11. Medical = oral drug, injections, acupuncture, surgery, or clinical pathways. Lifestyle = diet, exercise, self-management programs, devices, topical therapies. B)~~ Number (and percentage) of studies that met each criteria, separated by ~~medical~~ clinician- or patient-based ~~lifestyle~~ intervention, and combined.

Supplementary Figure 1. Flowchart of literature search strategy.

Supplementary Figure 2. Distribution of summed scores for each pragmatic trial evaluated (N=61), with a maximum possible score of 11. Clinician-based intervention (black bars) = oral drug, injections, acupuncture, surgery, or clinical pathways. Patient-based intervention (grey bars) = diet, exercise, self-management programs, devices, topical therapies.

Supplementary Table 1. Summary of included studies.

Supplementary Table 2. Evaluation of included studies using 11 criteria for pragmatic trials.

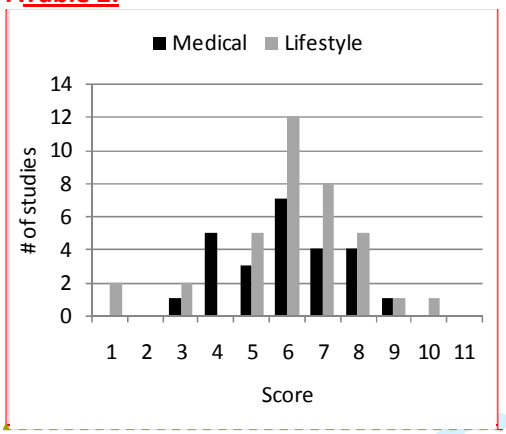
Table 1.

	Design (PRECIS)	Reporting (CONSORT)	A pragmatic trial in osteoarthritis research:
1	Participant eligibility criteria	Participants	Captures the target population (e.g. does not exclude people with co-morbidities)
	Experimental intervention	Interventions	
2	Flexibility	Generalizability	Implements an intervention that can be delivered after the study concludes
3	Practitioner expertise		Relies on a general practitioner or other typical OA care provider
	Comparison intervention	Background	
4	Flexibility		Describes current standard of care, does not alter it (e.g. by providing pamphlets)
5	Practitioner expertise		Relies on a general practitioner or other typical OA care provider
6	Follow-up intensity	Outcomes	Measures outcomes infrequently, and at least 6 months following the intervention
7	Primary trial outcome	Sample Size	Uses minimally invasive outcomes that are meaningful to the participant (e.g. function)
8	Participant compliance		Does not track participant compliance (e.g. with self-reports in diaries/logs)
9	Practitioner adherence		Does not monitor general practitioner/OA care provider adherence to study protocol
10	Analysis of primary outcome	Participant Flow	Includes all participants in an intention-to-treat analysis of the primary outcome
11		Blinding	Provides an explanation for blinding decisions

Table 2.

Criteria	Clinician-based intervention (N=25)	Patient-based intervention (N=36)	Combined (N=61)
Participant eligibility criteria	12 (48%)	13 (36%)	25 (41%)
Experimental intervention			
Flexibility	13 (52%)	18 (50%)	31 (51%)
Practitioner expertise	5 (20%)	1 (3%)	6 (10%)
Comparison intervention			
Flexibility	12 (48%)	17 (47%)	29 (48%)
Practitioner expertise	9 (36%)	12 (33%)	21 (34%)
Follow-up intensity	17 (68%)	30 (83%)	47 (77%)
Primary trial outcome	19 (76%)	31 (86%)	50 (82%)
Participant compliance	14 (56%)	19 (53%)	33 (54%)
Practitioner adherence	21 (84%)	27 (75%)	48 (79%)
Analysis of primary outcome	19 (76%)	34 (94%)	53 (87%)
Blinding	8 (32%)	18 (50%)	26 (43%)

~~A~~Table 2.



~~B~~

Criteria	Clinician-based intervention ~~Medical~~ (N=25)	Patient-based intervention ~~Lifestyle~~ (N=36)	Combined (N=61)
Participant eligibility criteria	12 (48%)	13 (36%)	25 (41%)
Experimental intervention			
Flexibility	13 (52%)	18 (50%)	31 (51%)
Practitioner expertise	5 (20%)	1 (3%)	6 (10%)
Comparison intervention			
Flexibility	12 (48%)	17 (47%)	29 (48%)
Practitioner expertise	9 (36%)	12 (33%)	21 (34%)
Follow-up intensity	17 (68%)	30 (83%)	47 (77%)
Primary trial outcome	19 (76%)	31 (86%)	50 (82%)
Participant compliance	14 (56%)	19 (53%)	33 (54%)
Practitioner adherence	21 (84%)	27 (75%)	48 (79%)
Analysis of primary outcome	19 (76%)	34 (94%)	53 (87%)
Blinding	8 (32%)	18 (50%)	26 (43%)

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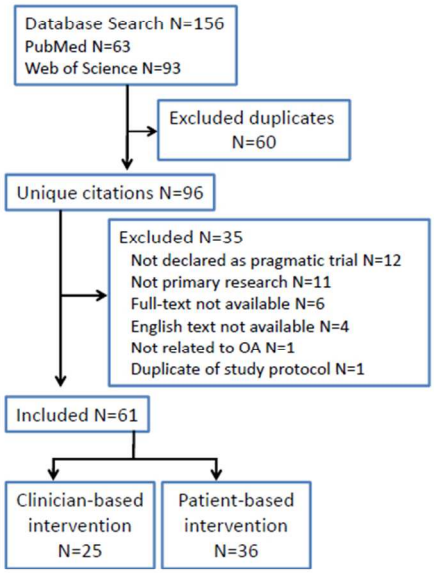
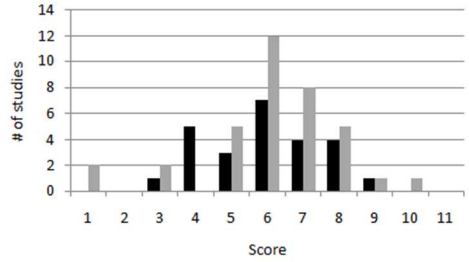
~~Figure 1.~~



Supplementary Figure 1.

215x279mm (96 x 96 DPI)



Supplementary Figure 2.

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Supplementary Table 1. Summary of included studies

Citation	Study question	Intervention	Protocol paper	Pragmatic score
Bilkman T, Rienstra W, Raaij T, Hagen A, Dijkstra B, Zijlstra W, et al. Duloxetine in OsteoArthritis (DOA) study: study protocol of a pragmatic open-label randomised controlled trial assessing the effect of preoperative pain treatment on postoperative outcome after total hip or knee arthroplasty. BMJ Open. 2016;6(3).	What are the effects of preoperative pain treatment on postoperative outcomes using duloxetine for hip or knee OA?	drug	protocol	7
Callahan LF, Callahan LF, Cleveland RJ, Altpeter M, Hackney B. Evaluation of Tai Chi Program Effectiveness for People with Arthritis in the Community: A Randomized Controlled Trial. Journal of aging and physical activity. 2016;24(1):101.	What is the effectiveness of the Arthritis Foundation Tai Chi Program for community participants with arthritis?	exercise		8
Deyle G, Gill N, Rhon D, Allen C, Allison S, Hando B, et al. A multicentre randomised, 1-year comparative effectiveness, parallel-group trial protocol of a physical therapy approach compared to corticosteroid injections. BMJ Open. 2016;6(3).	What is the effectiveness of physical therapy compared to corticosteroid injections alone for knee OA?	physiotherapy	protocol	4
Yu SP, Williams M, Eyles JP, Chen JS, Makovey J, Hunter DJ. Effectiveness of knee bracing in osteoarthritis: pragmatic trial in a multidisciplinary clinic. International Journal of Rheumatic Diseases. 2016;19(3):279-286.	What is the effectiveness of bracing treatment for tibiofemoral osteoarthritis (OA) and patellofemoral OA in patients with knee OA?	bracing		6
Beard D, Rees J, Rombach I, Cooper C. Trials: The CSAW Study (Can Shoulder Arthroscopy Work?) - a placebo-controlled surgical intervention trial assessing the clinical and cost effectiveness of arthroscopic subacromial decompression for shoulder pain: study protocol for a randomised controlled trial. Trials. 2015;16(5):210.	What is the efficacy and cost-effectiveness of ASAD (Arthroscopic subacromial decompression) in patients with subacromial pain?	surgery	protocol	5

Cuperus N, Hoogeboom T, Kersten C, et al. Randomized trial of the effectiveness of a non-pharmacological multidisciplinary face-to-face treatment program on daily function compared to a telephone-based treatment program in patients with generalized osteoarthritis. Osteoarthritis and Cartilage 2015. 23:1267–1275.	How effective is non-pharmacological multidisciplinary face-to-face group-based treatment program versus a telephone-delivered treatment program on daily function for patients with generalized OA?	self-management		6
Eymard F, Charles-Nelson A, Katsahian S, Chevalier X, Bercovy M. “Forgotten knee” after total knee replacement: A pragmatic study from a single-centre cohort. Joint Bone Spine. 2015;82(3):177-181.	What is the prevalence of “forgotten knee” (FK) after TKR in a prospective pragmatic cohort, with comparison to conventional scores?	surgery		4
Kingsbury SR, Tharmanathan P, Arden NK, Batley M, Birrell F, Cocks K, et al. Pain reduction with oral methotrexate in knee osteoarthritis, a pragmatic phase iii trial of treatment effectiveness (PROMOTE): study protocol for a randomized controlled trial. Trials. 2015;16:77.	How effective is oral methotraxate for reducing synovitis (and pain) patients with knee OA?	methotrexate	protocol	5
Moonaz SH, Bingham CO, Wissow L, Bartlett SJ. Yoga in Sedentary Adults with Arthritis: Effects of a Randomized Controlled Pragmatic Trial. The Journal of Rheumatology. 2015;42(7):1194–1202.	Can integral-based hatha yoga improve fitnesss, mood, stress and quality of life for people with knee RA or OA?	yoga		5
Teirlinck CH, Luijsterburg PA, Dekker J, Bohnen AM, Verhaar JA, Koopmanschap MA, et al. Effectiveness of exercise therapy added to general practitioner care in patients with hip osteoarthritis: a pragmatic randomized controlled trial. Osteoarthritis and Cartilage. 2015;24(1):82-90.	How effective is exercise at improving function and pain for individuals with hip OA?	exercise therapy		7
Bevers K, Zweers MC, Vriezekolk JE, Bijlsma JW, den Broeder AA. Are ultrasonographic signs of inflammation predictors for response to intra-articular glucocorticoids in knee osteoarthritis? Clinical and Experimental Rheumatology. 2014;32(6):930–934.	What is the predictive value of ultrasound characteristics for the effect of intra-articular glucocorticoids in knee OA?	glucocorticoid injection		6

Broderick JE, Keefe FJ, Bruckenthal P, Junghaenel DU, Schneider S, Schwartz JE, et al. Nurse practitioners can effectively deliver pain coping skills training to osteoarthritis patients with chronic pain: A randomized, controlled trial. Pain. 2014;155(9):1743–1754.	How effectiveness are 10 education sessions about pain management faciliated by health nurses for patients with OA of knee or hip?	coping		7
Dobson F, Hinman RS, French S, Rini C, Keefe F, Nelligan R, et al. Internet-mediated physiotherapy and pain coping skills training for people with persistent knee pain (IMPACT – knee pain): a randomised controlled trial protocol. BMC Musculoskelet Disorders. 2014;15:279.	Is an internet-delivered intervention that combines PCST and physiotherapist-guided exercise more effective than online educational material in people with persistent knee pain?	coping/physio/exercise	protocol	6
Foster NE, Healey EL, Holden MA, Nicholls E, Whitehurst DG, Jowett S, et al. A multicentre, pragmatic, parallel group, randomised controlled trial to compare the clinical and cost-effectiveness of three physiotherapy-led exercise interventions for knee osteoarthritis in older adults: the BEEP trial protocol (ISRCTN: 93634563). BMC Musculoskelet Disorders. 2014;15:254.	How effective are individuallly tailored exercise programs versus usual physiptherapy care for adherence?	physio/exercise	protocol	6
Hermann M, Nilsen T, Eriksen CS, Slatkowsky-Christensen B, Haugen IK, Kjeken I. Effects of a soft prefabricated thumb orthosis in carpometacarpal osteoarthritis. Scandinavian Journal of Occupational Therapy. 2014;21:31-39.	How does the use of a hand orthosis versus no orthosis affect pain?	orthosis		7
Janke E, Fritz M, Hopkins C, Haltzman B, Sautter J, Ramirez M. A randomized clinical trial of an integrated behavioral self-management intervention Simultaneously Targeting Obesity and Pain: the STOP trial. BMC Public Health. 2014;14:621.	What is the effectiveness of an integrated treatment (STOP) for weight loss and reduction in pain intensity?	behavioral self-management intervention	protocol	3

Kjeken I, Berdal G, Bo I, Dager T, Dingsor A, Hagfors J, et al. Evaluation of a structured goal planning and tailored follow-up programme in rehabilitation for patients with rheumatic diseases: protocol for a pragmatic, stepped-wedge cluster randomized trial. BMC Musculoskeletal Disorders. 2014;15:153.	What is the clinical and cost-effectiveness of a structured goal planning and tailored follow-up rehabilitation programme for patients with rheumatic diseases?	goal planning and tailored follow-up programme	protocol	5
Martins F, Kaster T, Schützler L, Witt CM. Factors Influencing Further Acupuncture Usage and a more positive outcome in patients with osteoarthritis of the knee and the hip: a 3-year follow-up of a randomized pragmatic trial. The Clinical Journal of Pain. 2014;30(11):953–959.	How does immediate versus delayed acupuncture affect the long term outcomes for people with OA?	acupuncture		6
Rabago D, Patterson JJ, Mundt M, Zgierska A, Fortney L, Grettie J, et al. Dextrose and Morrhuate Sodium Injections (Prolotherapy) for Knee Osteoarthritis: A prospective open-label trial. Journal of Alternative and Complementary Medicine. 2014;20(5):383–391.	Do scheduled hypertonic dextrose and morrhuate sodium injections improved knee pain, function and stiffness for knee osteoarthritis?	dextrose & morrhuate sodium		6
Beard D, Price A, Cook J, Fitzpatrick R, Carr A, Campbell M, et al. Total or Partial Knee Arthroplasty Trial - TOPKAT: study protocol for a randomised controlled trial. Trials. 2013;14:292.	What is the clinical and cost effectiveness of total knee replacements versus unicompartmental replacements for patients with medial compartment osteoarthritis?	total vs. unicompartment replacement	protocol	4
Kim EJ, Lim CY, Lee EY, Lee SD, Kim KS. Comparing the effects of individualized, standard, sham and no acupuncture in the treatment of knee osteoarthritis: a multicenter randomized controlled trial. Trials. 2013;14:129.	How efficient is meridian-based syndrome differentiation and Sa-am for reducing pain in knee OA?	acupunture	protocol	6
Lee S, Kim KH, Kim TH, Kim JE, Kim JH, Kang JW, et al. Moxibustion for treating knee osteoarthritis: study protocol of a multicentre randomised controlled trial. BMC Complementary and Alternative Medicine. 2013;13:59.	Determined if moxibustin (orietal therapy where herbs are burned on certain areas of skin) could reduce pain and improve activity for knee OA.	moxibustion + acupuncture	protocol	6

Salisbury C, Montgomery AA, Hollinghurst S, Hopper C. Effectiveness of PhysioDirect telephone assessment and advice services for patients with musculoskeletal problems: pragmatic randomised controlled trial. British Medical Journal. 2013;346:f43.	What is the clinical effectiveness, effect on waiting times, and patient acceptability of PhysioDirect services in patients with musculoskeletal problems?	telephone assessment and advice service		3
Uehleke B, Müller J, Stange R, Kelber O, Melzer J. Willow bark extract STW 33-I in the long-term treatment of outpatients with rheumatic pain mainly osteoarthritis or back pain. Phytomedicine. 2013;20(11):980–984.	Does Willow bark extract reduce long term pain in individuals with OA or back pain?	STW 33-I		8
Adams J, Bridle C, Dosanjh S, Heine P, Lamb SE, Lord J, et al. Strengthening and stretching for rheumatoid arthritis of the hand (SARAH): design of a randomised controlled trial of a hand and upper limb exercise intervention. BMC Musculoskeletal Disorders. 2012;13:230.	What is the clinical and cost effectiveness of an optimized exercise programme for hand and upper limb OA?	exercise program		5
Bennell KL, Egerton T, Bills C, Gale J, Kolt GS, Bunker SJ, et al. Addition of telephone coaching to a physiotherapist-delivered physical activity program in people with knee osteoarthritis: a randomised controlled trial protocol. BMC Musculoskeletal Disorders. 2012;13:246.	Does adding telephone coaching to a physiotherapist-delivered physical activity improve clinical and cost effectiveness of the intervention for people with knee OA?	telephone-coaching	protocol	5
Dakin H, Gray A, Fitzpatrick R, MacLennan G, Murray D. Rationing of total knee replacement: a cost-effectiveness analysis on a large trial data set. BMJ Open. 2012;2:e000332.	What is the cost-effectiveness of total knee replacements versus no knee replacement patients with OA?	TKA cost effectiveness		9
Gooch K, Marshall DA, Faris PD, Khong H, Wasylak T, Pearce T, et al. Comparative effectiveness of alternative clinical pathways for primary hip and knee joint replacement patients: a pragmatic randomized, controlled trial. Osteoarthritis and Cartilage. 2012;20(10):1086–1094.	How effective is the new clinical pathway (featuring central intake clinics, dedicated inpatient resources, care guidelines and efficiency benchmarks) vs the standard of care for THR or Total k nee replacement for OA?	clinical pathway		8

Hinman RS, McCrory P, Pirotta M, Relf I, Crossley KM, Reddy P, et al. Efficacy of acupuncture for chronic knee pain: protocol for a randomised controlled trial using a Zelen design. BMC Complementary and Alternative Medicine. 2012;12:161.	What is the cost-effectiveness and efficiency for needle and laser apcupuncture for relieving chronic knee pain?	acupuncture	protocol	7
Hurley MV, Walsh NE, Mitchell H, Nicholas J, Patel A. Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: a pragmatic, cluster randomized, controlled trial. Arthritis Care & Research. 2012;64(2):238–247.	What is the long-term (up to 30 months) clinical and cost effectiveness of a rehabilitation program combining self-management and exercise?	self-management		6
Rathleff M, Roos E, Olesen J, Rasmussen S. Early intervention for adolescents with Patellofemoral Pain Syndrome - a pragmatic cluster randomised controlled trial. BMC Musculoskeletal Disorders. 2012;13:9.	What is the short- and long-term effectiveness of patient education compared with patient education and physiotherapy for patellofemoral pain syndrome in adolescents?	patient education and physiotherapy	protocol	6
Breeman S, Campbell M, Dakin H, Fiddian N, Fitzpatrick R, Grant A, et al. Patellar resurfacing in total knee replacement: five-year clinical and economic results of a large randomized controlled trial. The Journal of Bone and Joint Surgery-American Volume. 2011;93(16):1473–1481.	What are the advantages and disadvantages of patellar resurfacing and selective resurfacing?	surgical effectiveness		8
Christensen P, Bliddal H, Riecke BF, Leeds AR, Astrup A, Christensen R. Comparison of a low-energy diet and a very low-energy diet in sedentary obese individuals: a pragmatic randomized controlled trial. Clinical Obesity. 2011;1(1):31–40.	Does a very low-energy formula diet cause greater weight loss than a formula 810 kcal d-1LED in older sedentary individuals?	diet		1
Juhakoski R, Tenhonen S, Malmivaara A, Kiviniemi V, Anttonen T, Arokoski JP. A pragmatic randomized controlled study of the effectiveness and cost consequences of exercise therapy in hip osteoarthritis. Clinical Rehabilitation. 2011;25(4):370–383.	What is the short- and long-term effectiveness of exercise training in relation to pain, function and direct costs to health care systems attributable to hip OA?	exercise		6

Minns Lowe CJ, Wilson MS, Sackley CM, Barker KL. Blind outcome assessment: the development and use of procedures to maintain and describe blinding in a pragmatic physiotherapy rehabilitation trial. Clinical Rehabilitation. 2011;25(3):264–274.	What is the effectiveness of a postdischarge physiotherapy intervention in improving patient function after total knee arthroplasty for OA?	blinding (physio)		7
Cadmus L, Patrick MB, Maciejewski ML, Topolski T, Belza B, Patrick DL. Community-Based Aquatic Exercise and Quality of Life in Persons with Osteoarthritis. Medicine & Science in Sports & Exercise. 2010;42(1):8–15.	What is the effectiveness of a community-based aquatic exercise program to improve quality of life among persons with osteoarthritis?	aquatic exercise		8
Moe RH, Uhlig T, Kjeken I, Hagen KB, Kvien TK, Grotle M. Multidisciplinary and multifaceted outpatient management of patients with osteoarthritis: protocol for a randomised, controlled trial. BMC Musculoskeletal Disorders. 2010;11:253.	What are the effects of a multidisciplinary outpatient clinic with a brief group-based educational programme, versus a traditional individual outpatient clinic for patients with hip, knee, hand or generalized OA?	self-management	protocol	7
Riecke BF, Christensen R, Christensen P, Leeds AR, Boesen M, Lohmander LS, et al. Comparing two low-energy diets for the treatment of knee osteoarthritis symptoms in obese patients: a pragmatic randomized clinical trial. Osteoarthritis and Cartilage. 2010;18(6):746–754.	What is the symptom response for patients assigned a very low energy diet versus a low energy diet, for patients who are obese and have knee OA?	diet		1
Gooch, K.L., Smith, D., Wasylak, T., Faris, P.D., Marshall, D.A., Khong, H., Hibbert, J.E., Parker, R.D., Zernicke, R.F., Beaupre, L., Pearce, T., Johnston, D.W.C. and Frank, C.B. The Alberta hip and knee replacement project: A model for health technology assessment based on comparative effectiveness of clinical pathways. International Journal of Technology Assessment in Health Care. 2009;25(2):113-123.	Can the Alberta Hip and Knee Replacement Project be used as a model as a model for health technology assessment based on comparative effectiveness of alternative clinical pathways?	study effectiveness of clinical pathway		8

Harmer AR, Naylor JM, Crosbie J, Russell T. Land-based versus water-based rehabilitation following total knee replacement: A randomized, single-blind trial. Arthritis Care & Research. 2009;61(2):184-191.	What are the outcomes for land-based and water-based exercise programs after total knee replacement (TKR)?	exercise program		8
Jenkinson CM, Doherty M, Avery AJ, Read A, Taylor MA, Sach TH, et al. Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: randomised controlled trial. The BMJ. 2009;339:b3170.	How do dietary intervention plus quadriceps strengthening exercises; dietary intervention alone; quadriceps strengthening exercises alone; advice leaflet only (control group) effect knee pain in obese patients?	diet + exercise		7
Jessep SA, Walsh NE, Ratcliffe J, Hurley MV. Long-term clinical benefits and costs of an integrated rehabilitation programme compared with outpatient physiotherapy for chronic knee pain. Physiotherapy. 2009;95(2):94–102.	What is the feasibility of ESCAPE-knee pain, clinical effectiveness and costs versus outpatient physiotherapy?	physio/exercise		6
Lansdown H, Howard K, Brealey S, MacPherson H. Acupuncture for pain and osteoarthritis of the knee: a pilot study for an open parallel-arm randomised controlled trial. BMC Musculoskeletal Disorders. 2009;10:130.	How effective is acupuncture versus usual care to reduce knee OA pain?	acupuncture		7
Lin CC, March L, Crosbie J, Crawford R, Graves S, Naylor J, et al. Maximum recovery after knee replacement – the MARKER study rationale and protocol. BMC Musculoskeletal Disorders. 2009;10:69.	What is the clinical and cost effectiveness of an initial home exercise programme followed by higher intensity outpatient exercise classes after knee replacement?	exercise program	protocol	6
Rahmann AE, Brauer SG, Nitz JC. A specific inpatient aquatic physiotherapy program improves strength after total hip or knee replacement surgery: a randomized controlled trial. Archives of Physical Medicine and Rehabilitation. 2009;90(5):745–755.	What is the effect of inpatient aquatic physiotherapy versus regular physiotherapy to recover of strength, function, and gait speed after total hip or knee replacement surgery due to OA?	aquatic physio		6

Ravaud P, Flipo R-M, Boutron I, Roy C, Mahmoudi A, Giraudeau B et al. ARTIST (osteoarthritis intervention standardized) study of standardised consultation versus usual care for patients with osteoarthritis of the knee in primary care in France: pragmatic randomised controlled trial. British Medical Journal. 2009; 338:b421.	What is the impact of standardized consultations on patients with osteoarthritis of the knee?	standardised consultations	5	6
Itoh K, Hirota S, Katsumi Y, Ochi H, Kitakoji H. Trigger point acupuncture for treatment of knee osteoarthritis - a preliminary RCT for a pragmatic trial. Acupuncture in Medicine. 2008;26(1):17-26.	What is the effect of trigger point acupuncture on pain and quality-of-life in knee osteoarthritis patients, compared with acupuncture at standard points, and sham acupuncture?	accupuncture		4
Brealey SD, (Direct Access to Magnetic Resonance Imaging: Assessment for Suspect Knees) Trial Team. Influence of magnetic resonance imaging of the knee on GPs' decisions: a randomised trial. The British Journal of General Practice. 2007;57(541):622-629.	What is the effect of early access to MRI, compared with referral to an orthopaedic specialist for knee problems?	MRI		4
Brinks A, van Rijn R, Bohnen A, Slee G, Verhaar J, Koes B, et al. Effect of corticosteroid injection for trochanter pain syndrome: design of a randomised clinical trial in general practice. BMC Musculoskeletal Disorders. 2007;8:95.	What is the efficacy of local corticosteroid injections in the trochanter syndrome in the general practice?	corticosteroid injection	protocol	6
Hurley MV, Walsh NE, Mitchell HL, Pimm TJ, Patel A, Williamson E, et al. Clinical effectiveness of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain: A cluster randomized trial. Arthritis Care & Research. 2007;57(7):1211-1219.	Is a rehabilitation program integrating exercise, self-management, and active coping strategies effective for OA?	rehabilitation program		9

Rosemann T, Joos S, Laux G, Gensichen J, Szecsenyi J. Case management of arthritis patients in primary care: A cluster-randomized controlled trial1. Arthritis Care & Research. 2007;57(8):1390-1397.	Does providing information on arthritis self-management through general practitioners (GPs) increase quality of life and does additional case management provided by practice nurses shows better results?	providing information and case-management	8
Hay, E, Foster N, Thomas E, Peat G, Phelan M, Yates H et al. Effectiveness of community physiotherapy and enhanced pharmacy review for knee pain in people aged over 55 presenting to primary care: Pragmatic randomised trial. British Medical Journal. 2006;333(7576), 995-998.	What is the effectiveness of enhanced pharmacy review and community physiotherapy for knee pain?	pharmacy review and community physiotherapy	6
Rabenda V, Burlet N, Belaiche J, Raeman F, Richy F, Reginster JY. Determinants of gastro-protective drugs co-prescription during treatment with nonselective NSAIDs: a prospective survey of 2197 patients recruited in primary care. Osteoarthritis and Cartilage. 2006;14(7):625-630.	What is the effectiveness of gastro-protective drugs (GPDs) during treatment with nonselective NSAIDs?	drug	7
Mitchell C, Walker J, Walters S, Morgan AB, Binns T, Mathers N. Costs and effectiveness of pre- and post-operative home physiotherapy for total knee replacement: randomized controlled trial. J.Eval.Clin.Pract. 2005;11(3):283-292.	What is the effectiveness of pre- and post-operative physiotherapy at home for unilateral total knee replacement (TKR)?	physiotherapy	5
Mccarthy C, McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N et al. Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: A randomised controlled trial and health economic analysis. Health Technology Assessment. 2004;8(46).	What is the effectiveness of a home-based exercise programme with a class-based programme for OA?	home-based exercise programme with class-based programme	8

Raynauld J-, Torrance GW, Band PA, Goldsmith CH, Tugwell P, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis and Cartilage. 2002;10(7):506-517.	What is the clinical and cost effectiveness of hylan G-F 20 for knee OA?	hylan G-F 20	3
Thomas K, Muir K, Doherty M, Jones A, O'Reilly S, & Bassey E. Home Based Exercise Programme For Knee Pain And Knee Osteoarthritis: Randomised Controlled Trial. British Medical Journal. 2002;325(7367): 752-755.	Can home-based exercise programme improve outcomes in patients with knee pain?	home-based exercise programme	7
Torrance GW, Raynauld JP, Walker V, Goldsmith CH, Bellamy N, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. Osteoarthritis and Cartilage. 2002;10(7):518-527.	What is the effectiveness of viscosupplementation of hylan G-F 20 for OA?	hylan G-F 20	5
Barlow JH, Turner AP, Wright CC. A randomized controlled study of the Arthritis Self-Management Programme in the UK. Health Educ.Res. 2000;15(6):665-680.	Does Arthritis Self-Management Programmes (ASMP) improve perceptions of control, health behaviours and health status, and change the use of health care resources?	arthritis self-management programme	10
van Haselen RA, Fisher PAG. A randomized controlled trial comparing topical piroxicam gel with a homeopathic gel in osteoarthritis of the knee. Rheumatology. 2000;39(7):714.	What is the effectiveness of a homeopathic gel vs an NSAID (piroxicam) gel in the treatment of osteoarthritis of the knee?	homeopathic piroxicam gel	7
Fagnani F, Bouvenot G, Valat J, Bardin T, Berdah L, Lafuma A, et al. Medico-economic analysis of diacerein with or without standard therapy in the treatment of osteoarthritis. PharmacoEconomics. 1998;13(1 Pt 2):135-46.	What is the effectiveness of diacerein with or without standard therapy in knee and hip OA?	diacerein	6

Supplementary Table 2. Detailed evaluation of pragmatic trials in osteoarthritis research.

			Intervention										
			Experimental		Comparison								
First Author	Year	Participant eligibility criteria	Flexibility	Practitioner expertise	Flexibility	Practitioner expertise	Follow-up intensity	Primary trial outcome	Participant compliance	Practitioner adherence	Analysis of primary outcome	Explanation for Blinding	**SUM**
Blikman et al.	2016	1	0	1	1	1	0	1	0	1	1	0	**7**
Callahan et al.	2016	1	0	0	1	1	1	1	1	1	1	0	**8**
Deyle et al.	2016	0	1	0	0	0	0	1	1	0	0	1	**4**
Yu et al.	2016	1	0	0	1	0	0	1	1	1	1	0	**6**
Beard et al.	2015	0	0	0	0	0	1	1	0	1	1	1	**5**
Cuperus et al.	2015	0	0	0	0	0	1	1	1	1	1	1	**6**
Eymard et al.	2015	1	0	0	1	0	0	1	1	0	0	0	**4**
Kingsbury et al.	2015	0	0	1	0	1	0	0	0	1	1	1	**5**
Moonaz et al.	2015	0	0	0	1	1	1	1	0	1	0	0	**5**
Teirlinck et al.	2015	0	1	0	1	1	0	1	1	1	1	0	**7**
Bevers et al.	2014	1	1	0	0	0	1	0	1	1	1	0	**6**
Broderick et al.	2014	0	0	0	1	1	1	1	1	1	1	0	**7**
Dobson et al.	2014	0	1	0	0	1	1	1	0	1	1	0	**6**
Foster et al.	2014	0	0	0	0	0	1	1	1	1	1	1	**6**
Hermann et al.	2014	1	1	0	0	0	1	0	1	1	1	1	**7**
Janke et al.	2014	1	0	0	0	0	0	1	0	0	1	0	**3**
Kjeken et al.	2014	1	0	0	0	0	1	1	0	0	1	1	**5**
Martins et al.	2014	1	1	0	0	0	1	1	1	1	0	0	**6**
Rabago et al.	2014	0	1	0	0	0	1	1	1	1	1	0	**6**
Beard et al.	2013	0	1	0	0	0	0	1	0	1	1	0	**4**
Kim et al.	2013	0	1	0	1	0	0	1	0	1	1	1	**6**
Lee et al.	2013	0	0	0	0	1	1	0	1	1	1	1	**6**
Salisbury et al.	2013	1	0	0	0	0	1	0	0	0	0	1	**3**
Uehleke et al.	2013	1	1	1	1	1	0	1	0	1	1	0	**8**
Adams et al.	2012	1	0	0	0	0	1	1	0	0	1	1	**5**
Bennell et al.	2012	0	1	0	0	0	1	1	0	1	1	0	**5**
Dakin et al.	2012	1	0	1	1	1	1	1	1	1	1	0	**9**
Gooch et al.	2012	1	1	0	1	0	1	1	1	1	1	0	**8**
Hinman et al.	2012	0	1	0	0	0	1	1	1	1	1	1	**7**
Hurley et al.	2012	0	0	0	1	1	0	1	1	1	1	0	**6**
Rathleff et al.	2012	1	0	0	1	0	1	0	0	1	1	1	**6**

Breeman et al.	2011	1	1	0	1	0	1	1	1	1	1	0	**8**
Christensen et al.	2011	0	0	0	0	0	0	0	0	0	1	0	**1**
Juhakoski et al.	2011	0	0	0	1	0	1	1	1	1	1	0	**6**
Minns Lowe et al.	2011	0	1	0	1	0	1	1	0	1	1	1	**7**
Cadmus et al.	2010	0	1	0	1	1	1	1	1	1	1	0	**8**
Moe et al.	2010	0	1	0	1	0	1	1	0	1	1	1	**7**
Riecke et al.	2010	0	0	0	0	0	0	0	0	0	1	0	**1**
Gooch et al.	2009	1	0	0	1	1	1	0	1	1	1	1	**8**
Harmer et al.	2009	1	1	0	0	0	1	1	1	1	1	1	**8**
Jenkinson et al.	2009	0	1	0	0	1	1	1	1	1	1	0	**7**
Jessep et al.	2009	0	1	0	0	0	1	1	1	1	1	0	**6**
Lansdown et al.	2009	0	1	0	1	1	1	1	0	1	1	0	**7**
Lin et al.	2009	0	0	0	1	0	1	1	0	1	1	1	**6**
Rahmann et al.	2009	1	0	0	0	0	1	1	1	0	1	1	**6**
Ravaud et al.	2009	0	1	0	1	0	1	1	0	0	1	1	**6**
Itoh et al.	2008	0	0	0	0	0	0	1	1	1	0	1	**4**
Brealey et al.	2007	0	1	0	0	0	1	1	0	0	1	0	**4**
Brinks et al.	2007	0	0	0	1	1	1	1	1	0	1	0	**6**
Hurley et al.	2007	0	1	0	1	1	1	1	1	1	1	1	**9**
Rosemann et al.	2007	1	1	0	1	1	1	1	0	1	1	0	**8**
Hay et al.	2006	0	1	0	0	0	1	1	1	0	1	1	**6**
Rabenda et al.	2006	1	1	1	1	1	1	0	0	1	0	0	**7**
Mitchell et al.	2005	0	1	0	0	0	1	1	0	1	1	0	**5**
McCarthy et al.	2004	1	1	0	0	0	1	1	1	1	1	1	**8**
Raynauld et al.	2002	0	0	0	0	0	1	1	0	1	0	0	**3**
Thomas et al.	2002	0	0	0	1	1	1	1	0	1	1	1	**7**
Torrance et al.	2002	1	0	0	0	0	1	0	1	1	1	0	**5**
Barlow et al.	2000	1	1	1	1	1	1	1	1	1	1	0	**10**
van Haselen et al.	2000	0	1	0	0	0	1	1	1	1	1	1	**7**
Fagnani et al.	1998	1	0	0	1	0	1	1	0	1	1	0	**6**