PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Using serum urate as a validated surrogate endpoint for flares in patients with gout: protocol for a systematic review and meta-regression analysis.

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date

Give the date when the systematic review commenced, or is expected to commence.

28/12/2015

4 Anticipated completion date

Give the date by which the review is expected to be completed.

31/10/2016

5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started √

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

William Taylor

7 Named contact email

Enter the electronic mail address of the named contact.

will.taylor@otago.ac.nz

8 Named contact address

Enter the full postal address for the named contact.

Rehabilitation Teaching and Research Unit Department of Medicine University of Otago, Wellington p.o Box 7343 Wellington 6242 New Zealand

9 Named contact phone number

Enter the telephone number for the named contact, including international dialing code.

(+64) 4 385 5227

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed

as 'None' if the review is not affiliated to any organisation.
Rehabilitation Teaching and Research Unit Department of Medicine University of Otago, Wellington p.o Box 7343 Wellington 6242 New Zealand

Website address:

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Dr	Lisa	Stamp, Ph.d, FRACP	Department of medicine, University of Otago, Christchurch, New Zealand
Dr	William	Taylor, PhD, FRACP	Department of medicine, University of Otago, Wellington, New Zealand
Mrs	Melanie	Morillon, MD	Department of Rheumatology, Odense University Hospital, Denmark et Musculoskeletal Statistics unit, The Parker institute, Department of Rheumatology, Copenhagen University Hospitals, Bispebjerg and Frederiksberg Denmark
Dr	Jaap	Fransen	Department of Rheumatology, Radboud University Medical centre, Nijmegen, The Nederlands
Dr	Nicola	Dalbeth, MD, FRACP	Department of Medicine, University of Auckland, New Zealand
Dr	Marissa	Lassere, MBBS (Hons) Grad Dip Epi PhD FRACP FAFPHM	Department of Rheumatology, St George Hospital, University of NSW, Sydney, Australia
Dr	Jasvinder A	Singh, MD, MPH	Department of Medicine, University of Alabama at Birmingham et Birmingham Veterans Affairs Medical Center, Birmingham, Alabama, USA
Dr	Robin	Christensen, MSc, PhD	Musculoskeletal Statistics unit, The Parker institute, Department of Rheumatology, Copenhagen University Hospitals, Bispebjerg and Frederiksberg Denmark

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
Musculoskeletal Statistics Unit, The Parker Institute, is supported by grants from the Oak Foundation

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
1) To determine the strength of the relationship between SU (serum urate) and patient relevant outcomes, including flares, tophi, HRQOL and function using meta-regression of randomised controlled trials.

2) To evaluate whether SU is a surrogate endpoint for clinically relevant outcomes in patients with gout as defined by the BSES3 framework.

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
The following electronic databases will be searched: PubMed, MEDLINE, EMBASE, the Cochrane Library including the Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR), and abstracts from ACR and EULAR meetings (2012 to 2015). The search will be limited to English language studies in humans, but not limited by year of publication or type of publication. The reference lists from comprehensive reviews and identified clinical trials are also manually searched.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
No

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Gout is the most common inflammatory arthritis in men over 40 years. Long term urate-lowering therapy is considered a key strategy for effective gout management. The primary outcome measure for efficacy in clinical trials of urate lowering therapy is serum urate levels, effectively acting as a surrogate for patient-centred outcomes such as frequency of gout attacks or pain. Yet it is not clearly demonstrated that the strength of the relationship between serum urate and clinically relevant outcomes is sufficiently strong for serum urate to be considered an adequate surrogate.

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Patients at least 18 years of age meeting the preliminary American College of Rheumatology (ACR) criteria for acute arthritis of primary gout or given a diagnosis of gout as described by the authors.

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Patients who have been exposed to urate- lowering therapy: Allopurinol, Benzbromarone, Febuxostat, Pegloticase, Probenecid, Lesinurad or Rasburicase.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Any control group

22 Types of study to be included initially
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Any randomised controlled trial, controlled clinical trial, or open label trial, and observational studies.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
The eligibility criteria for objective 1 is any randomised controlled trial comparing an active drug (alone or in combination) in patients with gout with any control or placebo, with a minimum duration of three months. The eligibility criteria for objective 2 are any randomised controlled trial, controlled clinical trial, or open label trial (OLT) comparing an (apparently) active drug (alone or in combination) in patients with gout with any control or placebo, with a minimum

duration of three months and longitudinal observational studies of gout with a minimum duration of 3 months.

24 Primary outcome(s)

Give the most important outcomes.

The clinical endpoints (dependent variables) are defined as follows: • Major outcome: number and risk of developing gout-flares reported • Minor outcomes: size of sentinel tophus (if size was not measured, we will use number, or presence/absence in order of preference) and pain at final study visit.

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

Exploratory analysis: health related quality of life (HRQOL) (SF36), patient global assessment of disease activity, and physical disability (activities limitation) (HAQ).

Give information on timing and effect measures, as appropriate.

26 Data extraction, (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Results of the various searches will be reviewed independently by two authors (LS and MM). Titles and abstracts will be reviewed and if further information is required (to assess eligibility criteria), the full text will be obtained. A record of reasons for excluding studies will be kept enabling generation of a figure illustrating the flow of information through the different phases of the systematic review continuing to meta-regression analysis. Disagreements will be resolved by discussion until consensus is reached. EndNote X7 software will be used to manage the records retrieved from searches of electronic databases. Results from hand searches will be tracked on a Microsoft Excel spreadsheet. A customised data extraction form will be created in Microsoft Excel to capture all the information available for each individual trial.

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

The RCTs will be assessed for methodological quality (i.e. internal validity) using the Cochrane Risk of Bias tool. If at least one of the domains is rated as high, the trial will be considered at high risk of bias. If all domains are judged as low, the trial will be considered at low risk of bias. Otherwise, the trial is considered as having unclear risk of bias. Data extraction and risk-of-bias assessment will be performed independently by 2 reviewers; disagreements will be resolved by a third reviewer. GRADE (Grading of Recommendations Assessment, Development and Evaluation) will be used to rate the overall quality of the evidence for risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect; i.e., the GRADE ratings of very low–, low-, moderate-, or high-quality evidence per outcome will reflect the extent to which we are confident that the effect estimates are correct.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

To combine the individual study results, we will perform meta-analyses using SAS software (PROC MIXED version 9. 3; SAS Institute Inc., Cary, NC, USA), applying a restricted maximum likelihood (REML) method to estimate the between-study variance (i.e. T2) and the combined estimate of effect. We will estimate the anticipated heterogeneity between trials with a standard (Cochran's) Q-test statistic, and we will evaluate this based on the I2 value, which is interpreted as the percentage of variability in treatment effect estimates that is due to between study heterogeneity rather than chance. The primary purpose of this project is to evaluate the surrogacy status of SU as a "predictor" of gout flare rate reduction using meta-regression of randomised controlled trials. Randomisation is essential for the causal surrogacy relationship, therefore, only randomised controlled trials will be included in the main meta-regression analysis. Non-randomised study designs will be summarised separately by meta-regression to confirm the consistency of association between the biomarker and clinical endpoints in other contexts. Cohort studies will be summarised as a narrative review. The analyses of both randomised and non-randomised studies contribute to the evaluation of serum urate within the BSES3 framework. Furthermore, in the meta-regression, the relationship between serum urate and clinically relevant outcomes can be undertaken using different outcome metrics. We will define these as primary and secondary analyses. In the primary analysis the dependent variable is a rate ratio (i.e. an

incidence density ratio) comparing the ratio of incidence rates of gout flare events in active versus control arms occurring at any given point in time; incidence rate is the occurrence of an event over person-time (i.e., in this setting in person-months). The rate ratio allows trials of different duration to be included in the analysis. The independent variable is between arm difference of within-arm change (on-trial SU from baseline SU) of SU. Therefore, in a trial of 3 months duration, flare rate over 3 months is the dependent variable and change in SU over 3 months is the independent variable.

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

In secondary analyses the dependent variable is risk ratio reduction (RRR) of within trial gout flare rate. The relative ratio reduction (also called the risk ratio reduction) is the flare risk in the control arm minus the flare risk in the active arm, divided by the flare risk in the control arm (this can also be calculated by 1- Relative Risk (RR), where relative risk is the flare risk in the active arm divided by the flare risk in the control arm). Therefore the relative risk reduction (RRR) is the difference in flare risk in two arms (control-active), expressed as a percentage of the risk of the control arm. The independent variable is within trial, by-arm difference of proportion with SU less than 6mg/dL at the end of the trial. A quantitative evaluation of trial-level statistical surrogacy using the BSES3 includes determining the slope coefficient of the surrogacy relationship, trial-level R2 (coefficient of determination) and the Surrogate Threshold Effect (STE) and Surrogate Threshold Effect Proportion (STEP) of the surrogate and true-clinical-endpoint relationship using data from a meta-regression of randomized controlled trials.

Review general information

30 Type of review

Select the type of review from the drop down list.

Prognostic

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Australia, Denmark, Netherlands, New Zealand, United States of America

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available

Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

The intended audience will include health care researchers, policymakers and clinicians. Results of the study will be disseminated by peer-review publication.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
Gout, biomarker, Surrogate, outcome, Rheumatology

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.