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Preoperative opioid use and complications following total joint replacement: A protocol for a systematic review and meta-analysis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035377
Article Type:	Protocol
Date Submitted by the Author:	30-Oct-2019
Complete List of Authors:	Shadbolt, Cade; The University of Melbourne, Department of Surgery, St Vincent's Gould, Daniel; The University of Melbourne, Department of Surgery, St Vincent's Camacho, Ximena; The University of Melbourne, Melbourne School of Population and Global Health Knight, Josh; The University of Melbourne, Centre for Health Policy, Melbourne School of Population and Global Health Thuraisingam, Sharmala; The University of Melbourne, Department of Surgery, St Vincent's; The University of Melbourne, Department of General Practice Zhang, Yuting; The University of Melbourne, Melbourne Institute: Applied Economic and Social Research, Faculty of Business & Economics Dowsey, Michelle; University of Melbourne, Department of Surgery, St.Vincent's; St Vincent's Hospital, Melbourne, Department of Orthopaedics Choong, Peter; The University of Melbourne, Department of Surgery, St Vincent's ; St Vincent's Hospital, Melbourne, Department of Orthopaedics
Keywords:	SURGERY, Elbow & shoulder < ORTHOPAEDIC & TRAUMA SURGERY, Foot & ankle < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY

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Preoperative opioid use and complications following total joint replacement: A protocol for a systematic review and meta-analysis.

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Word count:

3117

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-035377 on 16 June 2020. Downloaded from <http://bmjopen.bmj.com/> on April 18, 2024 by guest. Protected by copyright.

ABSTRACT

Introduction:

Mounting evidence now indicates that preoperative opioid use is associated with an array of complications following total joint replacement (TJR). However, evidence of these risks remains fragmented. A comprehensive and well-integrated understanding of this body of evidence is necessary to appropriately inform treatment decisions, the allocation of limited healthcare resources, and the direction of future clinical research. The proposed systematic review and meta-analysis aims to identify and synthesize the available evidence of an association between opioid use prior to TJR and postoperative complications, categorized by complication type.

Methods and Analysis:

We will search MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science, and Google Scholar from inception to September 2019. Observational and experimental studies that compare either preoperative opioid users or chronic preoperative opioid users who have undergone elective total joint replacement (TJR) to opioid naïve TJR patients will be included. The primary outcomes will be postoperative complications, which will be categorized as either mortality, morbidity, or joint-related complications. The secondary outcomes will be persistent postoperative opioid use, readmission, and length of stay. Individual study quality will be assessed using the relevant NIH-NHLBI Study Quality Assessment Tools. Findings will be reported in narrative and tabular form, and, where possible, risk ratios (dichotomous outcomes) or standardized mean differences (continuous outcomes) will be reported with 95% confidence intervals. Where appropriate, random effect meta-analyses will be conducted for each outcome, and heterogeneity will be quantified using I^2 statistic. This study will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.

Ethics and dissemination:

Ethics approval will not be required as no primary or private data is being collected. Findings will be disseminated through peer-reviewed publication and presentation at academic conferences.

Protocol registration:

PROSPERO (Submitted - Awaiting confirmation)

Keywords: Opioid, Total Joint Replacement, Complications, Systematic review, Meta-analysis

Article Summary: Strengths and Limitations of this Study

- This systematic review will be the first to identify complications that are associated with preoperative opioid use among TJR patients.
- The comprehensive *a priori* categorization of complications will ensure that this review highlights specific areas in which further research is needed.
- The search strategy has been designed using key terms, synonyms, and database specific vocabulary across a range of carefully selected databases to ensure comprehensive coverage of both peer reviewed and grey literature.
- The recent nature of much of the research in this domain may limit the amount of data available for some of the pre-defined outcome categories.

BACKGROUND

Total joint replacement is a safe and effective surgery, which aims to restore physical function and offer long-term pain relief to patients suffering from severe arthritis.[1-3] In recent decades, the number of total joint replacements (TJR) performed each year has risen substantially. Between 2000 and 2014, the number of total hip replacement (THR) and total knee replacement (TKR) surgeries performed annually in the United States more than doubled.[4] Over a similar period, opioid use has become more prevalent among patients presenting for TJR. Data from Australia indicate that the prevalence of preoperative opioid use increased between 2001 and 2012 from 37% to 49% in TKR patients and 44% to 54% in THR patients.[5] In the United States, where opioid misuse has been declared a public health emergency,[6] this trend is likely even more pronounced; with one recent study reporting that more than 87% of commercially-insured TJR patients had received an opioid prescription in the year leading up to their procedure.[7]

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4 There is now mounting evidence that opioid use prior to TJR is associated with an array
5 of surgical complications.[8-11] Despite this, a number of recent reviews[12-14] have
6 failed to report that preoperative opioid use is associated with an increased risk of
7 certain serious complications among TJR patients. In a 2016 systematic review,
8 Kunutsor and colleagues did not report preoperative opioid use as a risk factor for
9 periprosthetic infections following TJR.[12] Similarly, a 2016 scoping review conducted
10 by Jasper and colleagues, which aimed to identify factors associated with revision
11 following TKR, did not identify preoperative opioid use as a relevant risk factor.[14]
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13 There is now evidence that preoperative opioid use places patients at an increased risk
14 of experiencing the specific outcomes examined in both of these reviews.[10][11] These
15 omissions are largely due to the relatively recent nature of much of the evidence linking
16 preoperative opioid use with these important complications. Nonetheless, this
17 underreporting within the review literature suggests that the risks associated with
18 preoperative opioid use among TJR patients remains underrecognized.
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32 In addition to being underreported in reviews examining specific complications, the
33 more general evidence of an association between preoperative opioid use and
34 complications following TJR remains fragmented. To date, no systematic reviews have
35 examined the evidence of such an association. The only systematic review specifically
36 examining the impact of preoperative opioid use on outcomes following TJR focused
37 exclusively on patient reported pain and function outcomes.[15] This review, which was
38 conducted by Goplen and colleagues,[15] found that preoperative opioid users
39 experienced worse pain and function improvements between 6 and 58 months following
40 TJR, when compared to opioid-naïve patients. While pain and function outcomes are
41 undoubtedly central to decisions made about TJR procedures,[16] prudent decision-
42 making requires that such factors be weighed against all risks associated with the
43 procedure.
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4 A comprehensive and well-integrated understanding of complications associated with
5 opioid use prior to TJR is necessary to appropriately inform treatment decisions, the
6 allocation of limited healthcare resources, and the direction of future clinical research.
7 Awareness of these potential complications also allows clinicians to appropriately inform
8 patients who are using opioids about the risks of their procedure. Importantly, such
9 awareness may also encourage surgeons and patients to treat preoperative opioid use
10 as a modifiable risk factor that can be targeted to improve the quality and safety of
11 surgical care. With these considerations in mind, the proposed systematic review and
12 meta-analysis seeks to identify and synthesize available evidence of an association
13 between opioid use prior to TJR and postoperative complications, categorized by
14 complication type.
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24 **METHODS AND ANALYSIS:**

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27 This protocol was developed in accordance with 'Preferred Reporting Items for
28 Systematic reviews and Meta-Analysis - Protocol' (PRISMA-P)[17, 18] and 'Meta-
29 analysis of Observational Studies in Epidemiology' (MOOSE)[19] guidelines. The review
30 has been prospectively registered with the PROSPERO database (registration number)
31 Throughout the process of conducting this review, disagreement will be resolved
32 through discussion between these independent reviewers (CS and DG) where possible.
33 When consensus cannot be achieved through discussion, a third author (MD) will be
34 consulted.
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43 **Criteria for consideration in this review.**

44 *Types of Studies*

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46 This systematic review will include both descriptive (e.g. case series, cross-sectional)
47 and analytic (e.g. retrospective cohort, prospective cohort, case-control) observational
48 studies, as well as experimental studies (e.g. randomized controlled trials, quasi-
49 experimental designs). Although we will include studies using experimental designs, we
50 expect that most – if not all – of the data will be drawn from observational studies. Case
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3 reports, editorials, commentaries, qualitative studies, and literature reviews will be
4 excluded. However, reference lists from relevant literature reviews identified in the initial
5 screening process will be searched to identify additional original studies. We will only
6 include studies published in English.
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10 11 *Type of Population*

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14 Adult patients (≥ 18 years of age) who have undergone elective total joint replacement
15 (TJR). Total hip, knee, shoulder, elbow, ankle, and wrist replacement patients will be
16 included in this review. Studies exclusively examining patients who have undergone
17 partial joint replacement will be excluded. In the instance that a study does not clearly
18 distinguish between total and partial joint replacement, the study will be included in the
19 primary analysis given that a vast majority of all such procedures are for total joint
20 replacements.[20, 21] The impact of including these studies will be tested through
21 sensitivity analyses. Studies specifically examining patients who have undergoing non-
22 elective TJR will be excluded. Study that do not clearly distinguish between elective and
23 non-elective procedures will be included in the primary analysis. The impact of including
24 these studies will also evaluated through sensitivity analyses. Studies of surgical
25 populations that include patients undergoing procedures other than joint replacement
26 will only be included only if sufficient data is available to isolate measures of association
27 for TJR patients.
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40 41 *Type of Exposure*

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44 The two exposures of interest are *preoperative opioid use* and *chronic preoperative*
45 *opioid use*. As there is no standard definition of preoperative opioid use in the literature,
46 we expect this concept to be characterized heterogeneously between studies. For this
47 reason, studies will be included in our analysis of preoperative opioid use if they report
48 that the patient has been prescribed opioids at any time prior to admission for TJR.
49 Studies will be excluded if they determine patients' exposure status based upon less
50 than 30 days of preoperative data. Informed by the *Centre for Disease Control's*
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4 recommendation that long-term opioid therapy be reviewed at least every three
5 months,[22] chronic preoperative opioid use will be defined as ongoing use for ≥ 90
6 days prior to presenting for surgery. Findings related to preoperative use and chronic
7 preoperative use will be reported and analyzed separately.
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11 Opioid use in the perioperative period (i.e. once a patient been admitted for surgery) will
12 not be considered a relevant exposure. Studies examining preemptive analgesia will
13 also be excluded, as will studies explicitly examining the impact of preoperative opioid
14 abuse, addiction, or dependence. To this end, studies specifically examining patients
15 who used buprenorphine or methadone before surgery will not be included, as these
16 medications are predominately prescribed for the treatment of opioid use disorder.[23]
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23 *Type of Comparison*

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26 The comparison of interest is adult (≥ 18 years of age) total joint replacement patients
27 who have not used or been prescribed opioids in the lead up to admission for surgery
28 (i.e. opioid naïve patients). Studies will only be included if they consider patients opioid
29 naïve based on at least the 30 days immediately before presenting for surgery. Studies
30 that only compare preoperative opioid use with the use of other medications (e.g.
31 benzodiazepines) will be excluded.
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38 *Types of Outcome Measure*

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41 The primary outcomes of interest in this systematic review are complications, which
42 provide a direct measure of the patient's physical or psychological health following the
43 indexed procedure. Informed by Australian national quality and safety measures[24] and
44 previously published work examining complications associated with preoperative
45 smoking[25] and alcohol consumption,[26] the primary outcomes will be categorized as
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- 1 • **Mortality:** Any measure of mortality within one year of the indexed procedure will
2 be included in our analysis; however, analyses of mortality will be stratified by the
3 timeframe examined (e.g. 30-days, 90-days, 1-year).
- 4 • **Morbidity:** Measures of morbidity occurring within either 30 or 90-days of the
5 indexed procedure will be categorized as: general complications, medication-
6 related complications, wound complications, general infections, pulmonary
7 complications, cardiovascular complications, neurological complications,
8 gastrointestinal complications, renal/urinary complication, falls resulting in
9 fracture or intracranial injury, unplanned returns to theatre or additional invasive
10 interventions, bleedings, unplanned ICU admissions, and other complications.
- 11 • **Joint-related complications:** Any complications that are specific to the TJR
12 procedure (e.g. revision, joint infection, or stiffness requiring manipulation under
13 anesthetic)[27, 28] will be reported separately where possible. As these
14 complications are necessarily tied to the indexed procedure, no time restrictions
15 will be placed on measures relating to these outcomes.

16 The secondary outcomes of interest for this review provide valuable, but indirect,
17 measures of the patient's course of recovery following the indexed procedure.

- 18 • **Persistent postoperative opioid use:** Any measure which includes patients
19 receiving a prescription of opioids \geq 90 days after the indexed procedure will be
20 included in the analysis. This was informed by the CDC's recommendation that
21 long-term opioid therapy be reviewed at least every three months.[22]
- 22 • **Unplanned readmission:** Measures of readmission within 90-days of discharge
23 will be included in our analysis; however, all analyses of readmission will be
24 stratified by the timeframe examined (e.g. 30-day, 90-day).
- 25 • **Length of stay:** Studies examining length of hospital stay following surgery will be
26 included in our analysis.

Despite the importance of information about pain and function to decisions regarding TJR, to avoid duplicating work done in a recent systematic review by Goplen and colleagues,[15] patient reported pain and function outcomes will be excluded from this review.

Search Strategy

A comprehensive literature search of MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science from inception to September 2019 will be conducted. These databases have been selected to maximize the coverage of the literature search.[29] The search strategy will be formulated by two authors (CS and DG) in consultation with an external research librarian. The search will be tailored to each database using keywords, database-specific vocabulary (e.g. Medical Subject Headings), and relevant Boolean operators to cover the following conceptual groups: (1) opioids; and (2) total joint replacement; and (3) risk or outcomes or complications or mortality or morbidity. See Table 1 for the full search MEDLINE search strategy. A narrower supplementary search will be conducted using Google Scholar, as this has been shown to regularly capture eligible studies not returned by other databases.[29, 30] Articles which referenced (“forward citation tracking”) or were referenced by (“backwards citation tracking”) included studies and relevant published literature reviews will be searched to identify additional eligible studies.[31]

Table 1: Full Medline Search Strategy via OVID

- 1 exp Narcotics/ or exp Analgesics, Opioid/ or opioid*.mp. or opiate*.mp. or narcotic*.mp.
- 2 exp Arthroplasty/ or (arthroplasty or joint replacement or shoulder replacement or knee replacement or hip replacement or elbow replacement or wrist replacement or ankle replacement).mp.
- 3 exp Treatment Outcome/ or exp "Outcome Assessment (Health Care)"/ or outcome*.mp.

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4 exp Health Risk Behaviors/ or exp Risk/ or exp Risk Factors/ or risk*.mp.
5 morbidity.mp. or exp Morbidity/ or mortality.mp. or exp Mortality/or exp
6 Intraoperative Complications/ or exp Postoperative Complications/ or
7 complication*.mp.
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11 **Final Search: 1 and 2 and (3 or 4 or 5)**
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14 15 16 **Data Collection and Management**

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18 To avoid issues with the export functionality of Google Scholar, Harzing's Publish or
19 Perish (V.7) will be used to extract relevant information from the supplementary search.
20 Covidence will be used for deduplication, screening, and data extraction. Statistical
21 analysis will be conducted using Review Manager software.
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26 27 **Study Selection**

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29 Two reviewers (CS and DG) will independently screen the titles and abstracts of all
30 items identified through the search process. After 10% of studies have been screened,
31 the selection process will be reviewed to ensure that eligibility criteria are consistently
32 applied. The full text documents of potentially relevant studies will then be compiled and
33 reviewed against the inclusion and exclusion criteria by two reviewers (CS and DG).
34 Forward and backward citation tracking of all studies that remain after full text screening
35 will be used to identify additional potentially eligible studies. The full text of studies
36 identified through this final stage of the search will then be independently assessed for
37 inclusion by two reviewers (CS and DG). The study selection process will be reported
38 using a PRISMA flow diagram.[32]
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48 49 **Data Extraction**

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51 Data will be extracted independently by two reviewers (CS and DG) using a
52 standardized data collection form. The following details will be extracted from all
53 included articles:
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- Publication details: First author, year of publication, title, publication venue
- Study design: Study design, data source, sample size, funding source.
- Clinical setting: Location, public/private/veterans' institution
- Population characteristics: Demographic information (e.g. age, sex, BMI), comorbidities
- Surgery type: Primary/revision/undefined, hip/knee/shoulder/elbow/ankle/wrist, indication for surgery, TJR clearly defined, elective TJR clearly defined.
- Exposure: Preoperative opioid use definition, prolonged preoperative opioid use definition.
- Outcomes: Outcome class, outcome definition
- Results summary: Relative risk or standard mean difference and 95% confidence intervals for each outcome measure, degree of effect size adjustment.

Where adjusted and unadjusted measures are reported for a given outcome, the most comprehensively adjusted outcome measures will be used. Where outcomes are measured at multiple time points, the effects measured at the longest relevant time points will be recorded. Missing values will be calculated whenever there is sufficient data available to do so. Study authors will be contacted to obtain missing data, and response rates will be reported in the published review.

Individual Study Quality Assessment

The quality of all included studies will be independently assessed by two reviewers (CS and DG) using the appropriate NIH/NHLBI *Study Quality Assessment Tool*.^[33] The appropriate tool will be determined for each included study based upon the research design that was used. These tools include items to evaluate potential flaws in study method or implementation, including sources of bias, study power, confounding, and other factors. In response to each item included in these tools, reviewers will select "yes," "no," or "cannot determine/not reported/not applicable". Responses to each of these items will inform a judgment of each study as either of "good," "fair," or "poor"

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4 quality. Where studies are deemed to be of poor quality, explicit justification will be
5 offered and reported in the published review.
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8 **Data synthesis and subgroup analysis.**

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10 The characteristics of all included studies will be reported in narrative and tabular form.
11 Where the outcomes reported are considered sufficiently similar from a clinical and
12 methodological perspective,[34] meta-analyses will be conducted for each of the
13 predefined primary and secondary outcome categories. In all instances, outcomes
14 associated with preoperative opioid use and chronic preoperative use will be analyzed
15 and reported separately. For data that can be meaningfully pooled, a random effect
16 model will be used for meta-analysis as we expect significant between study
17 heterogeneity.[35] For dichotomous outcomes, relative risk (RR) will be reported and
18 standardized mean difference (SMD) will be used for the analysis of continuous
19 outcome variables. 95% confidence intervals will be reported for all effect estimates.
20 Sensitivity analysis will explore the impact of including both unadjusted and adjusted
21 effect size estimates in our analysis, and wherever possible adjusted effect sizes will be
22 reported alongside overall pooled effect sizes. Sensitivity analyses will also be
23 conducted to evaluate the impact of including studies of imprecisely defined
24 populations. To account for expected heterogeneity, which will be assessed visually and
25 using the I^2 statistic, subgroup analyses will be conducted where possible. Planned
26 subgroup analyses include: geographic location, type of surgery, and preoperative
27 opioid use categorization. Where meta-analysis is deemed inappropriate for a given
28 outcome variable, the results will be included in a narrative synthesis. In the instance
29 that no studies have reported on an outcome relevant to one of the predefined outcome
30 categories, this will be explicitly reported during the narrative synthesis.
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50 **Meta-bias assessment**

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52 We have aimed to minimize the effect of publication bias on the findings of this review
53 by placing no restrictions on the inclusion of 'grey literature'. [36] Furthermore, our
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4 search strategy has been designed to ensure comprehensiveness by drawing upon a
5 database that is commonly overlooked by systematic reviewers (i.e. Google Scholar),
6 despite having been shown to be effective at capturing grey literature.[29, 30] To
7 investigate the potential residual effects of publication bias, funnel plots will be
8 generated for meta-analyses that include ten or more studies.[37] Where significant
9 asymmetry is detected in the funnel plot, potential sources of this asymmetry will be
10 explored and, if deemed appropriate, the trim and fill method may be used to account
11 for the possibility of publication bias.[37, 38]

19 **Confidence in cumulative evidence**

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21 Two reviewers (CS and DG) will independently assess the quality of cumulative
22 evidence in relation to each reported outcome measures using the Grades of
23 Recommendation, Assessment, Development and Evaluation (GRADE) approach.[39-
24 41] The five GRADE considerations – study limitations, imprecision, inconsistency,
25 indirectness, and publication bias – will be used to assess each study before reporting
26 the quality of evidence as high, moderate, low, or very low.[41] The results of the
27 cumulative quality assessment will be presented in a Summary of Findings table.[41,
28 42] Care will be taken to include all outcome categories specified in this protocol in this
29 table, to ensure that the absence of evidence relating to particular types of
30 complications is reported clearly and consistently.

41 **Ethics and dissemination**

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44 Ethics approval will not be required for the proposed study, as it draws on previously
45 published data and will not impact upon the privacy of any individual patients. The
46 results of the systematic review will be disseminated through publication in a peer-
47 reviewed journal, and through presentation at relevant academic conferences. It will
48 also be disseminated to members of the *Consortium Against the overuse of Opiates in*
49 *Surgery* (CAOS), which is a recently formed multinational initiative that aims to address
50 issues relating to opioid use among surgical patients.
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DISCUSSION

As it currently stands, the available research examining the impact of opioid use prior to TJR on postoperative complications remains fragmented. Not only does this mean that the scope of the available evidence is difficult to interpret, it has also resulted in some serious risks associated with opioid use prior to TJR potentially remaining underrecognized. The proposed systematic review and meta-analysis aims to provide some much-needed order and clarity to the growing body of research in this domain. By providing a comprehensive and well-integrated understanding of complications associated with opioid use prior to TJR, this review will allow clinicians to inform preoperative opioid users about the risks of their procedure more appropriately. The findings of the proposed review will also offer insight that is necessary if both clinicians and patients are to make prudent treatment decisions. Finally, and perhaps most importantly, the information gleaned from this review will clarify the extent to which targeting preoperative opioid use may improve the quality and safety of surgical care for patients undergoing total joint replacement.

Contributions:

All authors contributed to the conception and design of the protocol; CS wrote the first draft; All authors contributed to revising the manuscript for critically important intellectual content, and read and approved the submitted version. CS is the guarantor of this review.

Competing interests:

Dr. Dowsey reports personal fees from Pfizer and grants from Medacta, outside the submitted work; Dr. Choong reports personal fees from Stryker, Johnson & Johnson, and Kluwer, and grants from Medacta, outside the submitted work. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding:

This work was funded by a Melbourne School of Population & Global Health and Department of Surgery (Melbourne Medical School) Collaborative Research Grant, University of Melbourne. The funding organization had no input into the design of this protocol.

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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.

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In your methods section, say that you used the PRISMA-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.

			Page Number
Title			
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

1 **Registration**

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4 [#2](#) If registered, provide the name of the registry (such as 2

5 PROSPERO) and registration number

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10 **Authors**

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13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all 1

14 protocol authors; provide physical mailing address of

15 corresponding author

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20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the 10

21 guarantor of the review

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26 **Amendments**

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29 [#4](#) If the protocol represents an amendment of a previously n/a

30 completed or published protocol, identify as such and list

31 changes; otherwise, state plan for documenting important

32 protocol amendments

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39 **Support**

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42 **Sources** [#5a](#) Indicate sources of financial or other support for the review 10

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45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor 10

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48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), 10

49 funder if any, in developing the protocol

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53 **Introduction**

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56 **Rationale** [#6](#) Describe the rationale for the review in the context of what is 3-4

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

Confidence in [#17](#) Describe how the strength of the body of evidence will be
cumulative assessed (such as GRADE)
evidence

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

BMJ Open

Preoperative opioid use and complications following total joint replacement: A protocol for a systematic review and meta-analysis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035377.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Apr-2020
Complete List of Authors:	Shadbolt, Cade; The University of Melbourne, Department of Surgery, St Vincent's Gould, Daniel; The University of Melbourne, Department of Surgery, St Vincent's Camacho, Ximena; The University of Melbourne, Centre for Digital Transformation of Health, Faculty of Medicine, Dentistry and Health Sciences Knight, Josh; The University of Melbourne, Centre for Health Policy, Melbourne School of Population and Global Health Rele, Siddharth; The University of Melbourne, Department of Surgery, St Vincent's; The University of Melbourne, Melbourne Medical School Thuraisingam, Sharmala; The University of Melbourne, Department of Surgery, St Vincent's; The University of Melbourne, Department of General Practice Zhang, Yuting; The University of Melbourne, Melbourne Institute: Applied Economic and Social Research, Faculty of Business & Economics Dowsey, Michelle; University of Melbourne, Department of Surgery, St.Vincent's; St Vincent's Hospital, Melbourne, Department of Orthopaedics Choong, Peter; The University of Melbourne, Department of Surgery, St Vincent's ; St Vincent's Hospital, Melbourne, Department of Orthopaedics
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Pharmacology and therapeutics, Epidemiology
Keywords:	SURGERY, Elbow & shoulder < ORTHOPAEDIC & TRAUMA SURGERY, Foot & ankle < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY

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4 1 **Preoperative opioid use and complications following total joint replacement:**
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28 **Word count:** 3790

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For peer review only

BMJ Open: first published as 10.1136/bmjopen-2019-035377 on 16 June 2020. Downloaded from <http://bmjopen.bmj.com/> on April 18, 2024 by guest. Protected by copyright.

31 ABSTRACT

32 Introduction:

33 Mounting evidence now indicates that preoperative opioid use is associated with an
34 array of complications following total joint replacement (TJR). However, evidence of
35 these risks remains fragmented. A comprehensive and well-integrated understanding of
36 this body of evidence is necessary to appropriately inform treatment decisions, the
37 allocation of limited healthcare resources, and the direction of future clinical research.
38 The proposed systematic review and meta-analysis aims to identify and synthesize the
39 available evidence of an association between opioid use prior to TJR and postoperative
40 complications, categorized by complication type.

41 Methods and Analysis:

42 We will search MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science from
43 inception to April 2020. Observational and experimental studies that compare
44 preoperative opioid users who have undergone elective total joint replacement (TJR) to
45 opioid naïve TJR patients will be included. The primary outcomes will be postoperative
46 complications, which will be categorized as either mortality, morbidity, or joint-related
47 complications. The secondary outcomes will be persistent postoperative opioid use,
48 readmission, and length of stay. Individual study quality will be assessed using the
49 relevant NIH-NHLBI Study Quality Assessment Tools. Findings will be reported in
50 narrative and tabular form, and, where possible, odds ratios (dichotomous outcomes) or
51 standardized mean differences (continuous outcomes) will be reported with 95%
52 confidence intervals. Where appropriate, random effect meta-analyses will be
53 conducted for each outcome, and heterogeneity will be quantified using the I^2 statistic
54 and Cochran's Q test. This study will be reported in accordance with the Preferred
55 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-
56 analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.

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4 57 **Ethics and dissemination:**

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6 58 Ethics approval will not be required as no primary or private data is being collected.
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8 59 Findings will be disseminated through peer-reviewed publication and presentation at
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10 60 academic conferences.

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12 61 **Protocol registration:**

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15 62 PROSPERO (CRD42020153047)
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20 64 **Keywords:** Opioid, Total Joint Replacement, Complications, Systematic review, Meta-
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22 65 analysis
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Article Summary: Strengths and Limitations of this Study

- This systematic review will be the first to identify complications that are associated with preoperative opioid use among TJR patients.
- The comprehensive *a priori* categorization of complications will ensure that this review highlights specific areas in which further research is needed.
- The search strategy has been designed using key terms, synonyms, and database specific vocabulary across a range of carefully selected databases to ensure comprehensive coverage of both peer reviewed and grey literature.
- The recent nature of much of the research in this domain may limit the amount of data available for some of the pre-defined outcome categories.
- As most included studies are expected to rely upon observational study methods, the strength of the conclusions drawn from this review will be limited by the quality of the evidence presented in the included studies.

68

69 BACKGROUND

70 Total joint replacement is a safe and effective surgery, which aims to restore physical
71 function and offer long-term pain relief to patients suffering from severe arthritis.[1-3] In
72 recent decades, the number of total joint replacements (TJR) performed each year has
73 risen substantially. Between 2000 and 2014, the number of total hip replacement (THR)
74 and total knee replacement (TKR) surgeries performed annually in the United States
75 more than doubled.[4] Over a similar period, opioid use has become more prevalent
76 among patients presenting for TJR. Data from Australia indicate that the prevalence of
77 preoperative opioid use increased between 2001 and 2012 from 37% to 49% in TKR
78 patients and 44% to 54% in THR patients.[5] In the United States, where opioid misuse
79 has been declared a public health emergency,[6] this trend is likely even more
80 pronounced; with one recent study reporting that more than 87% of commercially-

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4 81 insured TJR patients had received an opioid prescription in the year leading up to their
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6 82 procedure.[7]
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8 83 There is now mounting evidence that opioid use prior to TJR is associated with an array
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10 84 of surgical complications.[8-14] In 2017, Ben-Ari and colleagues were among the first to
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12 85 report that chronic opioid use was associated with an increased risk of early revision
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14 86 following TKR.[8] A study conducted by Bell and colleagues, published in 2018, was the
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16 87 first to highlight that preoperative opioid use may be a risk factor for peri-prosthetic
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18 88 infection following TJR.[9] Several other recent studies have supported these findings
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20 89 [10-12] while also demonstrating links between opioid use prior to TJR and opioid
21
22 90 overdose,[10] systemic infection,[11] unplanned readmission,[12] postoperative
23
24 91 delirium,[13] and in-hospital complications.[14] Given the recency of these findings, the
25
26 92 evidence of an association between preoperative opioid use and complications following
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28 93 TJR remains fragmented. To date, no systematic review has examined the evidence of
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30 94 such an association, which may be contributing to risks associated with preoperative
31
32 95 opioid use being under-recognized. The only systematic review specifically examining
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34 96 the impact of preoperative opioid use on outcomes following TJR focused exclusively on
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36 97 patient reported pain and function outcomes.[15] This review, which was conducted by
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38 98 Goplen and colleagues,[15] found that preoperative opioid users experienced worse
39
40 99 pain and function improvements between 6 and 58 months following TJR, when
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42 100 compared to opioid-naïve patients. While pain and function outcomes are undoubtedly
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44 101 central to decisions made about TJR procedures,[16] prudent decision-making requires
45
46 102 that such factors be weighed against all risks associated with the procedure.
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49 103 A comprehensive and well-integrated understanding of complications associated with
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51 104 opioid use prior to TJR is necessary to appropriately inform treatment decisions, the
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53 105 allocation of limited healthcare resources, and the direction of future clinical research.
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55 106 Awareness of these potential complications also allows clinicians to appropriately inform
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4 107 patients who are using opioids about the risks of their procedure. Importantly, such
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6 108 awareness may also encourage surgeons and patients to treat preoperative opioid use
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8 109 as a modifiable risk factor that can be targeted to improve the quality and safety of
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10 110 surgical care. With these considerations in mind, the proposed systematic review and
11
12 111 meta-analysis seeks to identify and synthesize available evidence of an association
13
14 112 between opioid use prior to TJR and postoperative complications, categorized by
15
16 113 complication type.

17 114 **METHODS AND ANALYSIS:**

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19
20 115 This protocol was developed in accordance with 'Preferred Reporting Items for
21
22 116 Systematic reviews and Meta-Analysis - Protocol' (PRISMA-P)[17, 18] and 'Meta-
23
24 117 analysis of Observational Studies in Epidemiology' (MOOSE)[19] guidelines. The review
25
26 118 has been prospectively registered with the PROSPERO database (CRD42020153047)

27 28 119 **Criteria for consideration in this review.**

29 30 31 120 *Types of Studies*

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33 121 This systematic review will include both descriptive (e.g. case series, cross-sectional)
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35 122 and analytic (e.g. retrospective cohort, prospective cohort, case-control) observational
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37 123 studies, as well as experimental studies (e.g. randomized controlled trials, quasi-
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39 124 experimental designs). Although we will include studies using experimental designs, we
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41 125 expect that the majority of the data will be drawn from observational studies. Studies
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43 126 reported in conference abstracts and other forms of grey literature will also be included
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45 127 in this review. Case reports, editorials, commentaries, qualitative studies, and literature
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47 128 reviews will be excluded. However, reference lists from relevant literature reviews
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49 129 identified in the initial screening process will be searched to identify additional original
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51 130 studies. We will only include studies published in English.

52 53 131 *Type of Population*

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4 132 The population of interest will be adult patients (≥ 18 years of age) who have undergone
5 133 elective total joint replacement. Total hip, knee, shoulder, elbow, ankle, and wrist
6 134 replacement patients will be included in this review. Studies exclusively examining
7 135 patients who have undergone partial joint replacement will be excluded. In the instance
8 136 that a study does not clearly distinguish between total and partial joint replacement, the
9 137 study will be included in the primary analysis given that a vast majority of all such
10 138 procedures are for total joint replacements.[20, 21] The impact of including these
11 139 studies will be tested through sensitivity analyses. Studies specifically examining
12 140 patients who have undergone non-elective TJR will be excluded. Studies that do not
13 141 clearly distinguish between elective and non-elective procedures will be included in the
14 142 primary analysis. The impact of including these studies will also be evaluated through
15 143 sensitivity analyses. Studies of surgical populations that include patients undergoing
16 144 procedures other than TJR will be included only if sufficient data is available to isolate
17 145 measures of association for TJR patients.

146 *Type of Exposure*

147 The two exposures of interest are *preoperative opioid use* and *chronic preoperative*
148 *opioid use*. As there is no standard definition of preoperative opioid use in the literature,
149 we expect this concept to be characterized heterogeneously between studies. For this
150 reason, studies will be included in our analysis of preoperative opioid use if they report
151 that the patient has been prescribed opioids at any time prior to admission for TJR.
152 Studies that rely upon patient reporting to identify preoperative opioid exposure will be
153 included in this more inclusive exposure group, unless patients specifically reported
154 chronic preoperative opioid use. Informed by the *Centre for Disease Control's*
155 recommendation that long-term opioid therapy be reviewed at least every three
156 months,[22] chronic preoperative opioid use will be defined as ongoing use for ≥ 90
157 days prior to presenting for surgery. Given the lack of a common definition, studies that
158 define chronic use more restrictively than this (e.g. by requiring 12 months of
159 preoperative use) will be included in our analyses of chronic use. The impact of different

160 definitions of chronic use will be assessed in sub-group analyses where possible, as will
161 the inclusion of studies relying on patient reported exposure status. Findings related
162 specifically to chronic preoperative use will be reported and analyzed separately to
163 findings related to preoperative use more generally.

164 Opioid use in the perioperative period (i.e. once a patient has been admitted for
165 surgery) will not be considered a relevant exposure. Studies examining preemptive
166 analgesia will also be excluded, as will studies explicitly examining the impact of
167 preoperative opioid abuse, addiction, or dependence. To this end, studies will be
168 excluded if they specifically examine patients who have been prescribed buprenorphine
169 or methadone to treat opioid use disorder before surgery.[23]

170 *Type of Comparison*

171 The comparison of interest is adult (≥ 18 years of age) total joint replacement patients
172 who have not used or been prescribed opioids in the lead up to admission for surgery
173 (i.e. opioid naïve patients). Studies that only compare preoperative opioid use with the
174 use of other medications (e.g. benzodiazepines) will be excluded.

175 *Types of Outcome Measure*

176 The primary outcomes of interest in this systematic review are complications, which
177 provide a direct measure of the patient's physical or psychological health following the
178 index procedure. Informed by Australian national quality and safety measures[24] and
179 previously published work examining complications associated with preoperative
180 smoking[25] and alcohol consumption,[26] the primary outcomes will be categorized as
181 follows:

- 182 • **Mortality:** Any measure of mortality within one year of the index procedure will be
183 included in our analysis; however, analyses of mortality will be stratified by the
184 timeframe examined (e.g. 30-days, 90-days, 1-year).

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4 185 • **Morbidity:** Measures of morbidity occurring within either 30 or 90-days of the
5 186 index procedure will be categorized as: general complications, medication-
6 187 related complications, wound complications, general infections, pulmonary
7 188 complications, cardiovascular complications, neurological complications,
8 189 gastrointestinal complications, renal/urinary complication, falls resulting in
9 190 fracture or intracranial injury, unplanned returns to theatre or additional invasive
10 191 interventions, bleedings, unplanned ICU admissions, and other complications.
11 192 • **Joint-related complications:** Any complications that are specific to the TJR
12 193 procedure (e.g. revision, joint infection, or stiffness requiring manipulation under
13 194 anaesthesia)[27, 28] will be reported separately where possible. As these
14 195 complications are necessarily tied to the index procedure, no time restrictions will
15 196 be placed on measures relating to these outcomes.

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27 197 The secondary outcomes of interest for this review provide valuable, but indirect,
28 198 measures of the patient's course of recovery following the index procedure.

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31 199 • **Persistent postoperative opioid use:** Any measure that includes patients receiving
32 200 a prescription of opioids ≥ 90 days after the index procedure will be included in
33 201 the analysis. This was informed by the CDC's recommendation that long-term
34 202 opioid therapy be reviewed at least every three months.[22]
35 203 • **Unplanned readmission:** Measures of readmission within 90-days of initial
36 204 discharge will be included in our analysis; however, all analyses of readmission
37 205 will be stratified by the timeframe examined (e.g. 30-day, 90-day).
38 206 • **Length of stay:** Studies examining length of hospital stay following surgery will be
39 207 included in our analysis.

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49 208 Despite the importance of information about pain and function to decisions regarding
50 209 TJR, to avoid duplicating work done in a recent systematic review by Goplen and
51 210 colleagues,[15] patient reported pain and function outcomes will be excluded from this
52 211 review.

212 Search Strategy

213 A comprehensive literature search of MEDLINE, EMBASE, CINAHL, PsycINFO, and
214 Web of Science from inception to April 2020 will be conducted. These databases have
215 been selected to maximize the coverage of the literature search.[29] The search
216 strategy has been formulated in consultation with two external research librarians. The
217 search will be tailored to each database using keywords, database-specific vocabulary
218 (e.g. Medical Subject Headings), and relevant Boolean operators to cover the
219 conceptual groups “opioids” (i.e. the exposure of interest) and “total joint replacement”
220 (i.e. the population of interest). In accordance with widely accepted
221 recommendations,[30] this strategy does not aim to narrow the scope of the search by
222 including specific conceptual groups for the outcomes or comparisons of interest. This
223 will ensure that the search strategy is sufficiently sensitive given the breadth of
224 outcomes that we are seeking to include in this review and the lack of an established
225 lexicon to describe the comparison of interest. See the supplementary materials for
226 details of the full search strategy.

227 A narrower set of supplementary searches will be conducted using Google Scholar, as
228 this has been shown to regularly capture eligible studies not returned by other
229 databases.[29, 31] To account for difficulties with replicating searches conducted in
230 Google Scholar, all results from this search that were not returned by our searches of
231 other databases will be reported in a supplement to the published review. Articles which
232 referenced (“forward citation tracking”) or were referenced by (“backwards citation
233 tracking”) included studies and relevant published literature reviews will be searched to
234 identify additional eligible studies.[32]

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236 Data Collection and Management

237 To avoid issues with the export functionality of Google Scholar, Harzing’s Publish or
238 Perish (V.7) will be used to extract relevant information from the supplementary search.

239 DistillSR will be used for deduplication, screening, and data extraction. Statistical
240 analysis will be conducted using Stata (V.16). Three reviewers (CS, DG and SR) will be
241 involved in the screening, study selection, data extraction, and quality assessment
242 process. Each study will be independently assessed by two of these reviewers at each
243 stage of this process. Disagreement will be resolved through discussion between these
244 reviewers where possible. When consensus cannot be achieved through discussion, a
245 fourth author (MD) will be consulted. Inter-rater agreement (kappa statistics) on the
246 study selection process will be reported.[30]

247 **Study Selection**

248 The titles and abstracts of all items identified through the search process will be
249 independently screened. After 10% of studies have been screened, the selection
250 process will be reviewed to ensure that eligibility criteria are consistently applied. The
251 full text documents of potentially relevant studies will then be compiled and reviewed
252 against the eligibility criteria. Forward and backward citation tracking of all studies that
253 remain after full text screening will be used to identify additional potentially eligible
254 studies. The full text of studies identified through this final stage of the search will then
255 be assessed for inclusion. The study selection process will be reported using a PRISMA
256 flow diagram.[33]

257 **Data Extraction**

258 Data will be extracted using a standardized data collection form. The following details
259 will be extracted from all included articles:

- 260 - Publication details: Authors, year of publication, title, publication venue
- 261 - Study design: Study design, data source(s), sample size, funding source.
- 262 - Clinical setting: Location (e.g. public/private/veterans' institution)
- 263 - Population characteristics: Demographic information (e.g. age, sex, BMI),
- 264 comorbidities

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4 265 - Surgery type: Primary/revision/undefined, hip/knee/shoulder/elbow/ankle/wrist,
5 266 indication for surgery, TJR clearly defined, elective TJR clearly defined.
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7 267 - Exposure: Preoperative opioid use definition, chronic preoperative opioid use
8 definition.
9 268
10 269 - Outcomes: Outcome class, outcome definition.
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12 270 - Results summary: Odd ratio or standard mean difference and 95% confidence
13 intervals for each outcome measure, use of univariate/multivariate analysis,
14 271 variables included in multivariate analysis.
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19 274 Where adjusted and unadjusted measures are reported for a given outcome, the most
20 275 comprehensively adjusted outcome measures will be used. Where outcomes are
21 276 measured at multiple time points, the effects measured at the longest relevant time
22 277 points will be recorded. Missing values will be calculated whenever there is sufficient
23 278 data available to do so. Study authors will be contacted to obtain missing data, and
24 279 response rates will be reported in the published review.
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31 280 **Individual Study Quality Assessment**

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34 281 The quality of all included studies will be assessed using the appropriate NIH/NHLBI
35 282 *Study Quality Assessment Tool*.^[34] The appropriate tool will be determined for each
36 283 included study based upon the research design that was used. These tools include
37 284 items to evaluate potential flaws in study methodology or implementation, including
38 285 sources of bias, study power, confounding, and other factors. In response to each item
39 286 included in these tools, reviewers will select "yes," "no," or "cannot determine/not
40 287 reported/not applicable". Responses to each of these items will inform a judgment of
41 288 each study as being of either "good," "fair," or "poor" quality. Where studies are deemed
42 289 to be of poor quality, explicit justification will be offered and reported in the published
43 290 review.
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53 291 **Data synthesis and subgroup analysis.**

292 Where the outcomes reported are considered sufficiently similar from a clinical and
293 methodological perspective, and where sufficient data is available to calculate a
294 common effect size,[30] meta-analyses will be conducted for each of the predefined
295 primary and secondary outcome categories. The primary meta-analyses reported for
296 each outcome will only include adjusted effect sizes as residual confounding is likely to
297 significantly impact unadjusted estimates. Outcomes associated with preoperative
298 opioid use and chronic preoperative use will be analyzed and reported separately. For
299 data that can be meaningfully pooled, a random effect model will be used for meta-
300 analysis as we expect significant between study heterogeneity.[35] For dichotomous
301 outcomes, odds ratios (OR) will be reported. Standardized mean difference (SMD) will
302 be used for the analysis of continuous outcome variables. 95% confidence intervals will
303 be reported for all effect estimates. Where outcomes are reported as risk ratios without
304 sufficient data available to manually compute the odds ratio, the odds ratio will be
305 computed using the formula described by Zhang and Yu.[36] The characteristics of all
306 eligible studies, including those not suitable for meta-analysis, will be reported in
307 narrative and tabular form.

308 Sensitivity analyses will explore the impact of including both unadjusted and adjusted
309 effect size estimates in our meta-analyses, and assess the impact of including studies
310 that rely on patient reported measures of opioid exposure. Sensitivity analyses will also
311 be conducted to evaluate the impact of including studies of imprecisely defined
312 populations (i.e. where it is not clear if the population also contains partial or non-
313 elective joint replacement patients). Heterogeneity will be assessed using the I^2 statistic
314 and Cochran's Q test. An I^2 statistic of greater than 50% will trigger investigation of
315 potential causes of heterogeneity through subgroup analyses.[30] Planned subgroup
316 analyses will be based on differences in study quality, geographic location, type of
317 surgery, and opioid exposure definitions. In the instance that no studies have reported
318 on an outcome relevant to one of the predefined outcome categories, this will be
319 explicitly reported in the narrative synthesis.

320 **Meta-bias assessment**

321 We have aimed to minimize the effect of publication bias on the findings of this review
322 by placing no restrictions on the inclusion of 'grey literature'.^[37] Furthermore, our
323 search strategy has been designed to ensure comprehensiveness by drawing upon a
324 database that is commonly overlooked by systematic reviewers (i.e. Google Scholar),
325 despite having been shown to be effective at capturing grey literature.^[31] To investigate
326 the potential residual effects of publication bias, funnel plots will be generated for meta-
327 analyses that include ten or more studies.^[34] Where significant asymmetry is detected
328 in the funnel plot, potential sources of this asymmetry will be explored and, if deemed
329 appropriate, the trim and fill method may be used to account for the possibility of
330 publication bias.^[30, 38]

331 **Confidence in cumulative evidence**

332 The quality of cumulative evidence in relation to each reported outcome measures will
333 be assessed using the Grades of Recommendation, Assessment, Development and
334 Evaluation (GRADE) approach.^[39-41] The five GRADE considerations – study
335 limitations, imprecision, inconsistency, indirectness, and publication bias – will be used
336 to assess each study before reporting the quality of evidence as high, moderate, low, or
337 very low.^[41] The results of the cumulative quality assessment will be presented in a
338 Summary of Findings table.^[41, 42] Care will be taken to include all outcome categories
339 specified in this protocol in this table, to ensure that the absence of evidence relating to
340 particular types of complications is reported clearly and consistently.

341 **Ethics and dissemination**

342 Ethics approval will not be required for the proposed study, as it draws on previously
343 published data and will not impact upon the privacy of any individual patients. The
344 results of the systematic review will be disseminated through publication in a peer-
345 reviewed journal, and through presentation at relevant academic conferences. It will
346 also be disseminated to members of the *Consortium Against the overuse of Opioids in*

347 *Surgery* (CAOS), which is a recently formed multinational initiative that aims to address
348 issues relating to opioid use among surgical patients.

349 **Patient and Public Involvement:**

350 No patients were involved in the planning or conduct of this review. The findings of this
351 review will be shared with members of the Centre for Research Excellence in Total Joint
352 Replacement's newly formed Arthritis Consumer and Community Involvement
353 Programme (ACCIP). Translation of these findings into future clinical trials will be
354 informed by members of ACCIP.

355 **DISCUSSION**

356 As it currently stands, the available research examining the impact of opioid use prior to
357 TJR on postoperative complications remains fragmented. Not only does this mean that
358 the scope of the available evidence is difficult to interpret, it has also potentially led to
359 serious risks associated with opioid use prior to TJR remaining underrecognized. The
360 proposed systematic review and meta-analysis aims to provide some much-needed
361 order and clarity to the growing body of research in this domain. By providing a
362 comprehensive and well-integrated understanding of complications associated with
363 opioid use prior to TJR, this review will allow clinicians to more appropriately inform
364 potential TJR patients who have been prescribed opioids about the risks associated
365 with their procedure. The findings of the proposed review will also offer insights that are
366 necessary for both clinicians and patients to make prudent treatment decisions.
367 However, as is the case with all systematic reviews, the strength of the conclusions that
368 can be drawn from this review will be determined by the quality of the available
369 evidence. Although we will only include adjusted estimates in our primary meta-
370 analyses, the possibility of residual confounding (e.g. confounding by indication) in the
371 included studies may limit the strength of the conclusions that can be drawn about the
372 links between the exposures and outcomes of interest.[43]Finally, and perhaps most

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4 373 importantly, the knowledge gleaned from this review will clarify the extent to which
5 374 targeting preoperative opioid use may improve the quality and safety of surgical care for
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7 375 patients undergoing total joint replacement.
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11 377 **Contributions:**

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15 378 CS, DG, XC, JK, ST, YZ, MD, PC originally conceived of this project. CS, DG, MD, PC
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17 379 initially refined the scope of the project. CS wrote the first draft. CS, DG, XC, JK, SR,
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19 380 ST, YZ, MD, PC contributed to revising various drafts of the protocol for critically
20
21 381 important intellectual content. ST provided statistical advice on the final protocol. CS,
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23 382 SR, and DG were responsible for designing the final search strategy. CS, DG, XC, JK,
24
25 383 SR, ST, YZ, MD, PC read and approved the submitted version. CS will be the guarantor
26
27 384 of this review.
28

29 385 **Competing interests:**

30
31 386 Dr. Dowsey reports personal fees from Pfizer and grants from Medacta, outside the
32
33 387 submitted work; Dr. Choong reports personal fees from Stryker, Johnson & Johnson,
34
35 388 and Kluwer, and grants from Medacta, outside the submitted work. All other authors
36
37 389 declare that the research was conducted in the absence of any commercial or financial
38
39 390 relationships that could be construed as a potential conflict of interest.
40
41

42 391 **Funding:**

43
44
45 392 This work was funded by a Melbourne School of Population & Global Health and
46
47 393 Department of Surgery (Melbourne Medical School) Collaborative Research Grant,
48
49 394 University of Melbourne. The funding organization had no input into the design of this
50
51 395 protocol.
52

53 396 **Acknowledgements:**

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4 397 We are thankful to Anna Lovang, Senior Research Librarian from the Carl de Gruchy
5
6 398 Library, for advice and feedback on the initial draft of our search strategy. We are also
7
8 399 grateful to Patrick Condron, Senior Liaison Librarian at the Brownless Biomedical
9
10 400 Library, for detailed guidance on the construction of the final search strategy. CS
11
12 401 acknowledges being supported by an Australian Government Research Training
13
14 402 Program Scholarship.

15 403

16 404

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Supplementary Material

Planned search strategies for primary databases

#	Medline
1	exp Analgesics, Opioid/
2	exp Narcotics/
3	(opiod* or opiate* or narcotic*).mp.
4	(Bezitramide or Burgodin or Bezitramida or Buprenorphine or Buprenorfina or Buprenex or Prefin or Subutex or Buprex or Temgesic or Butorphanol or Butorfanol or Beforal or Moradol or Stadol or Torbugesic or Apo-Butorphanol or Dolorex or Codeine or Codeinum or Methylmorphine or N-Methylmorphine or Isocodeine or Ardinex or Dextromoramide or Palphium or Pyrrolamidol or Pyrrolamidol or D-Moramide or D Moramide or Palfium or Dextropropoxyphene or Propoxyphene or D-Propoxyphene or Darvon or Dezocine or Dihydrocodeine or paramol or Rikodeine or Tiamon or Tosidrin or Contugesic or Dicodin or Paracodin or Paracodina or Fentanyl or Fentanil or Phentanyl or Fentanest or Sublimaze or Transmucosal or Duragesic or Durogesic or Fentora or Hydrocodone or Dihydrocodeinone or Hydrocodon or Hydrocone or Hydroconum or Idrocodone or Dicodid or Robidone or Hycodan or Hycon or Hydromorphone or Dihydromorphinone or Dimorphone or Hydromorphon or Palladone or Laudacon or Dilaudid or Ketobemidone or Cetobemidon or Levorphanol or Levodroman or Levorphan or Levo-Dromoran or Levo Dromoran or LevoDromoran or L-Dromoran or L Dromoran or Meperidine or Isonipecaïne or Pethidine or Isonipecaïn or Dolsin or Dolosal or Dolin or Operidine or Dolantin or Dolargan or Lidol or Lydol or Demerol or Dolcontral or Meptazinol or Meptid or Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict or Methadyl acetate or Acetylmethadol or Alphacetylmethadol or Amidolacetate or Dimepheptanol or Levomethadyl or Levoacetylmethadol or Levomethadyl or Methadol or Acemethadone or Morphine or Morphia or Morphium or Contin or Oramorph or Duramorph or Nalbuphine or Nubain or Nicomorphine or Vilan or Opium or Papaveretum or Omnopon or Pantopon or Oxycodone or Dihydrohydroxycodone or Dihydroxycodone or Oxymorphone or Dihydrohydroxymorphinone or Dihydroxymorphinone or Oximorphonum or Numorphan or Opana or Pentazocine or Talwin or Fortral or Lexir or Phenazocine or Phenethylazocine or Phenbenzorphin or Narphen or Piritramide or Piritramid or Dipidolor or Dipydolor or Tapentadol or Nucynta or Tilidine or Tilidate or Tilidin or Valoron or Valerone or Tramadol* or Tramundin or Biodalgic or Jutadol or MTW-Tramadol or MTWTramadol or Nobligan or Prontofort or Zytram or Takadol or Theradol or Tiral or Topalgic or Tradol or Tradol-Puren or TradolPuren or Tradonal or Traigiol or Trama AbZ or Trama KD or Trama-Dorsch or Trama Dorsch or TramaDorsch or Biokanol or Tramabeta or Tramadin or Tramadoc or Ranitidin or Trama or Trasedal or Ultram or Xymel or Zamudol or Zumalgic or Zydol or Tramadura or Tramagetic or Tramagit or Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol).mp.
5	1 or 2 or 3 or 4
6	Arthroplasty, Replacement/
7	Arthroplasty, Replacement, Ankle/
8	Arthroplasty, Replacement, Elbow/
9	Arthroplasty, Replacement, Hip/
10	Arthroplasty, Replacement, Knee/
11	Arthroplasty, Replacement, Shoulder/
12	((joint or shoulder or knee or hip or elbow or wrist or ankle) adj3 (replacement* or arthroplast*)).mp.
13	6 or 7 or 8 or 9 or 10 or 11 or 12
14	5 and 13
#	Embase
1	exp narcotic analgesic agent/
2	exp narcotic agent/

1
2
3 (opioid* or opiate* or narcotic*).mp.
4
5 4 (Bezitramide or Burgodin or Bezitramida or Buprenorphine or Buprenorfina or Buprenex or Pefin or Subutex or Buprex or Temgesic or
6 Butorphanol or Butorfanol or Beforal or Moradol or Stadol or Torbugesic or Apo-Butorphanol or Dolorex or Codeine or Codeinum or
7 Methylnorphine or N-Methylnorphine or Isocodeine or Ardinex or Dextromoramide or Palphium or Pyrrolamidol or Pyrrolamidol or
8 D-Moramide or D Moramide or Palfium or Dextropropoxyphene or Propoxyphene or D-Propoxyphene or Darvon or Dezocine or
9 Dihydrocodeine or paramol or Rikodeine or Tiamon or Tosidrin or Contugesic or Dicodin or Paracodin or Paracodina or Fentanyl or
10 Fentanil or Phentanyl or Fentanest or Sublimaze or Transmucosal or Duragesic or Durogesic or Fentora or Hydrocodone or
11 Dihydrocodeinone or Hydrocodon or Hydrocone or Hydroconum or Idrocodone or Dicodid or Robidone or Hycodan or Hycon or
12 Hydromorphone or Dihydromorphinone or Dimorphone or Hydromorphon or Palladone or Laudacon or Dilaudid or Ketobemidone or
13 Cetobemidon or Levorphanol or Levodroman or Levorphan or Levo-Dromoran or Levo Dromoran or LevoDromoran or L-Dromoran or
14 L Dromoran or Meperidine or Isonipecaine or Pethidine or Isonipecaïn or Dolsin or Dolosal or Dolin or Operidine or Dolantin or
15 Dolargan or Lidol or Lydol or Demerol or Dolconral or Meptazinol or Meptid or Methadone or Biodone or Dolophine or Metadol or
16 Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict or
17 Methadyl acetate or AcetylMethadol or Alphacetylmethadol or Amidolacetate or Dimephteptanol or Levomethadyl or
18 Levoacetylmethadol or Levomethadyl or Methadol or Acemethadone or Morphine or Morphia or Morphium or Contin or Oramorph or
19 Duramorph or Nalbuphine or Nubain or Nicomorphine or Vilan or Opium or Papaveretum or Omnopon or Pantopon or Oxycodone or
20 Dihydrohydroxycodone or Dihydroxycodone or Oxymorphone or Dihydrohydroxymorphinone or Dihydroxymorphinone or
21 Oximorphonum or Numorphan or Opana or Pentazocine or Talwin or Fortral or Lexir or Phenazocine or Phenethylazocine or
22 Phenbenzorphon or Narphen or Piritramide or Piritramid or Dipidolor or Dipydolor or Tapentadol or Nucynta of Tilidine or Tilidate or
23 Tilidin or Valeron or Valerone or Tramadol* or Tramundin or Biodalgic or Jutadol or MTW-Tramadol or MTWTramadol or Nobligan or
24 Prontofort or Zytram or Takadol or Theradol or Tiral or Topalgic or Tradol or Tradol-Puren or TradolPuren or Tradonal or Tralgiol or
25 Trama AbZ or Trama KD or Trama-Dorsch or Trama Dorsch or TramaDorsch or Biokanol or Tramabeta or Tramadin or Tramadoc or
26 Ranitidin or Trama or Trasedal or Ultram or Xymel or Zamudol or Zumalgic or Zydol or Tramadura or Tramagetic or Tramagit or
27 Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol).mp.

25 5 1 or 2 or 3 or 4
26 6 replacement arthroplasty/
27 7 ankle replacement/ or ankle arthroplasty/
28 8 elbow replacement/ or elbow arthroplasty/
29 9 hip replacement/ or hip arthroplasty/
30 10 knee replacement/ or knee arthroplasty/
31 11 shoulder arthroplasty/ or reverse shoulder arthroplasty/ or shoulder replacement/
32 12 ((joint or shoulder or knee or hip or elbow or wrist or ankle) adj3 (replacement* or arthroplast*)).mp.
33 13 6 or 7 or 8 or 9 or 10 or 11 or 12
34 14 5 and 13

Web of Science

1 TS=(narcotic* OR opioid* OR opiate*)
2 TS=(Bezitramide or Burgodin or Bezitramida or Buprenorphine or Buprenorfina or Buprenex or Pefin or Subutex or Buprex or
3 Temgesic or Butorphanol or Butorfanol or Beforal or Moradol or Stadol or Torbugesic or Apo-Butorphanol or Dolorex or Codeine or
4 Codeinum or Methylnorphine or N-Methylnorphine or Isocodeine or Ardinex or Dextromoramide or Palphium or Pyrrolamidol or
5 Pyrrolamidol or D-Moramide or D Moramide or Palfium or Dextropropoxyphene or Propoxyphene or D-Propoxyphene or Darvon or
6 Dezocine or Dihydrocodeine or paramol or Rikodeine or Tiamon or Tosidrin or Contugesic or Dicodin or Paracodin or Paracodina or
7 Fentanyl or Fentanil or Phentanyl or Fentanest or Sublimaze or Transmucosal or Duragesic or Durogesic or Fentora or Hydrocodone or
8 Dihydrocodeinone or Hydrocodon or Hydrocone or Hydroconum or Idrocodone or Dicodid or Robidone or Hycodan or Hycon or
9 Hydromorphone or Dihydromorphinone or Dimorphone or Hydromorphon or Palladone or Laudacon or Dilaudid or Ketobemidone or
10 Cetobemidon or Levorphanol or Levodroman or Levorphan or Levo-Dromoran or Levo Dromoran or LevoDromoran or L-Dromoran or
11 L Dromoran or Meperidine or Isonipecaïne or Pethidine or Isonipecaïn or Dolsin or Dolosal or Dolin or Operidine or Dolantin or
12 Dolargan or Lidol or Lydol or Demerol or Dolconral or Meptazinol or Meptid or Methadone or Biodone or Dolophine or Metadol or
13 Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict or

Methadyl acetate or Acetylmethadol or Alphacetylmethadol or Amidolacetate or Dimepheptanol or Levomethadyl or Levocetylmethadol or Levomethadyl or Methadol or Acemethadone or Morphine or Morphia or Morphinum or Contin or Oramorph or Duramorph or Nalbuphine or Nubain or Nicomorphine or Vilan or Opium or Papaveretum or Omnopon or Pantopon or Oxycodone or Dihydrohydroxycodone or Dihydroxycodone or Oxymorphone or Dihydrohydroxymorphinone or Dihydroxymorphinone or Oximorphonum or Numorphan or Opana or Pentazocine or Talwin or Fortral or Lexir or Phenazocine or Phenethylazocine or Phenbenzorphane or Narphen or Piritramide or Piritramid or Dipidolor or Dipydolor or Tapentadol or Nucynta of Tilidine or Tilidate or Tilidin or Valoron or Valerone or Tramadol* or Tramundin or Biodalgic or Jutadol or MTW-Tramadol or MTWTramadol or Nobligan or Prontofort or Zytram or Takadol or Theradol or Tiral or Topalgic or Tradol or Tradol-Puren or TradolPuren or Tradonal or Tralgiol or Trama AbZ or Trama KD or Trama-Dorsch or Trama Dorsch or TramaDorsch or Biokanol or Tramabeta or Tramadin or Tramadoc or Ranitidin or Trama or Trasedal or Ultram or Xymel or Zamudol or Zumalgic or Zydol or Tramadura or Tramagetic or Tramagit or Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol)

3 #1 OR 2

4 TS=((joint or shoulder or knee or hip or elbow or wrist or ankle) NEAR/3 (replacement* or arthroplast*))

5 #3 AND #4

PsychINFO

1 exp narcotic drugs/

2 exp Opiates

3 (opioid* or opiate* or narcotic*).mp.

4 (Bezitramide or Burgodin or Bezitramida or Buprenorphine or Buprenorfina or Buprenex or Prefin or Subutex or Buprex or Temgesic or Butorphanol or Butorfanol or Beforal or Moradol or Stadol or Torbugesic or Apo-Butorphanol or Dolorex or Codeine or Codeinum or Methylnormine or N-Methylnormine or Isocodeine or Ardinex or Dextromoramide or Palphium or Pyrrolamidol or Pyrrolamidol or D-Moramide or D Moramide or Palfium or Dextropropoxyphene or Propoxyphene or Darvon or Dezocine or Dihydrocodeine or paramol or Rikodeine or Tiamon or Tosidrin or Contugesic or Dicodin or Paracodin or Paracodina or Fentanyl or Fentanil or Phentanyl or Fentanest or Sublimaze or Transmucosal or Duragesic or Durogesic or Fentora or Hydrocodone or Dihydrocodeinone or Hydrocodon or Hydrocone or Hydroconum or Idrocodone or Dicodid or Robidone or Hycodan or Hycon or Hydromorphone or Dihydromorphinone or Dimorphone or Hydromorphon or Palladone or Laudacon or Dilaudid or Ketobemidone or Cetobemidon or Levorphanol or Levodroman or Levorphan or Levo-Dromoran or Levo Dromoran or LevoDromoran or L-Dromoran or L Dromoran or Meperidine or Isonipecaine or Pethidine or Isonipecaïn or Dolsin or Dolosal or Dolin or Operidine or Dolantin or Dolargan or Lidol or Lydol or Demerol or Dolcontral or Meptazinol or Meptid or Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict or Methadyl acetate or Acetylmethadol or Alphacetylmethadol or Amidolacetate or Dimepheptanol or Levomethadyl or Levocetylmethadol or Levomethadyl or Methadol or Acemethadone or Morphine or Morphia or Morphinum or Contin or Oramorph or Duramorph or Nalbuphine or Nubain or Nicomorphine or Vilan or Opium or Papaveretum or Omnopon or Pantopon or Oxycodone or Dihydrohydroxycodone or Dihydroxycodone or Oxymorphone or Dihydrohydroxymorphinone or Dihydroxymorphinone or Oximorphonum or Numorphan or Opana or Pentazocine or Talwin or Fortral or Lexir or Phenazocine or Phenethylazocine or Phenbenzorphane or Narphen or Piritramide or Piritramid or Dipidolor or Dipydolor or Tapentadol or Nucynta of Tilidine or Tilidate or Tilidin or Valoron or Valerone or Tramadol* or Tramundin or Biodalgic or Jutadol or MTW-Tramadol or MTWTramadol or Nobligan or Prontofort or Zytram or Takadol or Theradol or Tiral or Topalgic or Tradol or Tradol-Puren or TradolPuren or Tradonal or Tralgiol or Trama AbZ or Trama KD or Trama-Dorsch or Trama Dorsch or TramaDorsch or Biokanol or Tramabeta or Tramadin or Tramadoc or Ranitidin or Trama or Trasedal or Ultram or Xymel or Zamudol or Zumalgic or Zydol or Tramadura or Tramagetic or Tramagit or Tramake or Tramal or Tramex or Adolonta or Contramal or Amadol).mp.

5 1 or 2 or 3 or 4

6 ((joint or shoulder or knee or hip or elbow or wrist or ankle) adj3 (replacement* or arthroplast*)).mp.

7 5 and 6

CINAHL Complete Search

1 MH ("Analgesics, Opioid+" OR "Narcotics+") OR (TX ("opioid*" OR "opiate*" OR "narcotic*" OR "Bezitramide" OR "Burgodin" OR "Bezitramida" OR "Buprenorphine" OR "Buprenorfina" OR "Buprenex" OR "Prefin" OR "Subutex" OR "Buprex" OR "Temgesic" OR

"Butorphanol" OR "Butorfanol" OR "Beforal" OR "Moradol" OR "Stadol" OR "Torbugesic" OR "Apo-Butorphanol" OR "Dolorex" OR "Codeine" OR "Codeinum" OR "Methylmorphine" OR "N-Methylmorphine" OR "Isocodeine" OR "Ardinex" OR "Dextromoramide" OR "Palphium" OR "Pyrrolamidol" OR "Pyrrolamidol" OR "D-Moramide" OR "D Moramide" OR "Palfium" OR "Dextropropoxyphene" OR "Propoxyphene" OR "D-Propoxyphene" OR "Darvon" OR "Dezocine" OR "Dihydrocodeine" OR "paramol" OR "Rikodeine" OR "Tiamon" OR "Tosidrin" OR "Contugesic" OR "Dicodin" OR "Paracodin" OR "Paracodina" OR "Fentanyl" OR "Fentanil" OR "Phentanyl" OR "Fentanest" OR "Sublimaze" OR "Transmucosal" OR "Duragesic" OR "Durogesic" OR "Fentora" OR "Hydrocodone" OR "Dihydrocodeinone" OR "Hydrocodon" OR "Hydrocone" OR "Hydroconum" OR "Idrocodone" OR "Dicodid" OR "Robidone" OR "Hycodan" OR "Hycon" OR "Hydromorphone" OR "Dihydromorphinone" OR "Dimorphone" OR "Hydromorphon" OR "Palladone" OR "Laudacon" OR "Dilaudid" OR "Ketobemidone" OR "Cetobemidon" OR "Levorphanol" OR "Levodroman" OR "Levorphan" OR "Levo-Dromoran" OR "Levo Dromoran" OR "LevoDromoran" OR "L-Dromoran" OR "L Dromoran" OR "Meperidine" OR "Isonipecaine" OR "Pethidine" OR "Isonipecaïn" OR "Dolsin" OR "Dolosal" OR "Dolin" OR "Operidine" OR "Dolantin" OR "Dolargan" OR "Lidol" OR "Lydol" OR "Demerol" OR "Dolcontral" OR "Meptazinol" OR "Meptid" OR "Methadone" OR "Biodone" OR "Dolophine" OR "Metadol" OR "Metasedin" OR "Symoron" OR "Methadose" OR "Methex" OR "Phenadone" OR "Physeptone" OR "Phymet" OR "Pinadone" OR "Amidone" OR "Methadict" OR "Methadyl acetate" OR "Acetylmethadol" OR "Alphacetylmethadol" OR "Amidolacetate" OR "Dimpheptanol" OR "Levomethadyl" OR "Levoacetylmethadol" OR "Levomethadyl" OR "Methadol" OR "Acemethadone" OR "Morphine" OR "Morphia" OR "Morphium" OR "Contin" OR "Oramorph" OR "Duramorph" OR "Nalbuphine" OR "Nubain" OR "Nicomorphine" OR "Vilan" OR "Opium" OR "Papaveretum" OR "Omnopon" OR "Pantopon" OR "Oxycodone" OR "Dihydrohydroxycodone" OR "Dihydroxycodone" OR "Oxymorphone" OR "Dihydrohydroxymorphinone" OR "Dihydroxymorphinone" OR "Oximorphonum" OR "Numorphan" OR "Opana" OR "Pentazocine" OR "Talwin" OR "Fortral" OR "Lexir" OR "Phenazocine" OR "Phenethylazocine" OR "Phenbenzorphane" OR "Narphen" OR "Piritramide" OR "Piritramid" OR "Dipidolor" OR "Dipydolor" OR "Tapentadol" OR "Nucynta of Tilidine" OR "Tilidate" OR "Tilidin" OR "Valoron" OR "Valerone" OR "Tramadol*" OR "Tramundin" OR "Biodalgic" OR "Jutadol" OR "MTW-Tramadol" OR "MTWTramadol" OR "Nobligan" OR "Prontofort" OR "Zytram" OR "Takadol" OR "Theradol" OR "Tiral" OR "Topalgic" OR "Tradol" OR "Tradol-Puren" OR "TradolPuren" OR "Tradonal" OR "Tralgioi" OR "Trama AbZ" OR "Trama KD" OR "Trama-Dorsch" OR "Trama Dorsch" OR "TramaDorsch" OR "Biokanol" OR "Tramabeta" OR "Tramadin" OR "Tramadoc" OR "Ranitidin" OR "Trama" OR "Trasedal" OR "Ultram" OR "Xymel" OR "Zamudol" OR "Zumalgic" OR "Zydol" OR "Tramadura" OR "Tramagetic" OR "Tramagit" OR "Tramake" OR "Tramal" OR "Tramex" OR "Adolonta" OR "Contramal" OR "Amadol")

- 2 TX (("joint" OR "shoulder" OR "knee" OR "hip" OR "elbow" OR "wrist" OR "ankle") n3 ("replacement*" OR "arthroplast*")) OR (MH ("Arthroplasty, replacement" OR "Arthroplasty, Replacement, Elbow" OR "Arthroplasty, Replacement, Shoulder" OR "Arthroplasty, Replacement, Ankle" OR "Arthroplasty, Replacement, Knee" OR "Arthroplasty, Replacement, Hip"))
- 3 1 AND 2

Planned search strategy for supplementary database

Google Scholar searches

- 1 ("preoperative narcotic" OR "preoperative opioid" OR "preoperative opiate") AND ("total joint arthroplasty" OR "total knee arthroplasty" OR "total hip arthroplasty" OR "total ankle arthroplasty")
- 2 ("preoperative narcotic" OR "preoperative opioid" OR "preoperative opiate") AND ("total elbow arthroplasty" OR "total shoulder arthroplasty" OR "total wrist arthroplasty")
- 3 ("preoperative narcotic" OR "preoperative opioid" OR "preoperative opiate") AND ("total joint replacement" OR "total knee replacement" OR "total hip replacement" OR "total ankle replacement")
- 4 ("preoperative narcotic" OR "preoperative opioid" OR "preoperative opiate") AND ("total elbow replacement" OR "total shoulder replacement" OR "total wrist replacement")

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-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.

			Page Number
Title			
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

1 **Registration**

2
3
4 [#2](#) If registered, provide the name of the registry (such as 2
5
6 PROSPERO) and registration number
7
8

9 **Authors**

10
11
12
13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all 1
14
15 protocol authors; provide physical mailing address of
16
17 corresponding author
18

19
20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the 11
21
22 guarantor of the review
23
24

25 **Amendments**

26
27
28
29 [#4](#) If the protocol represents an amendment of a previously n/a
30
31 completed or published protocol, identify as such and list
32
33 changes; otherwise, state plan for documenting important
34
35 protocol amendments
36
37

38 **Support**

39
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42 **Sources** [#5a](#) Indicate sources of financial or other support for the review 11
43

44
45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor 11
46

47
48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), 11
49
50 funder
51 if any, in developing the protocol
52

53 **Introduction**

54
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56
57 **Rationale** [#6](#) Describe the rationale for the review in the context of what is 3-4
58

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

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4 Confidence in [#17](#) Describe how the strength of the body of evidence will be 9-10
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6 cumulative assessed (such as GRADE)
7
8 evidence
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14
15 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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