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Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

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Manuscripts

Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

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3 **Word count: 2,627**
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Abstract

Introduction: Acute, non-low back related musculoskeletal pain is common and associated with significant socioeconomic costs. No review has evaluated all interventional studies for acute musculoskeletal pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomised controlled trials evaluating therapies for acute musculoskeletal pain (excluding low back pain). We will identify eligible, English-language, trials by a systematic search of CINAHL, EMBASE, MEDLINE, PEDro and the Cochrane Central Registry of Controlled Trials. Eligible trials will: (1) enrol patients presenting with acute, non-low back related musculoskeletal pain, and (2) randomise patients to alternative interventions or an intervention and a placebo/sham arm. Fractures will be considered ineligible, unless they are non-surgical and therapy is directed at pain relief. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias.

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the quality of evidence supporting treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analysis to establish the effectiveness of therapeutic interventions on patient-important outcomes; and (2) multiple treatment comparison meta-analysis within a frequentist framework to assess the relative effects of treatments. We will use a priori hypotheses to explain heterogeneity between studies and conduct meta-regression and subgroup analyses consistent with current best practices. We will interpret subgroup results according to published credibility criteria.

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3 **Ethics and dissemination:** No research ethics approval is required for this systematic review.
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5 The results of this systematic review will be disseminated through publication in a peer-reviewed
6 journal, conference presentations, and will inform a clinical practice guideline.
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12 **Key Words:** acute pain; musculoskeletal; intervention; systematic review; network metanalysis
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17 **PROSPERO registration number:** CRD42018094412
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Article Summary

Strengths and limitations

- Our broad study eligibility criteria will increase generalizability of our results.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate our confidence in treatment effects.
- We will optimize interpretability by presenting risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.
- Findings from our review will inform a clinical practice guideline and identify key areas for future research.
- Our results will be limited by possible shortcomings of the primary studies.

Introduction

Acute non-low back related musculoskeletal (MSK) pain, which include strains and sprains, dislocations, and whiplash present for less than 1 month, are associated with considerable morbidity in North America. The Burden of Musculoskeletal Diseases in the United States, 3rd edition, found that sprains and strains are the most frequent injury type for which medical care is sought and the majority of MSK injuries occur among working-age adults.¹ In 2013 there were 2,807,880 emergency department (ED) visits for sports-related injuries in the US,² and over 70% of visits to the ED are because of pain-related complaints.³ Management often yields suboptimal outcomes: a survey of 842 acute pain patients at 20 US and Canadian hospitals found 40% reported their pain did not change or increased after visiting the ED, and 74% of patients were discharged in moderate to severe pain.⁴

Despite the prevalence of acute MSK complaints in primary care, a number of studies have highlighted inadequate pain education of among physicians.⁵⁻⁷ The availability of numerous pharmacologic and non-pharmacologic therapies complicates the management decisions. A recently published series of 24 systematic reviews of treatment for common acute MSK injuries,⁸ suffers from many important limitations, including: (1) selection bias due, in part, to exclusion of studies deemed to be at high risk of bias without empirically exploring if effect estimates differed from studies assigned low risk of bias, (2) interpreting results from individual studies as effective if the mean difference in a given outcome met the minimally important difference (MID) and ineffective if not - an interpretation relies on the unlikely assumption that all patients will experience the same degree of improvement, and fails to consider the distribution around the mean and the proportion of patients that achieve the MID, (3) no appraisal of the overall quality (confidence, certainty) of the evidence, and (4) no

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3 statistical pooling of treatment effects. We propose to conduct a systematic review of
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5 randomized trials to assess the comparative effectiveness of available treatments for acute MSK
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7 pain (excluding low back pain) and assess quality of evidence using GRADE methodology.
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Methods

Protocol registration

The protocol for this systematic review is registered with PROSPERO (CRD42018094412). This review was commissioned by the American Academy of Family Physicians and American College of Physicians and sponsored by the National Safety Council.

Standardized Reporting

We used the PRISMA-P checklist when writing our report.⁹

Information sources

We will identify eligible, English language, RCTs through a systematic search of MEDLINE, EMBASE, CINAHL, PEDro and CENTRAL, from inception of each database through February 2018. Our search has been refined for individual databases by an experienced medical librarian (Appendix). We will scan reference lists of relevant systematic reviews for additional articles.

Eligibility criteria and study selection

We will include therapeutic randomized trials that: 1) enroll adult patients (≥ 18 years) presenting with acute, non-low back related musculoskeletal (MSK) pain (pain with duration less than 4 weeks or defined by authors as “acute”) in an outpatient setting, and 2) randomise them to currently available alternative interventions directed at pain relief (pharmacological or non-pharmacological) or a currently available intervention directed at pain relief and a placebo/sham arm. Eligible MSK conditions include sprains and strains. Surgical fractures, non-surgical fractures unless therapy is directed at pain relief, low back pain, neuropathic pain, acute cancer

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3 pain, acute postoperative pain, acute dental pain, pain associated with labour and delivery,
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5 visceral pain, pain due to infection, and headaches will be excluded. We have excluded acute low
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7 back pain on request by the study funder, as they have previously commissioned evidence
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9 syntheses on this topic.^{10 11}

12 Trained reviewers will work independently in pairs to screen titles and abstracts of
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14 identified citations, using standardized, pilot-tested forms in DistillerSR, an online systematic
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16 review software (Evidence Partners, Ottawa, Canada; <http://systematic-review.net/>). Teams of
17
18 reviewers will screen full texts of any articles judged as potentially eligible. Reviewers will
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20 discuss disagreements to come to consensus, referring to an adjudicator if necessary. We will
21
22 measure agreement between reviewers to assess the reliability of full-text review; specifically,
23
24 we will calculate kappa (κ) values, and interpret them using the following thresholds: <0.20 as
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26 slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as
27
28 substantial agreement and >0.80 as almost perfect agreement.¹²

35 *Data abstraction*

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37 We designed standardized data abstraction forms and a detailed instruction video (accessible at:
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39 <https://www.youtube.com/watch?v=1nwFJ61K3sQ>). We will conduct calibration exercises prior
40
41 to beginning data abstraction to ensure consistency and accuracy of extractions. Teams of
42
43 reviewers will extract data independently and in duplicate. We will extract the following data
44
45 from eligible trials into a standardized spreadsheet: study characteristics (e.g. the first author,
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47 publication year, country of origin, and funding source), participant and trial characteristics (e.g.
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49 sample size, mean age of participants, clinical condition, type and severity of injury, proportion
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51 with known chronic pain/condition prior to acute injury, and the proportion receiving opioids at
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3 the time of enrollment), characteristics of interventions and comparators, patient-important
4 outcomes (pain, function, health-related quality of life, patient satisfaction, return to work,
5 proportion of patients with relief, re-injury and all reported adverse events). We used the longest
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10 follow-up reported.¹³
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14 *Risk of bias assessment*

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16 Among eligible studies, we will independently assess the following risk of bias issues: (1)
17 random sequence generation, (2) allocation concealment, (3) blinding of study participants,
18 personnel, and outcome assessors, and (4) incomplete outcome data ($\geq 20\%$ missing data will be
19 considered at high risk of bias).¹⁴ To assess the risk of bias we will use a modified version of the
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Cochrane risk of bias instrument.¹⁵ Our instrument will use the following responses: ‘definitely
yes’ or ‘probably yes’ (considered as low risk of bias), or ‘definitely no’ or ‘probably no’
(considered as high risk of bias). These response options have published evidence of validity for
assessing blinding.¹⁵ Any discrepancy in assessment of risk of bias will be resolved by
discussion, or third party adjudication if needed. We will contact authors for missing information
regarding risk of bias issues and unpublished data (e.g. effect estimates without accompanying
estimates of precision).

44 *Data synthesis*

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For the purposes of statistical pooling, we will explore treatment effects of interventions across
all MSK complaints eligible for this review. However, we will also explore if treatment effects
differ by clinical condition or injury severity (see Subgroup analyses, meta-regression and
sensitivity analysis, below). Clustering strategies for clinical condition and injury severity will be

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3 informed by the trials eligible for our review, which will be reviewed by our technical expert
4 panel (see Acknowledgement section), blinded to study results.
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10 *Methods for direct comparisons*

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12 We will pool dichotomous outcomes that are reported by >1 RCT and calculate the relative risk
13 and risk difference (RD), using baseline risk estimates from the placebo arm of eligible studies,
14 and the associated 95% confidence intervals (CIs). We will pool all continuous outcomes that are
15 reported by >1 study and calculate the weighted mean differences (WMDs) and associated 95%
16 CIs. We will employ methods described in Cochrane Handbook to estimate the mean and
17 standard deviation (SD) when median, range, and sample size are reported, and to impute the SD
18 if the standard error or SD for the differences are not reported.¹⁶ For continuous outcomes, when
19 studies reported effect estimates using different measurement instruments that tap into a common
20 construct (e.g. pain), we will first transform all outcomes to a common instrument on a domain-
21 by-domain basis.¹⁷ We will use change scores from baseline to end of follow-up rather than end-
22 of-study scores, in order to account for inter-patient variability. If authors do not report change
23 scores, we will calculate them using the baseline and end-of-study score and a correlation
24 coefficient derived from the largest trial at lowest risk of bias in the meta-analysis that does
25 report a change score. We will use DerSimonian–Laird random-effects models¹⁸ for all pairwise
26 comparisons.
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47 Interpreting effect estimates for continuous outcomes is challenging,¹⁹ and we will
48 present the minimally important difference (MID) for all pooled effect estimates. The MID is the
49 smallest amount of improvement in a treatment outcome that a patient would recognize as
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3 important.²⁰ If we find multiple MID estimates are available, we will use the smallest difference
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5 that has been validated.
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8 However, simply presenting the MID risks interpreting all mean effects that fall below
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10 the MID as unimportant, whereas we have found that, typically, mean differences of 1/2 the MID
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12 result in RDs of about 10% - a potential benefit that many patients would likely consider
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14 important.²¹ Thus, concluding that an effect is unimportant requires confidence that the mean
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16 difference is less than 1/2 the MID (and perhaps less). To optimize interpretability, we will
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18 calculate the RD of achieving the MID, as well as the associated 95% CIs, for all statistically
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20 significant WMDs. Specifically, for each individual study, we will assume that the SDs of
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22 outcome measurements are the same in both the treatment and control groups, and that change
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24 scores in both groups are normally distributed. We will use the median or mean, and SD of the
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26 control group, with the established MID for the outcome in question to estimate the probability
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28 of achieving \geq MID in the control group. We will use the pooled mean difference (and 95%CI) to
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30 estimate the mean (and 95%CI) in the treatment group and calculate the probability (and 95%CI)
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32 of achieving \geq MID in the treatment group. Finally, we will use risks in both groups to acquire
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34 the RD for achieving \geq MID.
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42 *Methods for network meta-analysis*

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44 We will perform network meta-analysis (NMA) to synthesize the available evidence from the
45
46 entire network of trials by integrating direct and indirect estimates for each comparison into a
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48 single summary treatment effect. We will use a frequentist random-effects model using the
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50 methodology of multivariable meta-analysis to assess the comparative effectiveness of eligible
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52 interventions.^{22 23}
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3 Although the assumptions for network meta-analysis are similar to conventional meta-
4 analysis, key extra assumptions are transitivity (there are no effect modifiers influencing the
5 indirect comparisons) and coherence (direct and indirect effect estimates being similar).²⁴ We
6 will identify issues of incoherence by comparing direct evidence (i.e. estimates from pairwise
7 comparisons) with indirect evidence (i.e. estimates from network meta-analysis) using the node
8 splitting method.^{25 26} In this approach, incoherence is assessed locally by evaluating the
9 consistency assumption in each closed loop of the network separately as the difference between
10 direct and indirect estimates for a specific comparison in the loop. We will assume a common
11 heterogeneity estimate within each loop. We will also confirm the coherence assumption in the
12 entire network using 'design-by-treatment' model as described by Higgins et al.²⁷ In case we find
13 significant incoherence in the network (highly significant p value from design-by-treatment
14 model), we will perform network meta-analysis using inconsistency model. If using
15 inconsistency model resulted in non-sensical results, we will explore the network for the
16 source(s) of incoherence and further expand (disintegrating interventions based on differences in
17 population or intervention characteristics) or exclude node(s) introducing incoherence in the
18 network (e.g., excluding node(s) with less than 20 events for binary outcomes or comparisons
19 with only one trial with very few participants for continuous outcomes).

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21 We will report our findings with probability statements of intervention effects.
22 Probability rankings allow us to report a chance percentage of which interventions rank higher,²⁸
23 however, simplifying the results of a network down to probabilities can lead to
24 misinterpretations, specifically, when particular comparisons (i.e. nodes) are not well-connected
25 or when the quality of evidence varies between comparisons.^{29 30} Following display of the rank
26 probabilities using rankogram, we will use the surface under the cumulative ranking (SUCRA)

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3 line to aid in interpretation of relative effect of the interventions. An intervention with a SUCRA
4 value of 100 is certain to be the most effective, whereas an intervention with 0 is certain to be the
5 least effective.²⁸ We will use STATA (StataCorp, Release 14.2, College Station, Texas, USA)
6 for all statistical analyses. All comparisons will be 2-tailed using a threshold $p \leq 0.05$.
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14 *Subgroup analyses, meta-regression and sensitivity analysis*

15 We will use the Q statistic and I^2 to determine statistical heterogeneity for direct meta-analysis.²⁵

16 We have developed five hypotheses to explain heterogeneity between trials: (1) different clinical
17 conditions will show different treatment effects; (2) more severe injuries will show smaller
18 treatment effects than less severe injuries; (3) older patients will show smaller treatment effects
19 than younger patients; (4) longer follow-up will show smaller treatment effects than shorter
20 follow-up; and (5) higher dose/intensity of treatment will show larger treatment effects. We will
21 perform subgroup analyses regardless of heterogeneity estimates. Moreover, we will explore the
22 effect of risk of bias (on a component-by-component basis) and reported vs. converted change
23 scores on treatment effects. We will perform a sensitivity analysis that restricts analyses to the
24 treatments for which there are a combined total of at least 500 patients.
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42 *Assessing quality of the evidence*

43 We will use the GRADE (Grading of Recommendations, Assessment, Development, and
44 Evaluation) approach to assess the quality of evidence on an outcome-by-outcome basis. The
45 starting point for quality of evidence for randomized trials is high, but may be rated down based
46 on limitations in risk of bias, imprecision, inconsistency, and indirectness and publication bias.³¹
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3 We will also use the GRADE approach to assess quality of evidence for indirect and
4 network (mixed) effect estimates.^{32, 33} Indirect effect estimates are calculated from available
5 'loops' of evidence, which includes first order loops (based on a single common comparator
6 treatment, the difference between the treatment A and B is based on comparisons of A and C as
7 well as B and C) or higher order loops (more than one intervening treatment connecting the two
8 interventions). We will visually examine the network map and where first order loops are
9 available for indirect comparisons, the quality of evidence will be the lower of the ratings for the
10 two direct estimates contributing to the first order loop. In the absence of a first order loop, a
11 higher order loop will be used to rate the quality of evidence and it will be the lower of the
12 quality ratings for the direct estimates contributing to the loop. Further, we may rate down
13 quality further for intransitivity.³³ The transitivity assumption implies similarity of trials in terms
14 of population, intervention, settings, and trial methodology.³⁴
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Ethics and Dissemination

No research ethics approval is required for this systematic review, as no confidential patient data will be used. The results of this systematic review will be disseminated through publication in a peer-reviewed journal and through conference presentations. Moreover, findings from our review will inform a clinical practice guideline. All amendments to the protocol will be reported in the PROSPERO trial registry.

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Discussion

With the high prevalence of acute non-low back MSK pain, the associated high socioeconomic burden and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent need for a high-quality systematic review to inform evidence-based management of these complaints.

Our proposed review has several strengths in relation to existing reviews. First, we will include all nonpharmacological and pharmacological treatment options for all acute MSK complaints (excluding low back pain). It is plausible that individual acute MSK complaints respond similarly to similar interventions, and thus by pooling across individual injuries, it may be possible to provide a more precise estimate of treatment effect. Second, we will update the search to present date. Third, we will use the GRADE approach to evaluate the quality of evidence supporting treatment effects. Fourth, we will ensure interpretability by presenting RDs and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.

A potential limitation will be the nature of available treatment comparisons to build robust networks for our analyses. The findings of our review will help inform patients with acute non-low back related MSK pain about their therapeutic options, identify key areas for research, and facilitate a clinical practice guideline for the management of acute, non-low back related MSK pain.

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3 **Acknowledgements:** We thanks the members of our Technical Expert Panel for assistance in
4 developing our study protocol: Robert McLean, MD; Devan Kansagara, MD; Dave O'Gurek,
5 MD; Kenny Lin, MD; Christina Mikosz, MD; John Riva, DC, MSc; Moin Khan, MD.
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11 **Author Contributions:** All authors made substantial contributions to conception and design.
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14 JWB and BS drafted the article, and SC, RC, PJH, YO, CM, AL and GHG revised it critically for
15 important intellectual content. All authors provided final approval of the version to be published.
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18 JWB is the guarantor of the review protocol.
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24 **Data sharing:** Statistical code and dataset available from Dr. Sadeghirad (e-mail:
25
26 b.sadeghirad@gmail.com).
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32 Council (NSC) (PI: JW Busse). The NSC partnered with the American Academy of Family
33 Physicians (AAFP) and the American College of Physicians (ACP) who helped to inform the
34 design of our review, but the NSC will have no role in the conduct of the study; collection,
35 management, analysis, and interpretation of the data; preparation, review, or approval of the
36 resulting manuscript; or decision to submit the manuscript for publication. Representatives from
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AAFP and ACP will have the right to review the manuscript and make non-binding comments
and suggestions.

51 **Competing interests:** None declared.
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3 **Patient consent:** Not required.
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8 **Provenance and peer review:** This review was commissioned and externally peer reviewed.
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4 rating the quality of treatment effect estimates from network meta-analysis. *BMJ*
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11 to rate the certainty in estimates from a network meta-analysis. *Journal of clinical*
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Appendix: Literature Search Strategies

Summary of search and strategies ACP Acute MSK Pain

Feb 14, 2018

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp arm injuries/ or athletic injuries/ or exp joint dislocations/ or exp fractures, bone/ or fractures, cartilage/ or exp hand injuries/ or exp hip injuries/ or exp leg injuries/ or exp neck injuries/ or occupational injuries/ or exp shoulder injuries/ or exp soft tissue injuries/ or exp "sprains and strains"/ or exp tendon injuries/ or exp Compartment Syndromes/ or exp Bone Malalignment/ (300813)

2 (exp Musculoskeletal system/ or musculoskeletal diseases/ or osteitis/ or exp cartilage diseases/ or exp fasciitis/ or exp bursitis/ or exp metatarsalgia/ or exp synovitis/ or muscle cramp/ or myalgia/ or exp tendinopathy/) and pain*.ti,ab. (87772)

3 Musculoskeletal Pain/ or Neck Pain/ or Acute Pain/ or exp Arthralgia/ (19422)

4 (Arthralgi* or bursitis or capsulit* or epicondylgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myositis* or osteitis or osteochondritis or osteomyelitis or polymyositis* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (111653)

5 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (14400)

6 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (235481)

7 or/1-6 (587971)

8 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (810530)

9 ((treatment or control) adj3 group*).ab. (511607)

10 (allocat* adj5 group*).ab. (20402)

11 ((clinical or control*) adj3 trial).ti,ab,kw. (226548)

12 or/8-11 (1258485)

13 7 and 12 (46565)

14 exp animals/ not humans.sh. (4424690)

15 13 not 14 (42705)

16 adult.mp. or middle aged.sh. or age:.tw. (8090446)

17 15 and 16 (30798)

18 limit 15 to "all adult (19 plus years)" (28434)

19 17 or 18 (31999)

20 treatment outcome/ (824861)

21 Pain Measurement/ (75370)

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2
3 22 "Recovery of Function"/ (42703)
4 23 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or
5 scale or status or test* or assess* or rating* or index or questionnaire)).mp. (586581)
6 24 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
7 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
8 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (628803)
9 25 Return to Work/ or Return to Sport/ or ((return or resump*) adj3 (work or sport or play or
10 activit*)).mp. (16520)
11 26 pain*.jw,ti. (199639)
12 27 pain*.ab. /freq=2 (243208)
13 28 or/20-27 (2035376)
14 29 19 and 28 (20709)
15 30 exp appendicitis/ or exp Back Pain/ or Labor Pain/ or exp Pain, Postoperative/ or exp
16 Toothache/ or headache/ or exp Headache disorders/ or exp dentistry/ or exp Neoplasms/
17 (3499077)
18 31 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or
19 sciatic* or cancer*)).mp. (118740)
20 32 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or
21 metastas*).mp. (463484)
22 33 or/30-32 (3631063)
23 34 29 not 33 (13769)
24 35 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
25 family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (7012189)
26 36 34 and 35 (9481)
27 37 Osteoarthritis/ (33247)
28 38 exp arthroplasty/ or exp arthroscopy/ or bone transplantation/ (101224)
29 39 su.fs. (1807708)
30 40 or/37-39 (1863671)
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36 Feb 14, 2018

37 Database: Embase <1974 to 2018 February 13>

38 Search Strategy:
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41 1 limb injury/ or exp arm injury/ or exp leg injury/ or exp limb fracture/ or sport injury/ or exp
42 joint injury/ or musculoskeletal injury/ or exp cartilage injury/ or exp "ligament and tendon
43 injury"/ or medial tibial stress syndrome/ or muscle injury/ or overexertion/ or exp sprain/ or
44 fracture/ or avulsion fracture/ or clavicle fracture/ or comminuted fracture/ or fracture
45 dislocation/ or exp fracture healing/ or intraarticular fracture/ or exp joint fracture/ or exp limb
46 fracture/ or exp multiple fracture/ or exp scapula fracture/ or stress fracture/ or neck injury/ or
47 whiplash injury/ or occupational accident/ or soft tissue injury/ or compartment syndrome/
48 (382802)
49

50 Annotation: includes arm injury/ or exp arm fracture/ or elbow dislocation/ or elbow injury/ or
51 exp forearm injury/ or exp hand injury/ or exp shoulder injury/ or exp wrist injury/ or leg injury/
52 or exp ankle injury/ or exp foot injury/ or exp hip injury/ or exp knee injury/ or exp leg fracture/
53 or tibia torsion/ or exp ankle injury/ or exp dislocation/ or exp hip injury/ or intraarticular
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3 fracture/ or exp joint fracture/ or exp knee injury/ or posttraumatic arthropathy/ or exp wrist
4 injury/

5 2 (exp musculoskeletal system/ or exp musculoskeletal disease/) and pain*.ti,ab. (312623)

6 3 musculoskeletal pain/ or neck pain/ or shoulder pain/ or arthralgia/ (86878)

7 4 or/1-3 (692780)

8 Annotation: emtree terms condition MSK pain

9 5 (Arthralgi* or bursitis or capsulit* or epicondylgia* or epicondylit* or fasciopath* or
10 fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myositis* or osteitis or
11 osteochondritis or osteomyelitis or polymyositis* or radiculopath* or radiculit* or synovit* or
12 tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (147804)

13 6 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or
14 teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis
15 or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair*
16 or imping* or sprain* or strain* or tear or torn)).tw. (16617)

17 7 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or
18 finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or
19 femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal*
20 or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or
21 scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair*
22 or fractur* or break* or broken or disorder* or pain*).tw. (305948)

23 8 or/5-7 (444822)

24 Annotation: free text terms condition MSK pain

25 9 4 or 8 (897318)

26 Annotation: MSK pain

27 10 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/
28 or animal cell/ or nonhuman/ (25540585)

29 11 human/ or normal human/ or human cell/ (19287963)

30 12 10 and 11 (19240053)

31 13 10 not 12 (6300532)

32 14 9 not 13 (837728)

33 15 random:.tw. or placebo:.mp. or double-blind:.tw. (1509046)

34 Annotation: HIRU specific RCT filter

35 16 ((treatment or control) adj3 group*).ab. (723604)

36 17 (allocat* adj5 group*).ab. (26448)

37 18 ((clinical or control*) adj3 trial).ti,ab,kw. (327340)

38 19 or/15-18 (2107446)

39 Annotation: modified RCT filter

40 20 14 and 19 (95790)

41 Annotation: MSK pain with mod RCT filter

42 21 treatment outcome/ (762155)

43 22 outcome assessment/ (400641)

44 23 pain measurement/ (4687)

45 24 exp pain assessment/ (134012)

46 25 convalescence/ (42381)

47 26 return to sport/ or return to work/ (4870)

48 27 work resumption/ (3467)

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3 28 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or
4 scale or status or test* or assess* or rating* or index or questionnaire)).mp. (790797)
5 29 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
6 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
7 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (911685)
8 30 ((return or resump*) adj3 (work or sport or play or activit*)).mp. (23514)
9 31 pain*.jw,ti. (269095)
10 32 pain*.ab. /freq=2 (358966)
11 33 or/21-32 (2816037)
12 34 20 and 33 (58373)

13
14
15 Annotation: MSK pain with mod RCT and outcome

16 35 exp appendicitis/ or exp backache/ or labor pain/ or exp postoperative complication/ or exp
17 tooth disease/ or headache/ or exp dentistry/ or exp malignant neoplasm/ or exp metastasis/
18 (4067682)

19 36 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or
20 sciatic* or cancer*)).mp. (189693)

21 37 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or metastas* or
22 appendicitis).mp. (778837)

23 38 35 or 36 or 37 (4238484)

24 39 34 not 38 (30664)

25
26 Annotation: mod RCT set

27 40 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
28 family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (9180696)

29
30 Annotation: Gill 2014 primary care plus sport

31 41 39 and 40 (21784)

32 42 exp osteoarthritis/ (110006)

33 43 bone transplantation/ or exp bone graft/ (46349)

34 44 exp orthopedic surgery/ (406039)

35
36 Annotation: includes exp joint surgery/ or exp arthroplasty/

37 45 su.fs. (1950489)

38 46 or/42-45 (2224706)

39
40 Cochrane Library

41 Search Name: 2017-08-22 ACP acute msk pain search

42 Date Run: 14/02/18 20:52:03.682

43
44 Description:

45
46 ID Search Hits

47 #1 Arthralgi* or bursitis or capsulit* or epicondylgia* or epicondyli* or fasciopath* or
48 fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or
49 osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or
50 tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD 13121

51 #2 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or
52 teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis
53 or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) near/3 (injur* or
54 impair* or imping* or sprain* or strain* or tear or torn)) 2044

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3 #3 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or
4 finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or
5 femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal*
6 or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or
7 scapula* or bone* or joint* or muscle* or shoulder*) near/3 (sprain* or strain* or injur* or
8 impair* or fractur* or break* or broken or disorder* or pain*)) 38249
9
10 #4 #1 or #2 or #3 47667
11 #5 ((disability or function* or recover* or pain* or analog*) near/3 (measur* or evaluat* or
12 scale or status or test* or assess* or rating* or index or questionnaire)) 109526
13 #6 VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
14 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
15 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement 139538
16 #7 ((return or resump*) near/3 (work or sport or play or activit*)) 3128
17 #8 pain*:so 8908
18 #9 pain*:ti 34759
19 #10 #5 or #6 or #7 or #8 or #9 214594
20 #11 #4 and #10 24648
21 #12 (pain* near/3 (chronic or dental or labo?r or back or low back or spine or spinal or
22 lumbar or sciatic* or cancer*)) 20816
23 #13 sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or
24 metastas* 27428
25 #14 #12 or #13 45616
26 #15 #11 not #14 18297
27 #16 clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
28 family or communit* or ambulatory or centre* or center* or office or sport* 937038
29 #17 #15 and #16 in Trials, with Wounds Group, Injuries Group, Pain, Palliative and
30 Supportive Care Group, Musculoskeletal Group, Bone, Joint and Muscle Trauma Group, Back
31 Group or Occupational Safety and Health Group in Review Groups
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CINAHL

S73 S66 NOT S72	5,571
S72 S67 OR S68 OR S69 OR S70 OR S71	224,577
S71 (MM "Surgery, Operative+")	211,375
S70 (MH "Arthroscopy")	4,418
S69 (MH "Arthroplasty")	1,646
S68 (MH "Bone Transplantation")	3,342
S67 (MH "Osteoarthritis+")	13,152
S66 S64 AND S65	8,761
S65 TI (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*) OR AB (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or	

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2		
3	family or communit* or ambulatory or centre* or center* or office or sport*)	
4	1,131,403	
5	S64 S51 NOT S63	15,217
6	S63 S60 OR S61 OR S62	359,216
7	S62 TX sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis	
8	or metastas*	35,825
9	S61 TX (pain* N3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar	
10	or sciatic* or cancer*))	49,583
11	S60 S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59	329,798
12	S59 (MH "Neoplasms+")	240,613
13	S58 (MH "Dentistry+")	47,838
14	S57 (MH "Headache+")	16,196
15	S56 (MH "Toothache")	327
16	S55 (MH "Postoperative Pain")	8,206
17	S54 (MH "Labor Pain")	1,533
18	S53 (MH "Back Pain+")	18,740
19	S52 (MH "Appendicitis")	1,293
20	S51 S17 AND S39 AND S48	20,097
21	S50 S48 AND S49	20,097
22	S49 S17 AND S39	33,880
23	S48 S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	457,089
24	S47 SO pain*	30,433
25	S46 TI pain*	68,365
26	S45 TX ((disability or function* or recover* or pain* or analog*) N3 (measur* or evaluat* or	
27	scale or status or test* or assess* or rating* or index or questionnaire)).	143,200
28	S44 TX VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or	
29	"Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"	
30	or SPDI or "mcgill pain" or BPI or "brief pain" or improvement	174,142
31	S43 TX ((return or resump*) N3 (work or sport or play or activit*))	6,311
32	S42 (MH "Job Re-Entry") OR (MH "Sports Re-Entry") OR (MH "School Re-Entry")	6,819
33	S41 (MH "Pain Measurement")	27,842
34	S40 (MH "Treatment Outcomes")	150,811
35	S39 S37 NOT S38	563,918
36	S38 (MH "Animals+")	37,258
37	S37 S24 OR S29 OR S36	568,264
38	S36 S30 OR S31 OR S32 OR S33 OR S34 OR S35	495,048
39	S35 (MH "Prospective Studies+")	213,854
40	S34 (MH "Evaluation Research+")	41,488
41	S33 (MH "Comparative Studies")	101,882
42	S32 "latin square"	138
43	S31 (MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")	
44	207,529	
45	S30 (MH "Random Sample+")	67,305
46	S29 S25 OR S26 OR S27 OR S28	211,728
47	S28 "random*"	203,059
48	S27 "placebo*"	33,694
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S26 (MH "Placebos")	8,296
S25 (MH "Placebo Effect")	1,210
S24 S18 OR S19 OR S20 OR S21 OR S22 OR S23	195,829
S23 "triple-blind"	136
S22 "single-blind"	8,460
S21 "double-blind"	29,322
S20 clinical W3 trial	124,429
S19 "randomi?ed controlled trial*"	69,029
S18 (MH "Clinical Trials+")	155,173
S17 S5 OR S10 OR S15	132,229
S16 S11 OR S15	132,229
S15 S12 OR S13 OR S14	98,300
S14 TX ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) N3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*))	78,680
S13 TX ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) N3 (injur* or impair* or imping* or sprain* or strain* or tear or torn))	10,622
S12 TX Arthralgi* or bursitis or capsulit* or epicondylalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD	20,095
S11 S5 OR S10	91,140
S10 S8 AND S9	Display
S9 TI pain* OR AB pain*	Display
S8 S6 OR S7	Display
S7 (MH "Musculoskeletal Diseases") OR (MH "Cartilage Diseases+") OR (MH "Fasciitis+") OR (MH "Foot Diseases+") OR (MH "Golf Elbow") OR (MH "Heel Pain") OR (MH "Joint Diseases") OR (MH "Muscular Diseases") OR (MH "Arthralgia+") OR (MH "Bursitis+") OR (MH "Contracture+") OR (MH "Metatarsalgia") OR (MH "Shoulder Instability, Anterior") OR (MH "Shoulder Instability, Multidirectional") OR (MH "Shoulder Instability, Posterior") OR (MH "Synovitis")	Display
S6 (MH "Musculoskeletal System") OR (MH "Cartilage+") OR (MH "Fascia+") OR (MH "Ligaments+") OR (MH "Muscles+") OR (MH "Bone and Bones") OR (MH "Arm Bones+") OR (MH "Foot Bones+") OR (MH "Leg Bones+") OR (MH "Pelvic Bones+") OR (MH "Joints+")	Display
S5 S1 OR S2 OR S3 OR S4	Display
S4 (MH "Neck Pain")	Display
S3 (MH "Arthralgia+")	Display
S2 (MH "Compartment Syndromes") OR (MH "Anterior Compartment Syndrome") OR (MH "Ischemic Contracture")	Display

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3 S1 (MH "Arm Injuries+") OR (MH "Athletic Injuries+") OR (MH "Dislocations+") OR (MH
4 "Fractures+") OR (MH "Hand Injuries+") OR (MH "Leg Injuries+") OR (MH "Ligament
5 Injuries+") OR (MH "Neck Injuries+") OR (MH "Occupational-Related Injuries") OR (MH
6 "Soft Tissue Injuries+") OR (MH "Sprains and Strains+") OR (MH "Tendon Injuries+")
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8 Display
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11 PEDro, yields 645
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13 March 13, 2018
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16 Abstract & Title: acute
17 AND
18 Problem: pain
19 AND
20 Method: Clinical trial
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4 & 8
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#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	16

		protocol amendments	
1			
2	Sources	#5a Indicate sources of financial or other support for the review	18
3			
4	Sponsor	#5b Provide name for the review funder and / or sponsor	18
5			
6			
7	Role of sponsor or	#5c Describe roles of funder(s), sponsor(s), and / or institution(s),	18
8	funder	if any, in developing the protocol	
9			
10			
11	Rationale	#6 Describe the rationale for the review in the context of what is	6
12		already known	
13			
14			
15	Objectives	#7 Provide an explicit statement of the question(s) the review will	7
16		address with reference to participants, interventions,	
17		comparators, and outcomes (PICO)	
18			
19			
20	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study design,	8 & 9
21		setting, time frame) and report characteristics (such as years	
22		considered, language, publication status) to be used as	
23		criteria for eligibility for the review	
24			
25			
26			
27	Information	#9 Describe all intended information sources (such as electronic	8
28	sources	databases, contact with study authors, trial registers or other	
29		grey literature sources) with planned dates of coverage	
30			
31			
32	Search strategy	#10 Present draft of search strategy to be used for at least one	25-32
33		electronic database, including planned limits, such that it	
34		could be repeated	
35			
36			
37	Study records -	#11a Describe the mechanism(s) that will be used to manage	9
38	data management	records and data throughout the review	
39			
40			
41	Study records -	#11b State the process that will be used for selecting studies (such	9
42	selection process	as two independent reviewers) through each phase of the	
43		review (that is, screening, eligibility and inclusion in meta-	
44		analysis)	
45			
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47			
48	Study records -	#11c Describe planned method of extracting data from reports	9 & 10
49	data collection	(such as piloting forms, done independently, in duplicate), any	
50	process	processes for obtaining and confirming data from investigators	
51			
52			
53	Data items	#12 List and define all variables for which data will be sought	9 & 10
54		(such as PICO items, funding sources), any pre-planned data	
55		assumptions and simplifications	
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1	Outcomes and	#13	List and define all outcomes for which data will be sought,	9 & 10
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
4				
5				
6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	10
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
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12				
13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	10 & 11
14			synthesised	
15				
16				
17		#15b	If data are appropriate for quantitative synthesis, describe	10-14
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
21				
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23				
24		#15c	Describe any proposed additional analyses (such as	14
25			sensitivity or subgroup analyses, meta-regression)	
26				
27				
28		#15d	If quantitative synthesis is not appropriate, describe the type	N/A
29			of summary planned	
30				
31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	14
32			publication bias across studies, selective reporting within	
33			studies)	
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37	Confidence in	#17	Describe how the strength of the body of evidence will be	14 & 15
38	cumulative		assessed (such as GRADE)	
39	evidence			
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BMJ Open

Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024441.R1
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Date Submitted by the Author:	30-Oct-2018
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Evidence based practice
Keywords:	acute pain, musculoskeletal, intervention, systematic review, network metanalysis

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Manuscripts

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3 **Management of acute musculoskeletal pain (excluding low back pain): a protocol for a**
4 **systematic review and network meta-analysis of randomised trials**
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3 **Word count: 3,030**
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For peer review only

Abstract

Introduction: Acute, non-low back related musculoskeletal pain is common and associated with significant socioeconomic costs. No review has evaluated all interventional studies for acute musculoskeletal pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomised controlled trials evaluating therapies for acute musculoskeletal pain (excluding low back pain). We will identify eligible, English-language, trials by a systematic search of CINAHL, EMBASE, MEDLINE, PEDro and the Cochrane Central Registry of Controlled Trials from inception to February 2018. Eligible trials will: (1) enrol patients presenting with acute, non-low back related musculoskeletal pain (duration of pain ≤ 4 weeks), and (2) randomise patients to alternative interventions or an intervention and a placebo/sham arm. Fractures will be considered ineligible, unless they are non-surgical and therapy is directed at pain relief. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias. Disagreements will be resolved through discussion to achieve consensus.

We will use the GRADE system to evaluate the quality of evidence supporting treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analysis to establish the effectiveness of therapeutic interventions on patient-important outcomes; and (2) multiple treatment comparison meta-analysis to assess the relative effects of treatments. We will use a priori hypotheses to explain heterogeneity between studies. We will use STATA 14.2 for all analyses.

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3 **Ethics and dissemination:** No research ethics approval is required for this systematic review.
4

5 The results of this systematic review will be disseminated through publication in a peer-reviewed
6 journal, conference presentations, and will inform a clinical practice guideline.
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12 **Key Words:** acute pain; musculoskeletal; intervention; systematic review; network meta-
13 analysis
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19 **PROSPERO registration number:** CRD42018094412
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Article Summary

Strengths and limitations

- Our broad study eligibility criteria will increase generalizability of our results.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate our confidence in treatment effects.
- We will optimize interpretability by presenting risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.
- Findings from our review will inform a clinical practice guideline and identify key areas for future research.
- Our results will be limited by possible shortcomings of the primary studies.

Introduction

Acute non-low back related musculoskeletal (MSK) pain, which include strains and sprains, dislocations, and whiplash present for less than 1 month¹, are associated with considerable morbidity in North America. The Burden of Musculoskeletal Diseases in the United States, 3rd edition, found that sprains and strains are the most frequent injury type for which medical care is sought and the majority of MSK injuries occur among working-age adults.² In 2013 there were 2,807,880 emergency department (ED) visits for sports-related injuries in the US,³ and over 70% of visits to the ED are because of pain-related complaints.⁴ Management often yields suboptimal outcomes: a survey of 842 acute pain patients at 20 US and Canadian hospitals found 40% reported their pain did not change or increased after visiting the ED, and 74% of patients were discharged in moderate to severe pain.⁵

Despite the prevalence of acute MSK complaints in primary care, a number of studies have highlighted inadequate pain education of among physicians.⁶⁻⁸ The availability of numerous pharmacologic and non-pharmacologic therapies further complicates management decisions. Currently available treatments include opioids, nonsteroidal anti-inflammatory drugs, muscle relaxants, acetaminophen, exercise, supervised rehabilitation, joint manipulation and mobilization, massage, acupuncture and acupressure, ultrasound, low-level laser therapy, and transcutaneous electrical nerve stimulation.

A recently published series of 24 systematic reviews of treatment for common acute MSK injuries,⁹ suffers from many important limitations, including: (1) selection bias due, in part, to exclusion of studies deemed to be at high risk of bias without empirically exploring if effect estimates differed from studies assigned low risk of bias, (2) interpreting results from individual studies as effective if the mean difference in a given outcome met the minimally

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3 important difference (MID) and ineffective if not - an interpretation that relies on the unlikely
4 assumption that all patients will experience the same degree of improvement, and fails to
5 consider the distribution around the mean and the proportion of patients that achieve the MID,
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8 (3) no appraisal of the overall quality (confidence, certainty) of the evidence, and (4) no
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10 statistical pooling of treatment effects. We propose to conduct a systematic review of
11
12 randomized trials to assess the comparative effectiveness of available non-surgical treatments for
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14 acute MSK pain (excluding low back pain) and assess quality of evidence using the Grading of
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16 Recommendations Assessment, Development and Evaluation (GRADE) methodology.
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Methods

Protocol registration

The protocol for this systematic review is registered with PROSPERO (CRD42018094412). This review was commissioned by the American Academy of Family Physicians and American College of Physicians and sponsored by the National Safety Council.

Standardized Reporting

We used the PRISMA-P checklist when writing our report.¹⁰

Information sources

We will identify eligible, English language, randomized clinical trials (RCTs) through a systematic search of MEDLINE, EMBASE, CINAHL, PEDro and CENTRAL, from inception of each database through February 2018. Our search has been refined for individual databases by an experienced medical librarian (Appendix). We will scan reference lists of included studies and relevant systematic reviews for additional eligible articles.

Eligibility criteria and study selection

We will include therapeutic trials that: 1) enroll adult patients (≥ 18 years) presenting with acute, non-low back related MSK pain (pain with duration < 4 weeks or defined by authors as “acute”) in an outpatient setting, and 2) randomise them to currently available, non-surgical, alternative interventions directed at pain relief (pharmacological or non-pharmacological) or a currently available, non-surgical, intervention directed at pain relief and a placebo/sham arm. Eligible MSK conditions include sprains and strains. Surgical fractures, non-surgical fractures unless

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3 therapy is directed at pain relief, low back pain, neuropathic pain, acute cancer pain, acute
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5 postoperative pain, acute dental pain, pain associated with labour and delivery, visceral pain,
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7 pain due to infection, and headaches will be excluded. We will exclude interventions targeted at
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9 treatment of acute low back pain on request by the study funder, as they have previously
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11 commissioned evidence syntheses on this topic.^{11 12}
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15 Ten teams of trained reviewers will work independently in pairs to screen titles and
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17 abstracts of identified citations, using standardized, pilot-tested forms in DistillerSR, an online
18
19 systematic review software (Evidence Partners, Ottawa, Canada; <http://systematic-review.net/>).
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21 The same teams of reviewers will screen full texts of any articles judged as potentially eligible.
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23 Reviewers will discuss disagreements to come to consensus, referring to an adjudicator if
24
25 necessary. We will measure agreement between reviewers by calculating kappa (κ) values to
26
27 assess the reliability of full-text review, and interpret them using the following thresholds: <0.20
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29 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as
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31 substantial agreement and >0.80 as almost perfect agreement.¹³
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38 *Data abstraction*

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40 We designed standardized data abstraction forms and a detailed instruction video (accessible at:
41
42 <https://www.youtube.com/watch?v=1nwFJ61K3sQ>). We will conduct calibration exercises prior
43
44 to beginning data abstraction to ensure consistency and accuracy of extractions. Seven teams of
45
46 reviewers will extract data independently and in duplicate. We will extract the following data
47
48 from eligible trials into a standardized spreadsheet: study characteristics (e.g. the first author,
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50 publication year, country of origin, and funding source), participant and trial characteristics (e.g.
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52 sample size, mean age of participants, clinical condition, type and severity of injury, proportion
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3 with known chronic pain/condition prior to acute injury, and the proportion receiving opioids at
4 the time of enrollment), characteristics of interventions and comparators, patient-important
5 outcomes (pain, function, health-related quality of life, patient satisfaction, return to work,
6 proportion of patients with relief, re-injury and all reported adverse events). We will extract pain
7 at any time-point, whereas for other outcomes, we will use the longest follow-up reported.¹⁴
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16 *Risk of bias assessment*

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18 Among eligible studies, we will independently assess the following risk of bias issues: (1) random
19 sequence generation, (2) allocation concealment, (3) blinding of study participants, personnel, and
20 outcome assessors, (4) incomplete outcome data ($\geq 20\%$ missing data will be considered at high
21 risk of bias), and (5) other sources of bias.¹⁵ To assess the risk of bias we will use a modified
22 version of the Cochrane risk of bias instrument.¹⁶ Our instrument will use the following responses:
23 ‘definitely yes’ or ‘probably yes’ (considered as low risk of bias), or ‘definitely no’ or ‘probably
24 no’ (considered as high risk of bias). These response options have published evidence of validity
25 for assessing blinding.¹⁶ Any discrepancy in assessment of risk of bias will be resolved by
26 discussion, or third party adjudication if needed. We will contact authors for missing information
27 regarding risk of bias issues and unpublished data (e.g. effect estimates without accompanying
28 estimates of precision).
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47 *Data synthesis*

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49 MSK complaints are increasingly being considered together as risk factors¹⁷, prognosis¹⁸ and,
50 because treatments are often similar, in guideline recommendations.^{19 20} For the purposes of
51 statistical pooling, we will explore treatment effects of interventions across all MSK complaints
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3 eligible for this review; however, we will also explore if treatment effects differ by clinical
4 condition or injury severity. Clustering strategies for clinical condition and injury severity will be
5 informed by the trials eligible for our review, which will be reviewed by a technical expert panel,
6 blinded to study results. Treatment effects will be pooled using the longest follow-up time
7 reported, except for pain, which will be pooled at the most commonly reported short, medium and
8 long-term follow-up times reported. For our review, these categories will be 30 to 120 minutes
9 post-treatment (short), 1 to 7 days post-treatment (medium), and 3 to 12 weeks post-treatment
10 (long). As such, a single trial could contribute to up to 3 time-points for our pooled results for pain
11 relief. Alternately, trials that reported pain relief at time points outside of these timeframes would
12 not contribute data for our analyses of pain relief.
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28 *Methods for direct comparisons*

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30 We will pool dichotomous outcomes that are reported by >1 RCT and calculate the relative risk
31 and risk difference (RD), using baseline risk estimates from the placebo arm of eligible studies,
32 and the associated 95% confidence intervals (CIs). We will pool all continuous outcomes that are
33 reported by >1 study and calculate the weighted mean differences (WMDs) and associated 95%
34 CIs. We will employ methods described in Cochrane Handbook to estimate the mean and standard
35 deviation (SD) when median, range, and sample size are reported, and to impute the SD if the
36 standard error or SD for the differences are not reported.²¹ For continuous outcomes, when studies
37 report effect estimates using different measurement instruments that tap into a common construct
38 (e.g. pain), we will first transform all outcomes to a common instrument on a domain-by-domain
39 basis.²² We will use change scores from baseline to end of follow-up rather than end-of-study
40 scores, in order to account for inter-patient variability. If authors do not report change scores, we
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3 will calculate them using the baseline and end-of-study score and a correlation coefficient derived
4 from the largest trial at lowest risk of bias in the meta-analysis that does report a change score. We
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6 will use DerSimonian–Laird random-effects models²³ for all pairwise comparisons.
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10 Interpreting effect estimates for continuous outcomes is challenging,²⁴ and we will present
11 the minimally important difference (MID) for all pooled effect estimates. The MID is the smallest
12 amount of improvement in a treatment outcome that a patient would recognize as important.²⁵ If
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14 we find multiple MID estimates are available, we will use the smallest difference that has been
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16 validated.
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21 However, simply presenting the MID risks interpreting all mean effects that fall below the
22 MID as unimportant, whereas we have found that, typically, mean differences of 1/2 the MID
23 result in RDs of about 10% - a potential benefit that many patients may consider important.²⁶ Thus,
24
25 concluding that an effect is unimportant requires confidence that the mean difference is less than
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27 1/2 the MID (and perhaps less). To optimize interpretability, we will calculate the RD of achieving
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29 the MID, as well as the associated 95% CIs, for all statistically significant WMDs. Specifically,
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31 for each individual study, we will assume that the SDs of outcome measurements are the same in
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33 both the treatment and control groups, and that change scores in both groups are normally
34
35 distributed. We will use the median or mean, and SD of the control group, with the established
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37 MID for the outcome in question to estimate the probability of achieving \geq MID in the control
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39 group. We will use the pooled mean difference (and 95% CI) to estimate the mean (and 95% CI)
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41 in the treatment group and calculate the probability (and 95% CI) of achieving \geq MID in the
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43 treatment group. Finally, we will use risks in both groups to acquire the RD for achieving \geq MID.
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54 *Methods for network meta-analysis*
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3 We will perform network meta-analysis to synthesize the available evidence from the entire
4 network of trials by integrating direct and indirect estimates for each comparison into a single
5 summary treatment effect. We will use a frequentist random-effects model using the methodology
6 of multivariable meta-analysis to assess the comparative effectiveness of eligible interventions.²⁷
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15 Although the assumptions for network meta-analysis are similar to conventional meta-
16 analysis, key extra assumptions are transitivity (there are no effect modifiers influencing the
17 indirect comparisons) and coherence (direct and indirect effect estimates being similar).²⁹ We will
18 identify issues of incoherence by comparing direct evidence (i.e. estimates from pairwise
19 comparisons) with indirect evidence (i.e. estimates from network meta-analysis) using the node
20 splitting method.^{30 31} In this approach, incoherence is assessed locally by evaluating the
21 consistency assumption in each closed loop of the network separately as the difference between
22 direct and indirect estimates for a specific comparison in the loop. We will assume a common
23 heterogeneity estimate within each loop. We will also confirm the coherence assumption in the
24 entire network using a ‘design-by-treatment’ model.³² In case we find significant incoherence in
25 the network (highly significant p value from design-by-treatment model), we will perform network
26 meta-analysis using an inconsistency model. If using an inconsistency model results in non-
27 sensical results, we will explore the network for the source(s) of incoherence and further expand
28 (disintegrating interventions based on differences in population or intervention characteristics) or
29 exclude the node(s) introducing incoherence into the network (e.g., excluding node(s) with less
30 than 20 events for binary outcomes or comparisons with only one trial with very few participants
31 for continuous outcomes).

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3 We will report our findings with probability statements of intervention effects. Probability
4 rankings allow us to report a chance percentage of which interventions rank higher,³³ however,
5 simplifying the results of a network down to probabilities can lead to misinterpretations,
6 specifically, when particular comparisons (i.e. nodes) are not well-connected or when the quality
7 of evidence varies between comparisons.^{34 35} Following display of the rank probabilities using
8 rankogram, we will use the surface under the cumulative ranking (SUCRA) line to aid in
9 interpretation of relative effect of the interventions. An intervention with a SUCRA value of 100
10 is certain to be the most effective, whereas an intervention with 0 is certain to be the least
11 effective.³³ We will use STATA (StataCorp, Release 14.2, College Station, Texas, USA) for all
12 statistical analyses. All comparisons will be 2-tailed using a threshold $p \leq 0.05$.
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28 *Subgroup analyses, meta-regression and sensitivity analysis*

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30 We will use Cochran's Q statistic and I^2 to determine statistical heterogeneity for direct meta-
31 analysis.³⁰ We have developed five hypotheses to explain heterogeneity between trials: (1)
32 different clinical conditions will show different treatment effects; (2) more severe injuries will
33 show smaller treatment effects than less severe injuries (e.g. higher grades of strains and sprains
34 vs. lower grades); (3) older patients will show smaller treatment effects than younger patients; (4)
35 longer follow-up will show smaller treatment effects than shorter follow-up; and (5) higher
36 dose/intensity of treatment will show larger treatment effects. We will perform subgroup analyses
37 regardless of heterogeneity estimates. Moreover, we will explore the effect of risk of bias (on a
38 component-by-component basis) and reported vs. converted change scores on treatment effects.
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54 *Assessing quality of the evidence*

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3 We will use the GRADE approach to assess the quality of evidence on an outcome-by-outcome
4 basis. The starting point for quality of evidence for RCTs is high, but may be rated down based on
5 limitations in risk of bias, imprecision, inconsistency, and indirectness and publication bias.³⁶
6
7 When there are at least 10 studies for meta-analysis^{37 38}, we will assess publication bias by visual
8 assessment of asymmetry of the funnel plot and calculated Begg's test.
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14 We will also use the GRADE approach to assess quality of evidence for indirect and
15 network (mixed) effect estimates.^{39 40} Indirect effect estimates are calculated from available
16 'loops' of evidence, which includes first order loops (based on a single common comparator
17 treatment, the difference between the treatment A and B is based on comparisons of A and C as
18 well as B and C) or higher order loops (more than one intervening treatment connecting the two
19 interventions). We will visually examine the network map and where first order loops are
20 available for indirect comparisons, the quality of evidence will be the lower of the ratings for the
21 two direct estimates contributing to the first order loop. In the absence of a first order loop, a
22 higher order loop will be used to rate the quality of evidence. We may rate down quality of
23 evidence further for intransitivity.⁴⁰ The transitivity assumption implies similarity of trials in
24 terms of population, intervention, settings, and trial methodology.⁴¹
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40 It is very rare for a network meta-analysis to establish a single treatment option as clearly
41 superior to all others. We will categorize interventions according to three categories: (1) those
42 that are clearly superior, (2) those with intermediate effectiveness, and (3) those that are inferior.
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44 Treatments no better than placebo will be in the lowest tier, those better than placebo in tier 1
45 (likely intermediate); those superior to at least 1 tier 1 treatment will be judged superior.
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47 Treatments will be further categorized according to quality of evidence supporting those
48 estimates (high and moderate vs. low or very low). Interventions with moderate or high quality
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3 evidence will be ranked as either ‘among the most effective’, ‘inferior to the most effective /
4 superior to the least effective’, or ‘among the least effective’. Interventions supported by low or
5 very low quality evidence will be ranked into the same 3 categories but prefaced with ‘may be’
6 to acknowledge the reduced confidence in supporting evidence (e.g. ‘may be among the most
7 effective’) and will be presented separately from those supported by moderate or high quality
8 evidence.
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19 **Ethics and Dissemination**

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21 No research ethics approval is required for this systematic review, as no confidential patient data
22 will be used. The results of this systematic review will be disseminated through publication in a
23 peer-reviewed journal and through conference presentations. Moreover, findings from our review
24 will inform a clinical practice guideline. All amendments to the protocol will be reported in the
25 PROSPERO trial registry.
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35 **Patient and Public Involvement**

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37 No patients were involved in setting the research question, in developing plans for design,
38 interpretation, reporting or implementation of the study. We plan to disseminate the results of
39 this study to organisations supporting patients with acute MSK pain.
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Discussion

With the high prevalence of acute non-low back MSK pain, the associated socioeconomic burden and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent need for a high-quality systematic review to inform evidence-based management of these complaints.

Our proposed review has several strengths in relation to existing reviews. First, we will explore all currently available non-pharmacological and pharmacological treatment options for all acute MSK complaints (excluding low back pain) reported among eligible trials. It is plausible that individual acute MSK complaints respond similarly to similar interventions, and thus by pooling across individual injuries, it may be possible to provide a more precise estimate of treatment effect. Second, we will update the search to present date. Third, we will use the GRADE approach to evaluate the quality of evidence supporting treatment effects. Fourth, we will ensure interpretability by presenting RDs and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.

A potential limitation will be the nature of available treatment comparisons to build robust networks for our analyses. The findings of our review will help inform patients with acute non-low back related MSK pain about their therapeutic options, identify key areas for research, and facilitate a clinical practice guideline for the management of acute, non-low back related MSK pain.

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2
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13
14 JWB and BS drafted the article, and SC, RC, PJH, YO, CM, AL and GHG revised it critically for
15 important intellectual content. All authors provided final approval of the version to be published.
16
17 JWB is the guarantor of the review protocol.
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35 management, analysis, and interpretation of the data; preparation, review, or approval of the
36 resulting manuscript; or decision to submit the manuscript for publication. Representatives from
37 AAFP and ACP will have the right to review the manuscript and make non-binding comments
38 and suggestions.
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3 **Patient consent:** Not required.
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Appendix: Literature Search Strategies

Summary of search and strategies ACP Acute MSK Pain

Feb 14, 2018

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp arm injuries/ or athletic injuries/ or exp joint dislocations/ or exp fractures, bone/ or fractures, cartilage/ or exp hand injuries/ or exp hip injuries/ or exp leg injuries/ or exp neck injuries/ or occupational injuries/ or exp shoulder injuries/ or exp soft tissue injuries/ or exp "sprains and strains"/ or exp tendon injuries/ or exp Compartment Syndromes/ or exp Bone Malalignment/ (300813)

2 (exp Musculoskeletal system/ or musculoskeletal diseases/ or osteitis/ or exp cartilage diseases/ or exp fasciitis/ or exp bursitis/ or exp metatarsalgia/ or exp synovitis/ or muscle cramp/ or myalgia/ or exp tendinopathy/) and pain*.ti,ab. (87772)

3 Musculoskeletal Pain/ or Neck Pain/ or Acute Pain/ or exp Arthralgia/ (19422)

4 (Arthralgi* or bursitis or capsulit* or epicondylalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyositis* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (111653)

5 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (14400)

6 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (235481)

7 or/1-6 (587971)

8 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (810530)

9 ((treatment or control) adj3 group*).ab. (511607)

10 (allocat* adj5 group*).ab. (20402)

11 ((clinical or control*) adj3 trial).ti,ab,kw. (226548)

12 or/8-11 (1258485)

13 7 and 12 (46565)

14 exp animals/ not humans.sh. (4424690)

15 13 not 14 (42705)

16 adult.mp. or middle aged.sh. or age:.tw. (8090446)

17 15 and 16 (30798)

18 limit 15 to "all adult (19 plus years)" (28434)

19 17 or 18 (31999)

20 treatment outcome/ (824861)

21 Pain Measurement/ (75370)

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3 22 "Recovery of Function"/ (42703)
4 23 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or
5 scale or status or test* or assess* or rating* or index or questionnaire)).mp. (586581)
6 24 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
7 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
8 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (628803)
9 25 Return to Work/ or Return to Sport/ or ((return or resump*) adj3 (work or sport or play or
10 activit*)).mp. (16520)
11 26 pain*.jw,ti. (199639)
12 27 pain*.ab. /freq=2 (243208)
13 28 or/20-27 (2035376)
14 29 19 and 28 (20709)
15 30 exp appendicitis/ or exp Back Pain/ or Labor Pain/ or exp Pain, Postoperative/ or exp
16 Toothache/ or headache/ or exp Headache disorders/ or exp dentistry/ or exp Neoplasms/
17 (3499077)
18 31 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or
19 sciatic* or cancer*)).mp. (118740)
20 32 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or
21 metastas*).mp. (463484)
22 33 or/30-32 (3631063)
23 34 29 not 33 (13769)
24 35 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
25 family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (7012189)
26 36 34 and 35 (9481)
27 37 Osteoarthritis/ (33247)
28 38 exp arthroplasty/ or exp arthroscopy/ or bone transplantation/ (101224)
29 39 su.fs. (1807708)
30 40 or/37-39 (1863671)
31
32
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36 Feb 14, 2018

37 Database: Embase <1974 to 2018 February 13>

38 Search Strategy:

39 -----
40
41 1 limb injury/ or exp arm injury/ or exp leg injury/ or exp limb fracture/ or sport injury/ or exp
42 joint injury/ or musculoskeletal injury/ or exp cartilage injury/ or exp "ligament and tendon
43 injury"/ or medial tibial stress syndrome/ or muscle injury/ or overexertion/ or exp sprain/ or
44 fracture/ or avulsion fracture/ or clavicle fracture/ or comminuted fracture/ or fracture
45 dislocation/ or exp fracture healing/ or intraarticular fracture/ or exp joint fracture/ or exp limb
46 fracture/ or exp multiple fracture/ or exp scapula fracture/ or stress fracture/ or neck injury/ or
47 whiplash injury/ or occupational accident/ or soft tissue injury/ or compartment syndrome/
48 (382802)
49

50 Annotation: includes arm injury/ or exp arm fracture/ or elbow dislocation/ or elbow injury/ or
51 exp forearm injury/ or exp hand injury/ or exp shoulder injury/ or exp wrist injury/ or leg injury/
52 or exp ankle injury/ or exp foot injury/ or exp hip injury/ or exp knee injury/ or exp leg fracture/
53 or tibia torsion/ or exp ankle injury/ or exp dislocation/ or exp hip injury/ or intraarticular
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1
2
3 fracture/ or exp joint fracture/ or exp knee injury/ or posttraumatic arthropathy/ or exp wrist
4 injury/

5 2 (exp musculoskeletal system/ or exp musculoskeletal disease/) and pain*.ti,ab. (312623)

6 3 musculoskeletal pain/ or neck pain/ or shoulder pain/ or arthralgia/ (86878)

7 4 or/1-3 (692780)

8 Annotation: emtree terms condition MSK pain

9 5 (Arthralgi* or bursitis or capsulit* or epicondylgia* or epicondylit* or fasciopath* or
10 fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myositis* or osteitis or
11 osteochondritis or osteomyelitis or polymyositis* or radiculopath* or radiculit* or synovit* or
12 tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (147804)

13 6 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or
14 teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis
15 or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair*
16 or imping* or sprain* or strain* or tear or torn)).tw. (16617)

17 7 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or
18 finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or
19 femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal*
20 or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or
21 scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair*
22 or fractur* or break* or broken or disorder* or pain*).tw. (305948)

23 8 or/5-7 (444822)

24 Annotation: free text terms condition MSK pain

25 9 4 or 8 (897318)

26 Annotation: MSK pain

27 10 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/
28 or animal cell/ or nonhuman/ (25540585)

29 11 human/ or normal human/ or human cell/ (19287963)

30 12 10 and 11 (19240053)

31 13 10 not 12 (6300532)

32 14 9 not 13 (837728)

33 15 random:.tw. or placebo:.mp. or double-blind:.tw. (1509046)

34 Annotation: HIRU specific RCT filter

35 16 ((treatment or control) adj3 group*).ab. (723604)

36 17 (allocat* adj5 group*).ab. (26448)

37 18 ((clinical or control*) adj3 trial).ti,ab,kw. (327340)

38 19 or/15-18 (2107446)

39 Annotation: modified RCT filter

40 20 14 and 19 (95790)

41 Annotation: MSK pain with mod RCT filter

42 21 treatment outcome/ (762155)

43 22 outcome assessment/ (400641)

44 23 pain measurement/ (4687)

45 24 exp pain assessment/ (134012)

46 25 convalescence/ (42381)

47 26 return to sport/ or return to work/ (4870)

48 27 work resumption/ (3467)

1
2
3 28 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or
4 scale or status or test* or assess* or rating* or index or questionnaire)).mp. (790797)
5 29 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
6 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
7 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (911685)
8 30 ((return or resump*) adj3 (work or sport or play or activit*)).mp. (23514)
9 31 pain*.jw,ti. (269095)
10 32 pain*.ab. /freq=2 (358966)
11 33 or/21-32 (2816037)
12 34 20 and 33 (58373)

13
14
15 Annotation: MSK pain with mod RCT and outcome

16 35 exp appendicitis/ or exp backache/ or labor pain/ or exp postoperative complication/ or exp
17 tooth disease/ or headache/ or exp dentistry/ or exp malignant neoplasm/ or exp metastasis/
18 (4067682)

19 36 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or
20 sciatic* or cancer*)).mp. (189693)

21 37 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or metastas* or
22 appendicitis).mp. (778837)

23 38 35 or 36 or 37 (4238484)

24 39 34 not 38 (30664)

25
26 Annotation: mod RCT set

27 40 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
28 family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (9180696)

29
30 Annotation: Gill 2014 primary care plus sport

31 41 39 and 40 (21784)

32 42 exp osteoarthritis/ (110006)

33 43 bone transplantation/ or exp bone graft/ (46349)

34 44 exp orthopedic surgery/ (406039)

35
36 Annotation: includes exp joint surgery/ or exp arthroplasty/

37 45 su.fs. (1950489)

38 46 or/42-45 (2224706)

39
40 Cochrane Library

41 Search Name: 2017-08-22 ACP acute msk pain search

42 Date Run: 14/02/18 20:52:03.682

43 Description:

44
45
46 ID Search Hits

47 #1 Arthralgi* or bursitis or capsulit* or epicondylgia* or epicondyli* or fasciopath* or
48 fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or
49 osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or
50 tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD 13121

51 #2 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or
52 teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis
53 or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) near/3 (injur* or
54 impair* or imping* or sprain* or strain* or tear or torn)) 2044

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2
3 #3 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or
4 finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or
5 femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal*
6 or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or
7 scapula* or bone* or joint* or muscle* or shoulder*) near/3 (sprain* or strain* or injur* or
8 impair* or fractur* or break* or broken or disorder* or pain*)) 38249
9
10 #4 #1 or #2 or #3 47667
11 #5 ((disability or function* or recover* or pain* or analog*) near/3 (measur* or evaluat* or
12 scale or status or test* or assess* or rating* or index or questionnaire)) 109526
13 #6 VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
14 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
15 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement 139538
16 #7 ((return or resump*) near/3 (work or sport or play or activit*)) 3128
17 #8 pain*:so 8908
18 #9 pain*:ti 34759
19 #10 #5 or #6 or #7 or #8 or #9 214594
20 #11 #4 and #10 24648
21 #12 (pain* near/3 (chronic or dental or labo?r or back or low back or spine or spinal or
22 lumbar or sciatic* or cancer*)) 20816
23 #13 sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or
24 metastas* 27428
25 #14 #12 or #13 45616
26 #15 #11 not #14 18297
27 #16 clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
28 family or communit* or ambulatory or centre* or center* or office or sport* 937038
29 #17 #15 and #16 in Trials, with Wounds Group, Injuries Group, Pain, Palliative and
30 Supportive Care Group, Musculoskeletal Group, Bone, Joint and Muscle Trauma Group, Back
31 Group or Occupational Safety and Health Group in Review Groups
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39 CINAHL

42 S73 S66 NOT S72	5,571
43 S72 S67 OR S68 OR S69 OR S70 OR S71	224,577
44 S71 (MM "Surgery, Operative+")	211,375
45 S70 (MH "Arthroscopy")	4,418
46 S69 (MH "Arthroplasty")	1,646
47 S68 (MH "Bone Transplantation")	3,342
48 S67 (MH "Osteoarthritis+")	13,152
49 S66 S64 AND S65	8,761
50 S65 TI (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or 51 consult* or family or communit* or ambulatory or centre* or center* or office or sport*) OR 52 AB (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or 53 54 55	

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2		
3	family or communit* or ambulatory or centre* or center* or office or sport*)	
4	1,131,403	
5	S64 S51 NOT S63	15,217
6	S63 S60 OR S61 OR S62	359,216
7	S62 TX sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis	
8	or metastas*	35,825
9	S61 TX (pain* N3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar	
10	or sciatic* or cancer*))	49,583
11	S60 S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59	329,798
12	S59 (MH "Neoplasms+")	240,613
13	S58 (MH "Dentistry+")	47,838
14	S57 (MH "Headache+")	16,196
15	S56 (MH "Toothache")	327
16	S55 (MH "Postoperative Pain")	8,206
17	S54 (MH "Labor Pain")	1,533
18	S53 (MH "Back Pain+")	18,740
19	S52 (MH "Appendicitis")	1,293
20	S51 S17 AND S39 AND S48	20,097
21	S50 S48 AND S49	20,097
22	S49 S17 AND S39	33,880
23	S48 S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	457,089
24	S47 SO pain*	30,433
25	S46 TI pain*	68,365
26	S45 TX ((disability or function* or recover* or pain* or analog*) N3 (measur* or evaluat* or	
27	scale or status or test* or assess* or rating* or index or questionnaire)).	143,200
28	S44 TX VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or	
29	"Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"	
30	or SPDI or "mcgill pain" or BPI or "brief pain" or improvement	174,142
31	S43 TX ((return or resump*) N3 (work or sport or play or activit*))	6,311
32	S42 (MH "Job Re-Entry") OR (MH "Sports Re-Entry") OR (MH "School Re-Entry")	6,819
33	S41 (MH "Pain Measurement")	27,842
34	S40 (MH "Treatment Outcomes")	150,811
35	S39 S37 NOT S38	563,918
36	S38 (MH "Animals+")	37,258
37	S37 S24 OR S29 OR S36	568,264
38	S36 S30 OR S31 OR S32 OR S33 OR S34 OR S35	495,048
39	S35 (MH "Prospective Studies+")	213,854
40	S34 (MH "Evaluation Research+")	41,488
41	S33 (MH "Comparative Studies")	101,882
42	S32 "latin square"	138
43	S31 (MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")	
44	207,529	
45	S30 (MH "Random Sample+")	67,305
46	S29 S25 OR S26 OR S27 OR S28	211,728
47	S28 "random*"	203,059
48	S27 "placebo*"	33,694
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3	S26 (MH "Placebos")	8,296
4	S25 (MH "Placebo Effect")	1,210
5	S24 S18 OR S19 OR S20 OR S21 OR S22 OR S23	195,829
6	S23 "triple-blind"	136
7	S22 "single-blind"	8,460
8	S21 "double-blind"	29,322
9	S20 clinical W3 trial	124,429
10	S19 "randomi?ed controlled trial*"	69,029
11	S18 (MH "Clinical Trials+")	155,173
12	S17 S5 OR S10 OR S15	132,229
13	S16 S11 OR S15	132,229
14	S15 S12 OR S13 OR S14	98,300
15	S14 TX ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or	
16	finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or	
17	femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal*	
18	or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or	
19	scapula* or bone* or joint* or muscle* or shoulder*) N3 (sprain* or strain* or injur* or impair*	
20	or fractur* or break* or broken or disorder* or pain*))	78,680
21	S13 TX ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor	
22	or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or	
23	fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) N3 (injur* or	
24	impair* or imping* or sprain* or strain* or tear or torn))	10,622
25	S12 TX Arthralgi* or bursitis or capsulit* or epicondylalgia* or epicondylit* or fasciopath* or	
26	fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or	
27	osteocondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or	
28	tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD	20,095
29	S11 S5 OR S10	91,140
30	S10 S8 AND S9	Display
31	S9 TI pain* OR AB pain*	Display
32	S8 S6 OR S7	Display
33	S7 (MH "Musculoskeletal Diseases") OR (MH "Cartilage Diseases+") OR (MH "Fasciitis+")	
34	OR (MH "Foot Diseases+") OR (MH "Golf Elbow") OR (MH "Heel Pain") OR (MH "Joint	
35	Diseases") OR (MH "Muscular Diseases") OR (MH "Arthralgia+") OR (MH "Bursitis+") OR	
36	(MH "Contracture+") OR (MH "Metatarsalgia") OR (MH "Shoulder Instability, Anterior") OR	
37	(MH "Shoulder Instability, Multidirectional") OR (MH "Shoulder Instability, Posterior") OR	
38	(MH "Synovitis")	Display
39	S6 (MH "Musculoskeletal System") OR (MH "Cartilage+") OR (MH "Fascia+") OR (MH	
40	"Ligaments+") OR (MH "Muscles+") OR (MH "Bone and Bones") OR (MH "Arm Bones+")	
41	OR (MH "Foot Bones+") OR (MH "Leg Bones+") OR (MH "Pelvic Bones+") OR (MH	
42	"Joints+")	Display
43	S5 S1 OR S2 OR S3 OR S4	Display
44	S4 (MH "Neck Pain")	Display
45	S3 (MH "Arthralgia+")	Display
46	S2 (MH "Compartment Syndromes") OR (MH "Anterior Compartment Syndrome") OR (MH	
47	"Ischemic Contracture")	Display
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3 S1 (MH "Arm Injuries+") OR (MH "Athletic Injuries+") OR (MH "Dislocations+") OR (MH
4 "Fractures+") OR (MH "Hand Injuries+") OR (MH "Leg Injuries+") OR (MH "Ligament
5 Injuries+") OR (MH "Neck Injuries+") OR (MH "Occupational-Related Injuries") OR (MH
6 "Soft Tissue Injuries+") OR (MH "Sprains and Strains+") OR (MH "Tendon Injuries+")
7
8 Display
9

10
11 PEDro, yields 645
12

13 March 13, 2018
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15
16 Abstract & Title: acute
17 AND
18 Problem: pain
19 AND
20 Method: Clinical trial
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4 & 8
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#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	16

1			protocol amendments	
2	Sources	#5a	Indicate sources of financial or other support for the review	18
3				
4	Sponsor	#5b	Provide name for the review funder and / or sponsor	18
5				
6				
7	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s),	18
8	funder		if any, in developing the protocol	
9				
10				
11	Rationale	#6	Describe the rationale for the review in the context of what is	6
12			already known	
13				
14	Objectives	#7	Provide an explicit statement of the question(s) the review will	7
15			address with reference to participants, interventions,	
16			comparators, and outcomes (PICO)	
17				
18				
19				
20	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design,	8 & 9
21			setting, time frame) and report characteristics (such as years	
22			considered, language, publication status) to be used as	
23			criteria for eligibility for the review	
24				
25				
26				
27	Information	#9	Describe all intended information sources (such as electronic	8
28	sources		databases, contact with study authors, trial registers or other	
29			grey literature sources) with planned dates of coverage	
30				
31				
32	Search strategy	#10	Present draft of search strategy to be used for at least one	25-32
33			electronic database, including planned limits, such that it	
34			could be repeated	
35				
36				
37	Study records -	#11a	Describe the mechanism(s) that will be used to manage	9
38	data management		records and data throughout the review	
39				
40				
41	Study records -	#11b	State the process that will be used for selecting studies (such	9
42	selection process		as two independent reviewers) through each phase of the	
43			review (that is, screening, eligibility and inclusion in meta-	
44			analysis)	
45				
46				
47				
48	Study records -	#11c	Describe planned method of extracting data from reports	9 & 10
49	data collection		(such as piloting forms, done independently, in duplicate), any	
50	process		processes for obtaining and confirming data from investigators	
51				
52				
53	Data items	#12	List and define all variables for which data will be sought	9 & 10
54			(such as PICO items, funding sources), any pre-planned data	
55			assumptions and simplifications	
56				
57				
58				
59				
60				

1	Outcomes and	#13	List and define all outcomes for which data will be sought,	9 & 10
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
4				
5				
6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	10
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
10				
11				
12				
13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	10 & 11
14			synthesised	
15				
16				
17		#15b	If data are appropriate for quantitative synthesis, describe	10-14
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
21				
22				
23				
24		#15c	Describe any proposed additional analyses (such as	14
25			sensitivity or subgroup analyses, meta-regression)	
26				
27				
28		#15d	If quantitative synthesis is not appropriate, describe the type	N/A
29			of summary planned	
30				
31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	14
32			publication bias across studies, selective reporting within	
33			studies)	
34				
35				
36				
37	Confidence in	#17	Describe how the strength of the body of evidence will be	14 & 15
38	cumulative		assessed (such as GRADE)	
39	evidence			
40				
41				

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 44 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024441.R2
Article Type:	Protocol
Date Submitted by the Author:	03-Feb-2019
Complete List of Authors:	Busse, Jason; McMaster University, Anesthesia; McMaster University, Clinical Epidemiology & Biostatistics Craigie, Samantha; McMaster University Sadeghirad, Behnam; McMaster University Couban, Rachel; McMaster University, Michael G. DeGroote Institute for Pain Research and Care Hong, Patrick; University of Ottawa Faculty of Medicine Oparin, Yvgeniy; McMaster University Department of Medicine May, Curtis; University of British Columbia Faculty of Medicine Lok, Annie; McMaster University Department of Anaesthesia Guyatt, Gordon; McMaster University, Clinical Epidemiology and Biostatistics
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Evidence based practice
Keywords:	acute pain, musculoskeletal, intervention, systematic review, network metanalysis

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Manuscripts

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3 **Management of acute musculoskeletal pain (excluding low back pain): a protocol for a**
4 **systematic review and network meta-analysis of randomised trials**
5
6
7

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For peer review only

Abstract

Introduction: Acute, non-low back related musculoskeletal pain is common and associated with significant socioeconomic costs. No review has evaluated all interventional studies for acute musculoskeletal pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomised controlled trials evaluating therapies for acute musculoskeletal pain (excluding low back pain). We will identify eligible, English-language, trials by a systematic search of CINAHL, EMBASE, MEDLINE, PEDro and the Cochrane Central Registry of Controlled Trials from inception to February 2018. Eligible trials will: (1) enrol patients presenting with acute, non-low back related musculoskeletal pain (duration of pain \leq 4 weeks), and (2) randomise patients to alternative interventions or an intervention and a placebo/sham arm. Fractures will be considered ineligible, unless they are non-surgical and therapy is directed at pain relief. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias. Disagreements will be resolved through discussion to achieve consensus.

We will use the GRADE system to evaluate the quality of evidence supporting treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analysis to establish the effectiveness of therapeutic interventions on patient-important outcomes; and (2) multiple treatment comparison meta-analysis to assess the relative effects of treatments. We will use a priori hypotheses to explain heterogeneity between studies. We will use STATA 14.2 for all analyses.

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3 **Ethics and dissemination:** No research ethics approval is required for this systematic review.
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5 The results of this systematic review will be disseminated through publication in a peer-reviewed
6 journal, conference presentations, and will inform a clinical practice guideline.
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12 **Key Words:** acute pain; musculoskeletal; intervention; systematic review; network meta-
13 analysis
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19 **PROSPERO registration number:** CRD42018094412
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Article Summary

Strengths and limitations

- Our broad study eligibility criteria will increase generalizability of our results.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate our confidence in treatment effects.
- We will optimize interpretability by presenting risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.
- Findings from our review will inform a clinical practice guideline and identify key areas for future research.
- Our results will be limited by possible shortcomings of the primary studies.

Introduction

Acute non-low back related musculoskeletal (MSK) pain, which include strains and sprains, dislocations, and whiplash present for less than 1 month¹, are associated with considerable morbidity in North America. The Burden of Musculoskeletal Diseases in the United States, 3rd edition, found that sprains and strains are the most frequent injury type for which medical care is sought and the majority of MSK injuries occur among working-age adults.² In 2013 there were 2,807,880 emergency department visits for sports-related injuries in the US,³ and over 70% of visits to the emergency department are because of pain-related complaints.⁴ Management often yields suboptimal outcomes: a survey of 842 acute pain patients at 20 US and Canadian hospitals found 40% reported their pain did not change or increased after visiting the emergency department, and 74% of patients were discharged in moderate to severe pain.⁵

Despite the prevalence of acute MSK complaints in primary care, a number of studies have highlighted inadequate pain education of among physicians.⁶⁻⁸ The availability of numerous pharmacologic and non-pharmacologic therapies further complicates management decisions. Currently available treatments include opioids, nonsteroidal anti-inflammatory drugs, muscle relaxants, acetaminophen, exercise, supervised rehabilitation, joint manipulation and mobilization, massage, acupuncture and acupressure, ultrasound, low-level laser therapy, and transcutaneous electrical nerve stimulation.⁹⁻¹²

A recently published series of 24 systematic reviews of treatment for common acute MSK injuries,¹³ suffers from many important limitations, including: (1) selection bias due, in part, to exclusion of studies deemed to be at high risk of bias without empirically exploring if effect estimates differed from studies assigned low risk of bias, (2) interpreting results from individual studies as effective if the mean difference in a given outcome met the minimally

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3 important difference (MID) and ineffective if not - an interpretation that relies on the unlikely
4 assumption that all patients will experience the same degree of improvement, and fails to
5 consider the distribution around the mean and the proportion of patients that achieve the MID,
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10 (3) no appraisal of the overall quality (confidence, certainty) of the evidence, and (4) no
11 statistical pooling of treatment effects. We propose to conduct a systematic review of
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14 randomized trials to assess the comparative effectiveness of available non-surgical treatments for
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16 acute MSK pain (excluding low back pain) and assess quality of evidence using the Grading of
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18 Recommendations Assessment, Development and Evaluation (GRADE) methodology.
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Methods

Protocol registration

The protocol for this systematic review is registered with PROSPERO (CRD42018094412). This review was commissioned by the American Academy of Family Physicians and American College of Physicians and sponsored by the National Safety Council.

Standardized Reporting

We used the PRISMA-P checklist when writing our report.¹⁴

Information sources

We will identify eligible, English language, randomized clinical trials (RCTs) through a systematic search of MEDLINE, EMBASE, CINAHL, PEDro and CENTRAL, from inception of each database through February 2018. Our search has been refined for individual databases by an experienced medical librarian (Appendix). We will scan reference lists of included studies and relevant systematic reviews for additional eligible articles.

Eligibility criteria and study selection

We will include therapeutic trials that: 1) enroll adult patients (≥ 18 years) presenting with acute, non-low back related MSK pain (pain with duration < 4 weeks or defined by authors as “acute”) in an outpatient setting, and 2) randomise them to currently available, non-surgical, alternative interventions directed at pain relief (pharmacological or non-pharmacological) or a currently available, non-surgical, intervention directed at pain relief and a placebo/sham arm. Eligible MSK conditions include sprains and strains. Surgical fractures, non-surgical fractures unless

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3 therapy is directed at pain relief, low back pain, neuropathic pain, acute cancer pain, acute
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5 postoperative pain, acute dental pain, pain associated with labour and delivery, visceral pain,
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7 pain due to infection, and headaches will be excluded. We will exclude interventions targeted at
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9 treatment of acute low back pain on request by the study funder, as they have previously
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11 commissioned evidence syntheses on this topic.^{9,10}
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15 Ten teams of trained reviewers will work independently in pairs to screen titles and
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17 abstracts of identified citations, using standardized, pilot-tested forms in DistillerSR, an online
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19 systematic review software (Evidence Partners, Ottawa, Canada; <http://systematic-review.net/>).
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21 The same teams of reviewers will screen full texts of any articles judged as potentially eligible.
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23 Reviewers will discuss disagreements to come to consensus, referring to an adjudicator if
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25 necessary. We will measure agreement between reviewers by calculating kappa (κ) values to
26
27 assess the reliability of full-text review, and interpret them using the following thresholds: <0.20
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29 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as
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31 substantial agreement and >0.80 as almost perfect agreement.¹⁵
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38 *Data abstraction*

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40 We designed standardized data abstraction forms and a detailed instruction video (accessible at:
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42 <https://www.youtube.com/watch?v=1nwFJ61K3sQ>). We will conduct calibration exercises prior
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44 to beginning data abstraction to ensure consistency and accuracy of extractions. Seven teams of
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46 reviewers will extract data independently and in duplicate. We will extract the following data
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48 from eligible trials into a standardized spreadsheet: study characteristics (e.g. the first author,
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50 publication year, country of origin, and funding source), participant and trial characteristics (e.g.
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52 sample size, mean age of participants, clinical condition, type and severity of injury, proportion
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3 with known chronic pain/condition prior to acute injury, and the proportion receiving opioids at
4 the time of enrollment), characteristics of interventions and comparators, patient-important
5 outcomes (pain, function, health-related quality of life, patient satisfaction, return to work,
6 proportion of patients with relief, re-injury and all reported adverse events). We will extract pain
7 at any time-point, whereas for other outcomes, we will use the longest follow-up reported.¹⁶
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16 *Risk of bias assessment*

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18 Among eligible studies, we will independently assess the following risk of bias issues: (1) random
19 sequence generation, (2) allocation concealment, (3) blinding of study participants, personnel, and
20 outcome assessors, (4) incomplete outcome data ($\geq 20\%$ missing data will be considered at high
21 risk of bias), and (5) other sources of bias.¹⁷ To assess the risk of bias we will use a modified
22 version of the Cochrane risk of bias instrument.¹⁸ Our instrument will use the following responses:
23 ‘definitely yes’ or ‘probably yes’ (considered as low risk of bias), or ‘definitely no’ or ‘probably
24 no’ (considered as high risk of bias). These response options have published evidence of validity
25 for assessing blinding.¹⁸ Any discrepancy in assessment of risk of bias will be resolved by
26 discussion, or third party adjudication if needed. We will contact authors for missing information
27 regarding risk of bias issues and unpublished data (e.g. effect estimates without accompanying
28 estimates of precision).
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47 *Data synthesis*

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49 MSK complaints are increasingly being considered together as risk factors,¹⁹ prognosis,²⁰ and
50 treatments are often similar in guideline recommendations.^{21,22} For the purposes of statistical
51 pooling, we will explore treatment effects of interventions across all MSK complaints eligible for
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3 this review; however, we will also explore if treatment effects differ by clinical condition or injury
4 severity. Clustering strategies for clinical condition and injury severity will be informed by the
5 trials eligible for our review, which will be reviewed by a technical expert panel, blinded to study
6 results. Treatment effects will be pooled using the longest follow-up time reported, except for pain,
7 which will be pooled at the most commonly reported short, medium and long-term follow-up times
8 reported by trials eligible for our review. For our review, these categories will be 30 to 120 minutes
9 post-treatment (short), 1 to 7 days post-treatment (medium), and 3 to 12 weeks post-treatment
10 (long). As such, a single trial could contribute to up to 3 time-points for our pooled results for pain
11 relief. Alternately, trials that reported pain relief at time points outside of these timeframes would
12 not contribute data for our analyses of pain relief.
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28 *Methods for direct comparisons*

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30 We will pool dichotomous outcomes that are reported by >1 RCT and calculate the relative risk
31 and risk difference (RD), using baseline risk estimates from the placebo arm of eligible studies,
32 and the associated 95% confidence intervals (CIs). We will pool all continuous outcomes that are
33 reported by >1 study and calculate the weighted mean differences (WMDs) and associated 95%
34 CIs. We will employ methods described in Cochrane Handbook to estimate the mean and standard
35 deviation (SD) when median, range, and sample size are reported, and to impute the SD if the
36 standard error or SD for the differences are not reported.²³ For continuous outcomes, when studies
37 report effect estimates using different measurement instruments that tap into a common construct
38 (e.g. pain), we will first transform all outcomes to a common instrument on a domain-by-domain
39 basis.²⁴ We will use change scores from baseline to end of follow-up rather than end-of-study
40 scores, in order to account for inter-patient variability. If authors do not report change scores, we
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3 will calculate them using the baseline and end-of-study score and a correlation coefficient derived
4 from the largest trial at lowest risk of bias in the meta-analysis that does report a change score. We
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6 will use DerSimonian–Laird random-effects models²⁵ for all pairwise comparisons.
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10 Interpreting effect estimates for continuous outcomes is challenging,²⁶ and we will present
11 the minimally important difference (MID) for all pooled effect estimates. The MID is the smallest
12 amount of improvement in a treatment outcome that a patient would recognize as important.²⁷ If
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14 we find multiple MID estimates are available, we will use the smallest difference that has been
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16 validated.
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21 However, simply presenting the MID risks interpreting all mean effects that fall below the
22 MID as unimportant, whereas we have found that, typically, mean differences of 1/2 the MID
23 result in RDs of about 10% - a potential benefit that many patients may consider important.²⁸ Thus,
24
25 concluding that an effect is unimportant requires confidence that the mean difference is less than
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27 1/2 the MID (and perhaps less). To optimize interpretability, we will calculate the RD of achieving
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29 the MID for all statistically significant WMDs. Specifically, for each individual study, we will
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31 assume that the SDs of outcome measurements are the same in both the treatment and control
32
33 groups, and that change scores in both groups are normally distributed. We will use the median or
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35 mean, and SD of the control group, with the established MID for the outcome in question to
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37 estimate the probability of achieving \geq MID in the control group. We will use the pooled mean
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39 difference to estimate the mean in the treatment group and calculate the probability of achieving
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41 \geq MID in the treatment group. Finally, we will use risks in both groups to acquire the RD for
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43 achieving \geq MID.
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54 *Methods for network meta-analysis*
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3 We will perform network meta-analysis to synthesize the available evidence from the entire
4 network of trials by integrating direct and indirect estimates for each comparison into a single
5 summary treatment effect. We will use a frequentist random-effects model using the methodology
6 of multivariable meta-analysis to assess the comparative effectiveness of eligible interventions.^{29,30}
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12 Although the assumptions for network meta-analysis are similar to conventional meta-
13 analysis, key extra assumptions are transitivity (there are no effect modifiers influencing the
14 indirect comparisons) and coherence (direct and indirect effect estimates being similar).³¹ We will
15 identify issues of incoherence by comparing direct evidence (i.e. estimates from pairwise
16 comparisons) with indirect evidence (i.e. estimates from network meta-analysis) using the node
17 splitting method.^{32,33} In this approach, incoherence is assessed locally by evaluating the
18 consistency assumption in each closed loop of the network separately as the difference between
19 direct and indirect estimates for a specific comparison in the loop. We will assume a common
20 heterogeneity estimate within each loop. We will also confirm the coherence assumption in the
21 entire network using a ‘design-by-treatment’ model.³⁴ In case we find significant incoherence in
22 the network (highly significant p value from design-by-treatment model), we will perform network
23 meta-analysis using an inconsistency model. If using an inconsistency model results in non-
24 sensical results, we will explore the network for the source(s) of incoherence and further expand
25 (disintegrating interventions based on differences in population or intervention characteristics) or
26 exclude the node(s) introducing incoherence into the network (e.g., excluding node(s) with less
27 than 20 events for binary outcomes or comparisons with only one trial with very few participants
28 for continuous outcomes).
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51 We will report our findings with probability statements of intervention effects. Probability
52 rankings allow us to report a chance percentage of which interventions rank higher;³⁵ however,
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3 simplifying the results of a network down to probabilities can lead to misinterpretations,
4 specifically, when particular comparisons (i.e. nodes) are not well-connected or when the quality
5 of evidence varies between comparisons.^{36,37} Following display of the rank probabilities using
6 rankogram, we will use the surface under the cumulative ranking (SUCRA) line to aid in
7 interpretation of relative effect of the interventions. An intervention with a SUCRA value of 100
8 is certain to be the most effective, whereas an intervention with 0 is certain to be the least
9 effective.³⁵ We will use STATA (StataCorp, Release 14.2, College Station, Texas, USA) for all
10 statistical analyses. All comparisons will be 2-tailed using a threshold $p \leq 0.05$.
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24 *Subgroup analyses, meta-regression and sensitivity analysis*

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26 We will use Cochran's Q statistic and I^2 to determine statistical heterogeneity for direct meta-
27 analysis.³² We have developed five hypotheses to explain heterogeneity between trials: (1)
28 different clinical conditions will show different treatment effects; (2) more severe injuries will
29 show smaller treatment effects than less severe injuries (e.g. higher grades of strains and sprains
30 vs. lower grades); (3) older patients will show smaller treatment effects than younger patients; (4)
31 longer follow-up will show smaller treatment effects than shorter follow-up; and (5) higher
32 dose/intensity of treatment will show larger treatment effects. We will perform subgroup analyses
33 regardless of heterogeneity estimates, if there are at least 2 trials in each subgroup. Moreover, we
34 will explore the effect of risk of bias (on a component-by-component basis) and reported vs.
35 converted change scores on treatment effects.
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51 *Assessing quality of the evidence*

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3 We will use the GRADE approach to assess the quality of evidence on an outcome-by-outcome
4 basis. The starting point for quality of evidence for RCTs is high, but may be rated down based on
5 limitations in risk of bias, imprecision, inconsistency, and indirectness and publication bias.³⁸
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7 When there are at least 10 studies for meta-analysis,^{39,40} we will assess publication bias by visual
8 assessment of asymmetry of the funnel plot and calculated Begg's test.
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14 We will also use the GRADE approach to assess quality of evidence for indirect and
15 network (mixed) effect estimates.^{41,42} Indirect effect estimates are calculated from available
16 'loops' of evidence, which includes first order loops (based on a single common comparator
17 treatment, the difference between the treatment A and B is based on comparisons of A and C as
18 well as B and C) or higher order loops (more than one intervening treatment connecting the two
19 interventions). We will visually examine the network map and where first order loops are
20 available for indirect comparisons, the quality of evidence will be the lower of the ratings for the
21 two direct estimates contributing to the first order loop. In the absence of a first order loop, a
22 higher order loop will be used to rate the quality of evidence. We may rate down quality of
23 evidence further for intransitivity.⁴² The transitivity assumption implies similarity of trials in
24 terms of population, intervention, settings, and trial methodology.⁴³
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40 It is very rare for a network meta-analysis to establish a single treatment option as clearly
41 superior to all others. We will categorize interventions according to three categories: (1) those
42 that are clearly superior, (2) those with intermediate effectiveness, and (3) those that are inferior.
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44 Treatments no better than placebo will be in the lowest tier, those better than placebo in tier 1
45 (likely intermediate); those superior to at least 1 tier 1 treatment will be judged superior.
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47 Treatments will be further categorized according to quality of evidence supporting those
48 estimates (high and moderate vs. low or very low). Interventions with moderate or high quality
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3 evidence will be ranked as either ‘among the most effective’, ‘inferior to the most effective /
4 superior to the least effective’, or ‘among the least effective’. Interventions supported by low or
5 very low quality evidence will be ranked into the same 3 categories but prefaced with ‘may be’
6 to acknowledge the reduced confidence in supporting evidence (e.g. ‘may be among the most
7 effective’) and will be presented separately from those supported by moderate or high quality
8 evidence.
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19 **Ethics and Dissemination**

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21 No research ethics approval is required for this systematic review, as no confidential patient data
22 will be used. The results of this systematic review will be disseminated through publication in a
23 peer-reviewed journal and through conference presentations. Findings from our review will
24 inform a clinical practice guideline. All amendments to the protocol will be reported in the
25 PROSPERO trial registry.
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35 **Patient and Public Involvement**

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37 No patients were involved in setting the research question, in developing plans for design,
38 interpretation, reporting or implementation of the study. We plan to disseminate the results of
39 this study to organisations supporting patients with acute MSK pain.
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Discussion

With the high prevalence of acute non-low back MSK pain, the associated socioeconomic burden and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent need for a high-quality systematic review to inform evidence-based management of these complaints.

Our proposed review has several strengths in relation to existing reviews. First, we will explore all currently available non-pharmacological and pharmacological treatment options for all acute MSK complaints (excluding low back pain) reported among eligible trials. It is plausible that individual acute MSK complaints respond similarly to similar interventions, and thus by pooling across individual injuries, it may be possible to provide a more precise estimate of treatment effect. Second, we will update the search to present date. Third, we will use the GRADE approach to evaluate the quality of evidence supporting treatment effects. Fourth, we will ensure interpretability by presenting RDs and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.

A potential limitation will be the nature of available treatment comparisons to build robust networks for our analyses. The findings of our review will help inform patients with acute non-low back related MSK pain about their therapeutic options, identify key areas for research, and facilitate a clinical practice guideline for the management of acute, non-low back related MSK pain.

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4 developing our study protocol: Robert McLean, MD; Devan Kansagara, MD; Dave O'Gurek,
5 MD; Kenny Lin, MD; Christina Mikosz, MD; John Riva, DC, MSc; Moin Khan, MD.
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12 **Author Contributions:** All authors made substantial contributions to conception and design.
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14 JWB and BS drafted the article, and SC, RC, PJH, YO, CM, AL and GHG revised it critically for
15 important intellectual content. All authors provided final approval of the version to be published.
16
17 JWB is the guarantor of the review protocol.
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24 **Data sharing:** Statistical code and dataset available from Dr. Sadeghirad (e-mail:
25 b.sadeghirad@gmail.com).
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32 Council (NSC) (PI: JW Busse). The NSC partnered with the American Academy of Family
33 Physicians (AAFP) and the American College of Physicians (ACP) who helped to inform the
34 design of our review, but the NSC will have no role in the conduct of the study; collection,
35 management, analysis, and interpretation of the data; preparation, review, or approval of the
36 resulting manuscript; or decision to submit the manuscript for publication. Representatives from
37 AAFP and ACP will have the right to review the manuscript and make non-binding comments
38 and suggestions.
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51 **Competing interests:** None declared.
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3 **Patient consent:** Not required.
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8 **Provenance and peer review:** This review was commissioned and externally peer reviewed.
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12 **Open Access:** This is an Open Access article distributed in accordance with the terms of the
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14 Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix,
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19 See: <http://creativecommons.org/licenses/by/4.0/>
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Appendix: Literature Search Strategies

Summary of search and strategies ACP Acute MSK Pain

Feb 14, 2018

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp arm injuries/ or athletic injuries/ or exp joint dislocations/ or exp fractures, bone/ or fractures, cartilage/ or exp hand injuries/ or exp hip injuries/ or exp leg injuries/ or exp neck injuries/ or occupational injuries/ or exp shoulder injuries/ or exp soft tissue injuries/ or exp "sprains and strains"/ or exp tendon injuries/ or exp Compartment Syndromes/ or exp Bone Malalignment/ (300813)

2 (exp Musculoskeletal system/ or musculoskeletal diseases/ or osteitis/ or exp cartilage diseases/ or exp fasciitis/ or exp bursitis/ or exp metatarsalgia/ or exp synovitis/ or muscle cramp/ or myalgia/ or exp tendinopathy/) and pain*.ti,ab. (87772)

3 Musculoskeletal Pain/ or Neck Pain/ or Acute Pain/ or exp Arthralgia/ (19422)

4 (Arthralgi* or bursitis or capsulit* or epicondylalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyositis* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (111653)

5 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (14400)

6 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (235481)

7 or/1-6 (587971)

8 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (810530)

9 ((treatment or control) adj3 group*).ab. (511607)

10 (allocat* adj5 group*).ab. (20402)

11 ((clinical or control*) adj3 trial).ti,ab,kw. (226548)

12 or/8-11 (1258485)

13 7 and 12 (46565)

14 exp animals/ not humans.sh. (4424690)

15 13 not 14 (42705)

16 adult.mp. or middle aged.sh. or age:.tw. (8090446)

17 15 and 16 (30798)

18 limit 15 to "all adult (19 plus years)" (28434)

19 17 or 18 (31999)

20 treatment outcome/ (824861)

21 Pain Measurement/ (75370)

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2
3 22 "Recovery of Function"/ (42703)
4 23 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or
5 scale or status or test* or assess* or rating* or index or questionnaire)).mp. (586581)
6 24 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
7 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
8 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (628803)
9 25 Return to Work/ or Return to Sport/ or ((return or resump*) adj3 (work or sport or play or
10 activit*)).mp. (16520)
11 26 pain*.jw,ti. (199639)
12 27 pain*.ab. /freq=2 (243208)
13 28 or/20-27 (2035376)
14 29 19 and 28 (20709)
15 30 exp appendicitis/ or exp Back Pain/ or Labor Pain/ or exp Pain, Postoperative/ or exp
16 Toothache/ or headache/ or exp Headache disorders/ or exp dentistry/ or exp Neoplasms/
17 (3499077)
18 31 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or
19 sciatic* or cancer*)).mp. (118740)
20 32 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or
21 metastas*).mp. (463484)
22 33 or/30-32 (3631063)
23 34 29 not 33 (13769)
24 35 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
25 family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (7012189)
26 36 34 and 35 (9481)
27 37 Osteoarthritis/ (33247)
28 38 exp arthroplasty/ or exp arthroscopy/ or bone transplantation/ (101224)
29 39 su.fs. (1807708)
30 40 or/37-39 (1863671)
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36 Feb 14, 2018

37 Database: Embase <1974 to 2018 February 13>

38 Search Strategy:
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41 1 limb injury/ or exp arm injury/ or exp leg injury/ or exp limb fracture/ or sport injury/ or exp
42 joint injury/ or musculoskeletal injury/ or exp cartilage injury/ or exp "ligament and tendon
43 injury"/ or medial tibial stress syndrome/ or muscle injury/ or overexertion/ or exp sprain/ or
44 fracture/ or avulsion fracture/ or clavicle fracture/ or comminuted fracture/ or fracture
45 dislocation/ or exp fracture healing/ or intraarticular fracture/ or exp joint fracture/ or exp limb
46 fracture/ or exp multiple fracture/ or exp scapula fracture/ or stress fracture/ or neck injury/ or
47 whiplash injury/ or occupational accident/ or soft tissue injury/ or compartment syndrome/
48 (382802)
49

50 Annotation: includes arm injury/ or exp arm fracture/ or elbow dislocation/ or elbow injury/ or
51 exp forearm injury/ or exp hand injury/ or exp shoulder injury/ or exp wrist injury/ or leg injury/
52 or exp ankle injury/ or exp foot injury/ or exp hip injury/ or exp knee injury/ or exp leg fracture/
53 or tibia torsion/ or exp ankle injury/ or exp dislocation/ or exp hip injury/ or intraarticular
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3 fracture/ or exp joint fracture/ or exp knee injury/ or posttraumatic arthropathy/ or exp wrist
4 injury/

5 2 (exp musculoskeletal system/ or exp musculoskeletal disease/) and pain*.ti,ab. (312623)

6 3 musculoskeletal pain/ or neck pain/ or shoulder pain/ or arthralgia/ (86878)

7 4 or/1-3 (692780)

8 Annotation: emtree terms condition MSK pain

9 5 (Arthralgi* or bursitis or capsulit* or epicondylgia* or epicondylit* or fasciopath* or
10 fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myositis* or osteitis or
11 osteochondritis or osteomyelitis or polymyositis* or radiculopath* or radiculit* or synovit* or
12 tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (147804)

13 6 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or
14 teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis
15 or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair*
16 or imping* or sprain* or strain* or tear or torn)).tw. (16617)

17 7 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or
18 finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or
19 femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal*
20 or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or
21 scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair*
22 or fractur* or break* or broken or disorder* or pain*).tw. (305948)

23 8 or/5-7 (444822)

24 Annotation: free text terms condition MSK pain

25 9 4 or 8 (897318)

26 Annotation: MSK pain

27 10 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/
28 or animal cell/ or nonhuman/ (25540585)

29 11 human/ or normal human/ or human cell/ (19287963)

30 12 10 and 11 (19240053)

31 13 10 not 12 (6300532)

32 14 9 not 13 (837728)

33 15 random:.tw. or placebo:.mp. or double-blind:.tw. (1509046)

34 Annotation: HIRU specific RCT filter

35 16 ((treatment or control) adj3 group*).ab. (723604)

36 17 (allocat* adj5 group*).ab. (26448)

37 18 ((clinical or control*) adj3 trial).ti,ab,kw. (327340)

38 19 or/15-18 (2107446)

39 Annotation: modified RCT filter

40 20 14 and 19 (95790)

41 Annotation: MSK pain with mod RCT filter

42 21 treatment outcome/ (762155)

43 22 outcome assessment/ (400641)

44 23 pain measurement/ (4687)

45 24 exp pain assessment/ (134012)

46 25 convalescence/ (42381)

47 26 return to sport/ or return to work/ (4870)

48 27 work resumption/ (3467)

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3 28 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or
4 scale or status or test* or assess* or rating* or index or questionnaire)).mp. (790797)
5 29 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
6 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
7 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (911685)
8 30 ((return or resump*) adj3 (work or sport or play or activit*)).mp. (23514)
9 31 pain*.jw,ti. (269095)
10 32 pain*.ab. /freq=2 (358966)
11 33 or/21-32 (2816037)
12 34 20 and 33 (58373)

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14
15 Annotation: MSK pain with mod RCT and outcome

16 35 exp appendicitis/ or exp backache/ or labor pain/ or exp postoperative complication/ or exp
17 tooth disease/ or headache/ or exp dentistry/ or exp malignant neoplasm/ or exp metastasis/
18 (4067682)

19 36 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or
20 sciatic* or cancer*)).mp. (189693)

21 37 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or metastas* or
22 appendicitis).mp. (778837)

23 38 35 or 36 or 37 (4238484)

24 39 34 not 38 (30664)

25
26 Annotation: mod RCT set

27 40 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
28 family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (9180696)

29
30 Annotation: Gill 2014 primary care plus sport

31 41 39 and 40 (21784)

32 42 exp osteoarthritis/ (110006)

33 43 bone transplantation/ or exp bone graft/ (46349)

34 44 exp orthopedic surgery/ (406039)

35
36 Annotation: includes exp joint surgery/ or exp arthroplasty/

37 45 su.fs. (1950489)

38 46 or/42-45 (2224706)

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40 Cochrane Library

41 Search Name: 2017-08-22 ACP acute msk pain search

42 Date Run: 14/02/18 20:52:03.682

43 Description:

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46 ID Search Hits

47 #1 Arthralgi* or bursitis or capsulit* or epicondylgia* or epicondyli* or fasciopath* or
48 fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or
49 osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or
50 tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD 13121

51 #2 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or
52 teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis
53 or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) near/3 (injur* or
54 impair* or imping* or sprain* or strain* or tear or torn)) 2044

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3 #3 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or
4 finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or
5 femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal*
6 or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or
7 scapula* or bone* or joint* or muscle* or shoulder*) near/3 (sprain* or strain* or injur* or
8 impair* or fractur* or break* or broken or disorder* or pain*)) 38249
9
10 #4 #1 or #2 or #3 47667
11 #5 ((disability or function* or recover* or pain* or analog*) near/3 (measur* or evaluat* or
12 scale or status or test* or assess* or rating* or index or questionnaire)) 109526
13 #6 VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or
14 "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index"
15 or SPDI or "mcgill pain" or BPI or "brief pain" or improvement 139538
16 #7 ((return or resump*) near/3 (work or sport or play or activit*)) 3128
17 #8 pain*:so 8908
18 #9 pain*:ti 34759
19 #10 #5 or #6 or #7 or #8 or #9 214594
20 #11 #4 and #10 24648
21 #12 (pain* near/3 (chronic or dental or labo?r or back or low back or spine or spinal or
22 lumbar or sciatic* or cancer*)) 20816
23 #13 sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or
24 metastas* 27428
25 #14 #12 or #13 45616
26 #15 #11 not #14 18297
27 #16 clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or
28 family or communit* or ambulatory or centre* or center* or office or sport* 937038
29 #17 #15 and #16 in Trials, with Wounds Group, Injuries Group, Pain, Palliative and
30 Supportive Care Group, Musculoskeletal Group, Bone, Joint and Muscle Trauma Group, Back
31 Group or Occupational Safety and Health Group in Review Groups
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CINAHL

S73 S66 NOT S72	5,571
S72 S67 OR S68 OR S69 OR S70 OR S71	224,577
S71 (MM "Surgery, Operative+")	211,375
S70 (MH "Arthroscopy")	4,418
S69 (MH "Arthroplasty")	1,646
S68 (MH "Bone Transplantation")	3,342
S67 (MH "Osteoarthritis+")	13,152
S66 S64 AND S65	8,761
S65 TI (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*) OR AB (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or	

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family or communit* or ambulatory or centre* or center* or office or sport*)	
1,131,403	
S64 S51 NOT S63	15,217
S63 S60 OR S61 OR S62	359,216
S62 TX sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas*	35,825
S61 TX (pain* N3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*))	49,583
S60 S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59	329,798
S59 (MH "Neoplasms+")	240,613
S58 (MH "Dentistry+")	47,838
S57 (MH "Headache+")	16,196
S56 (MH "Toothache")	327
S55 (MH "Postoperative Pain")	8,206
S54 (MH "Labor Pain")	1,533
S53 (MH "Back Pain+")	18,740
S52 (MH "Appendicitis")	1,293
S51 S17 AND S39 AND S48	20,097
S50 S48 AND S49	20,097
S49 S17 AND S39	33,880
S48 S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	457,089
S47 SO pain*	30,433
S46 TI pain*	68,365
S45 TX ((disability or function* or recover* or pain* or analog*) N3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).	143,200
S44 TX VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement	174,142
S43 TX ((return or resump*) N3 (work or sport or play or activit*))	6,311
S42 (MH "Job Re-Entry") OR (MH "Sports Re-Entry") OR (MH "School Re-Entry")	6,819
S41 (MH "Pain Measurement")	27,842
S40 (MH "Treatment Outcomes")	150,811
S39 S37 NOT S38	563,918
S38 (MH "Animals+")	37,258
S37 S24 OR S29 OR S36	568,264
S36 S30 OR S31 OR S32 OR S33 OR S34 OR S35	495,048
S35 (MH "Prospective Studies+")	213,854
S34 (MH "Evaluation Research+")	41,488
S33 (MH "Comparative Studies")	101,882
S32 "latin square"	138
S31 (MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")	207,529
S30 (MH "Random Sample+")	67,305
S29 S25 OR S26 OR S27 OR S28	211,728
S28 "random*"	203,059
S27 "placebo*"	33,694

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3	S26 (MH "Placebos")	8,296
4	S25 (MH "Placebo Effect")	1,210
5	S24 S18 OR S19 OR S20 OR S21 OR S22 OR S23	195,829
6	S23 "triple-blind"	136
7	S22 "single-blind"	8,460
8	S21 "double-blind"	29,322
9	S20 clinical W3 trial	124,429
10	S19 "randomi?ed controlled trial*"	69,029
11	S18 (MH "Clinical Trials+")	155,173
12	S17 S5 OR S10 OR S15	132,229
13	S16 S11 OR S15	132,229
14	S15 S12 OR S13 OR S14	98,300
15	S14 TX ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or	
16	finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or	
17	femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal*	
18	or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or	
19	scapula* or bone* or joint* or muscle* or shoulder*) N3 (sprain* or strain* or injur* or impair*	
20	or fractur* or break* or broken or disorder* or pain*))	78,680
21	S13 TX ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor	
22	or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or	
23	fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) N3 (injur* or	
24	impair* or imping* or sprain* or strain* or tear or torn))	10,622
25	S12 TX Arthralgi* or bursitis or capsulit* or epicondylgia* or epicondylit* or fasciopath* or	
26	fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or	
27	osteocondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or	
28	tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD	20,095
29	S11 S5 OR S10	91,140
30	S10 S8 AND S9	Display
31	S9 TI pain* OR AB pain*	Display
32	S8 S6 OR S7	Display
33	S7 (MH "Musculoskeletal Diseases") OR (MH "Cartilage Diseases+") OR (MH "Fasciitis+")	
34	OR (MH "Foot Diseases+") OR (MH "Golf Elbow") OR (MH "Heel Pain") OR (MH "Joint	
35	Diseases") OR (MH "Muscular Diseases") OR (MH "Arthralgia+") OR (MH "Bursitis+") OR	
36	(MH "Contracture+") OR (MH "Metatarsalgia") OR (MH "Shoulder Instability, Anterior") OR	
37	(MH "Shoulder Instability, Multidirectional") OR (MH "Shoulder Instability, Posterior") OR	
38	(MH "Synovitis")	Display
39	S6 (MH "Musculoskeletal System") OR (MH "Cartilage+") OR (MH "Fascia+") OR (MH	
40	"Ligaments+") OR (MH "Muscles+") OR (MH "Bone and Bones") OR (MH "Arm Bones+")	
41	OR (MH "Foot Bones+") OR (MH "Leg Bones+") OR (MH "Pelvic Bones+") OR (MH	
42	"Joints+")	Display
43	S5 S1 OR S2 OR S3 OR S4	Display
44	S4 (MH "Neck Pain")	Display
45	S3 (MH "Arthralgia+")	Display
46	S2 (MH "Compartment Syndromes") OR (MH "Anterior Compartment Syndrome") OR (MH	
47	"Ischemic Contracture")	Display
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3 S1 (MH "Arm Injuries+") OR (MH "Athletic Injuries+") OR (MH "Dislocations+") OR (MH
4 "Fractures+") OR (MH "Hand Injuries+") OR (MH "Leg Injuries+") OR (MH "Ligament
5 Injuries+") OR (MH "Neck Injuries+") OR (MH "Occupational-Related Injuries") OR (MH
6 "Soft Tissue Injuries+") OR (MH "Sprains and Strains+") OR (MH "Tendon Injuries+")
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8 Display
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11 PEDro, yields 645
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13 March 13, 2018
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15
16 Abstract & Title: acute
17 AND
18 Problem: pain
19 AND
20 Method: Clinical trial
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4 & 8
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#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	16

1			protocol amendments	
2	Sources	#5a	Indicate sources of financial or other support for the review	18
3				
4	Sponsor	#5b	Provide name for the review funder and / or sponsor	18
5				
6				
7	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s),	18
8	funder		if any, in developing the protocol	
9				
10				
11	Rationale	#6	Describe the rationale for the review in the context of what is	6
12			already known	
13				
14	Objectives	#7	Provide an explicit statement of the question(s) the review will	7
15			address with reference to participants, interventions,	
16			comparators, and outcomes (PICO)	
17				
18				
19				
20	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design,	8 & 9
21			setting, time frame) and report characteristics (such as years	
22			considered, language, publication status) to be used as	
23			criteria for eligibility for the review	
24				
25				
26				
27	Information	#9	Describe all intended information sources (such as electronic	8
28	sources		databases, contact with study authors, trial registers or other	
29			grey literature sources) with planned dates of coverage	
30				
31				
32	Search strategy	#10	Present draft of search strategy to be used for at least one	25-32
33			electronic database, including planned limits, such that it	
34			could be repeated	
35				
36				
37	Study records -	#11a	Describe the mechanism(s) that will be used to manage	9
38	data management		records and data throughout the review	
39				
40				
41	Study records -	#11b	State the process that will be used for selecting studies (such	9
42	selection process		as two independent reviewers) through each phase of the	
43			review (that is, screening, eligibility and inclusion in meta-	
44			analysis)	
45				
46				
47				
48	Study records -	#11c	Describe planned method of extracting data from reports	9 & 10
49	data collection		(such as piloting forms, done independently, in duplicate), any	
50	process		processes for obtaining and confirming data from investigators	
51				
52				
53	Data items	#12	List and define all variables for which data will be sought	9 & 10
54			(such as PICO items, funding sources), any pre-planned data	
55			assumptions and simplifications	
56				
57				
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1	Outcomes and	#13	List and define all outcomes for which data will be sought,	9 & 10
2	prioritization		including prioritization of main and additional outcomes, with	
3			rationale	
4				
5				
6	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	10
7	individual studies		individual studies, including whether this will be done at the	
8			outcome or study level, or both; state how this information will	
9			be used in data synthesis	
10				
11				
12				
13	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	10 & 11
14			synthesised	
15				
16				
17		#15b	If data are appropriate for quantitative synthesis, describe	10-14
18			planned summary measures, methods of handling data and	
19			methods of combining data from studies, including any	
20			planned exploration of consistency (such as I ² , Kendall's τ)	
21				
22				
23				
24		#15c	Describe any proposed additional analyses (such as	14
25			sensitivity or subgroup analyses, meta-regression)	
26				
27				
28		#15d	If quantitative synthesis is not appropriate, describe the type	N/A
29			of summary planned	
30				
31	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	14
32			publication bias across studies, selective reporting within	
33			studies)	
34				
35				
36				
37	Confidence in	#17	Describe how the strength of the body of evidence will be	14 & 15
38	cumulative		assessed (such as GRADE)	
39	evidence			
40				
41				

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 44 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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