

## Registering a review of animal studies on PROSPERO

PROSPERO for animal studies is an international database of prospectively registered systematic reviews of animal studies relevant to human health. Key features from the review protocol are recorded and maintained as a permanent record in PROSPERO. The aim is to provide a comprehensive listing of systematic reviews registered at inception, to help avoid unplanned duplication. By promoting transparency in the process and enabling comparison of reported review findings with what was planned in the protocol PROSPERO also aims to minimise the risk of bias in systematic review.

PROSPERO for animal studies has been developed and is managed by the SYRCLE-CAMARADES team and the Centre for Reviews and Dissemination (CRD) at the University of York. It is funded by the UK's National Institute for Health Research (NIHR).

## What does registration on PROSPERO involve?

Registration in PROSPERO involves the prospective submission and publication of key information about the design and conduct of a systematic review.

Registration on PROSPERO is free of charge. In return, registrants are accountable for the accuracy and updating of information submitted.

## Inclusion criteria

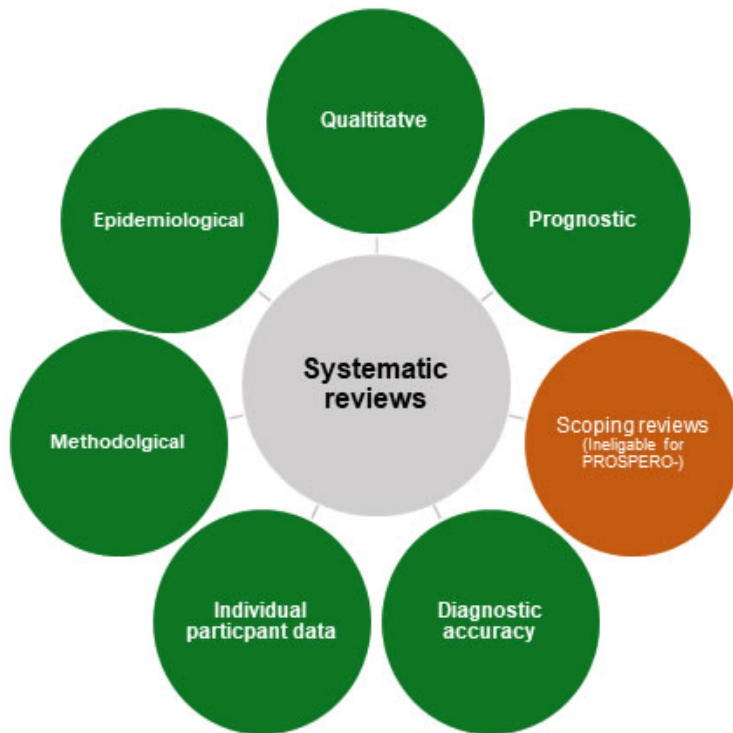
PROSPERO includes details of any planned or on-going systematic review that has a health related outcome.

## PROSPERO accepts:

Systematic review protocols assessing:

- Interventions (Including **qualitative** and **individual participant data reviews**)
- **Diagnostic accuracy**
- Prognostic factors
- Prevention
- Epidemiological reviews relevant to health and social care
- Public health
- Service delivery in health and social care
- **Methodological**

Further information on protocol development specific to review types is accessible below.



### Requirements for registration

- A full protocol should be ready before registering with PROSPERO
- Submissions must be made before data extraction commences (from October 2019)
- Registration forms must be complete.
- Submissions must be in English (search strategies and protocols attached to a record may be in any language).

### PROSPERO does not accept:

- Systematic reviews without an outcome of clear relevance to the health of humans
- **Scoping reviews**
- Literature reviews that use a systematic search
- Systematic reviews assessing sports performance as an outcome
- Methodological reviews that assess **ONLY** the quality of reporting

### Other considerations

- Cochrane protocols are automatically uploaded- To avoid duplication of records, Cochrane protocols **should not** be registered separately with PROSPERO.

If you are in any doubt about the eligibility of your review, including the stage of progress please contact [crd-register-2@york.ac.uk](mailto:crd-register-2@york.ac.uk) for advice.

### When to register your review

**Do not register too early. Your systematic review protocol should be complete before you submit your registration request**

Registering reviews that are never performed is unhelpful to the research community and may discredit the research team.

You should therefore have the necessary resources in place to complete the review before you register your

protocol (notification of award of research funding or firm commitment that author time is available for unfunded projects).


### Accessing and navigating the registration form

Obtain a username and password by following the 'Join' link in the top right hand corner of the PROSPERO website.

Once you have joined, you can 'Sign in' and then you will be able to select 'Register a review' in the left hand column. This opens a page that encourages you to check that your review will meet the inclusion criteria and that the review is not already registered. If you are happy to continue, open the registration form by clicking on the "Register a systematic review of animal research studies (study subjects are animals) that is of direct relevance to human health" link. This opens a page where you are asked to confirm your review is eligible for inclusion and sufficiently different from any other review registered. If you are happy to confirm the information you may proceed to the registration form by clicking on the "Register a review" link. This will take you to the electronic registration form which has 26 required fields and 14 optional fields. All subfields of required fields, marked with a red asterisk, must be completed before the protocol can be submitted. You may save and exit the form at any time, and return at a later date changes are also automatically saved when a field is exited. You are able to add or edit information at a later time by signing in at the main page and going to 'My PROSPERO records'.

Providing access to a protocol is not a substitute for entering data into the required fields.

Most registrants complete the form in 60 minutes or less.

Brief guidance about the information required in each field is given in the form by clicking the  icon or by clicking 'show help' at the top of the page and more detailed information, with examples, is given below for each section..

When you are ready, the form can be sent to the PROSPERO administrators by clicking on "Submit".

### What happens after submitting a form

Access to your record to make further changes or updates is suspended during the administrative process. Receipt of submission is acknowledged in an automated email sent to the named contact.

Registration forms are checked against the eligibility criteria for PROSPERO. If they meet the inclusion criteria, they are checked for clarity of content before either being approved and published on the register, returned for clarification, or rejected. We endeavour to provide an update within five working days. If you wish to enquire on the progress of your submission please contact the administration team at [crd-register-2@york.ac.uk](mailto:crd-register-2@york.ac.uk)

Once published on the register, the record will again become accessible for future editing. However, the original document submitted will remain in the register to provide a permanent record for the audit trail and for reference.

Should your submission be rejected for registration, the record will be locked and no further edits can be made. Further access to the record for editing is not possible without contacting us by email at [crd-register-2@york.ac.uk](mailto:crd-register-2@york.ac.uk). Please do not create a new record to substitute a rejected record without contacting us.

### Making changes, amendments and updating a published record

Changes, amendments and updates can be made to a published record by signing in, going to "My PROSPERO records" and opening the saved record. Once the changes have been made, click the "Submit" button. You will then be asked to give brief details of the changes made. The information entered here will appear in the public record and should inform users of the database of the nature of the changes made (e.g. removed one of the outcome measures; changed the anticipated completion date).

All submitted edits and changes to a PROSPERO record will be recorded, date stamped and be made available within the record. The most recent version will appear with previous versions accessible from dated links highlighted under the 'Versions' heading at the bottom of the form.

### What to do after completing a review and after publishing the findings

Records remain permanently on PROSPERO. Once the review is completed this information should be updated in the record together with the anticipated publication date. The bibliographic reference and electronic links to publications should be added to the record by the authors. In the absence of a publication, details of availability of the review's unpublished results, or reasons for the discontinuation of the review, should be documented. Reminder emails with detailed instructions on what to do, are sent on the anticipated

completion and publication dates.

### Registering an update of a completed review

If you decide to update the registration of a review you have already completed, you can access the record by signing in and going to “My PROSPERO records”. You can make changes to the protocol and submit it as an update and it will be processed as for a new review. It is important to decide if you are updating a review, or in fact are doing a new review because of changes to the protocol. The following definitions have been provided to help you decide.

#### *What is an update of a review?*

Updating a systematic review is a discrete event during which efforts are made to identify and incorporate new evidence into a previously completed systematic review

An ‘update’ may be any modified version of a review that includes the findings of a more recent search than the previously completed version of the review. It can still be considered an update even if the new search reveals no additional studies. Any newly identified studies should be assessed and, if appropriate, incorporated into the updated review. An update might also be an opportunity to conduct new analyses or add additional information to the review.

#### *What constitutes a new review rather than an update?*

It can be difficult to decide whether an update to a review is in fact a new review. There is little published guidance on this. PROSPERO adopts a pragmatic approach. If changes to the review questions or methods are so substantial that they require major changes to the original protocol, this should be regarded as a new review rather than an update. Examples that would constitute a new review:

- addition of new treatment comparisons e.g. direct comparison of different drugs, when the old review included only comparisons of drug with placebo;
- substantial changes to the population being studied e.g. adding non-rodents to a review that was previously restricted to rodents;
- exclusion criteria in the old review become inclusion criteria in the new review;
- introduction of new analysis techniques e.g. a switch from aggregate data meta-analyses to individual participant meta-analyses.

If in doubt, a new record for a new review should be created. This will minimise the complexity of the editing to the original record in PROSPERO and make it easier for users to distinguish between the original review and the later version. Links between the new and original review can be added in field #37 in the registration form.

### *Guide to completing the registration fields*

The following guidance notes follow the format of the registration form. The guidance includes a description and example of what is required for each of the fields within each section.

PROSPERO records need to be fully searchable. We can therefore not accept submissions in which only a link to a protocol registered elsewhere is provided, without providing the basic information in the fields.

#### **SPECIAL NOTES:**

**We accept information in good faith and rely upon the integrity of researchers to ensure the validity of all the data presented in PROSPERO records. Action will be taken if inaccuracies in data, particularly stage of review and anticipated completion date, are identified at any time.**

#### **1. Review title.**

This is a mandatory field

Give the working title of the review. This must be in English. The title should have the interventions or exposures being reviewed and the associated health or social problems.

Where appropriate, the title should use the PI(E)CO structure to contain information on the Population, Intervention (or Exposure) and Comparison groups, and the Outcomes to be measured. Acronyms may be included in titles, but should not be used alone without expansion unless they are regarded as more usual than the expansion (e.g. HIV). If the original title is in a different language, the English version must be entered here, with the non-English version entered into Field #2 (Original language title). If the final title of the (published) review differs from the one entered here, this can be recorded in Field #40 (Details of the final report/publication(s)).

**Example:** Efficacy of ischemic postconditioning against renal ischemia-reperfusion injury in animal models, a systematic review and meta-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.

This is a mandatory field

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

For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol, but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete when it is approved by a funder or the person commissioning the review, when peer review is complete, when the protocol is published, or when the authors decide that it is complete and they do not anticipate any major revisions to the design of the systematic review.

This field may be edited at any time. All edits to published records will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.

## 4. Anticipated completion date.

This is a mandatory field

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

In the absence of an agreed contractual date, a realistic anticipated date for completion should be set. It can be modified should the schedule change. When this date is reached, the named contact will receive an automated email to ask them to provide an update on progress.

This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.

## 5. Stage of review at time of this submission.

This is a mandatory field

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

**Example:** "Preliminary searches" ticked as completed, "Piloting of the study selection process" ticked as started.

## 6. Named contact.

This is a mandatory field

The named contact acts as the guarantor for the accuracy of the information presented in the register record. This should be the lead reviewer or a representative of the review team. This person is also responsible for submitting details of any amendments while the review is ongoing and publication details after the review is completed. The named contact is the person to whom users of PROSPERO would send questions or comments. This field is automatically populated from the named contact's signing in details. The named contact will be displayed in the public record.

**Example:** Dr Joseph Bloggs

### 7. Named contact email.

This is a mandatory field

Enter the electronic mail address of the named contact.

This may be a generic email address to which the named contact has access.

This field is automatically populated from the named contact's signing in details, but can be changed if required. The email address supplied here will be displayed in the public record.

**Examples:** joseph.bloggs@city.ac.uk; research.secretary@city.ac.uk

### 8. Named contact address.

PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information

This is a mandatory field

Enter the full postal address for the named contact.

This field is automatically populated from the named contact's signing in details.

This address will be displayed in the public record. If you do not wish it to appear in the public record delete the content of this field.

**Example:** Alcuin B Block, University of York, York, YO10 5DD, UK

### 9. Named contact phone number

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

This field is automatically populated from the named contact's signing in details. This number will be displayed in the public record. If you do not wish it to appear in the public record delete the content of this field.

**Example:** +44 (0)10904 32104

### 10. Organisational affiliation of the review.

This is a mandatory field

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.

**Example:** Radboud university medical center (Radboudumc)

### 11. Review team members and their organisational affiliations.

This is a mandatory field

Give the personal details and the organisational affiliations of each member of the review team. NOTE: email and country are now mandatory fields for each person..

Affiliation refers to groups or organisations to which review team members belong. The named contact will be automatically added to this field, but can be deleted if not a member of the review team. To place the named contact somewhere other than first in order, delete the automatic entry and enter members' details in the required order. Membership of the review team and details of affiliations can be updated at any time. All edits will appear in the record audit trail.

**Examples:** Mr Joseph Bloggs, Centre for Reviews and Dissemination, University of York, UK. Dr Jane Smith, Department of Health Sciences, University of York, UK. Prof. Steven Jones, Centre for Health Statistics, Medical Research Centre, Canada.

### 12. Funding sources/sponsors.

This is a mandatory field

Give details of the individuals, organisations, 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.

**Examples:** NIHR HTA Programme (Project ref 09/13/02). The Terry Fox New Frontiers Program in Cancer (Ref 201006TFL). Funding provided by Amgen, Merck, Roche, and Sanofi-aventis.

### 13. Conflicts of interest.

This is a mandatory field

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

The conflicts of interest listed should cover the review team as a whole, as well as individuals in the team. Conflicts of interest arise when a team member or the team as a whole (e.g. because of the team's institution) has financial or personal relationships that may inappropriately influence (bias) their actions (such relationships are also known as dual commitments, competing interests, or competing loyalties). These relationships vary from being negligible to having great potential for influencing judgement. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether a person believes that the relationship affects his or her scientific judgement. Financial relationships (such as employment, consultancies, stock ownership, honoraria, and paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the review. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion. For the purposes of disclosure, the term "competing interest" should be considered synonymous with conflict of interest.

**Example:** The lead reviewer (JB) has given talks on this topic at workshops, seminars, and conferences for which travel and accommodation has been paid for by the organisers. The other authors declare that they have no known conflicts of interest.

### 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.

**Example:** Dr Eric Porter, Oncologist, University Hospital, Brighton, UK. Clinical advisor.

### 15. Review question.

This is a mandatory field

Give details of the question to be addressed by the review, clearly and precisely. This should be clearly and precisely defined, but may be specific or broad. The question may be framed or refined using PICO where relevant. Further guidance is available in e.g. the [step by step search guide](#).

**Example:** Does analgesic treatment reduce the number or incidence of metastasis in animal cancer models?

### 16. Searches.

This is a mandatory field

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.

A [step by step search guide](#), as well as animal search filters for [Pubmed](#) and [EMBASE](#), are available to facilitate the search process. List all sources that will be used to identify studies for the review. Sources include (but are not limited to) bibliographic databases, reference lists of eligible studies and review articles, key journals, trials registers, conference proceedings, internet resources and contact with experts and manufacturers.

**Example:** We will search the following electronic bibliographic databases: MEDLINE, EMBASE, and Web of Science. The full search strategy (see pdf) is based on the search components "animal" (using Pubmed and EMBASE search filters [ref, ref]), "laparoscopic surgery" and "renal function". No publication date or language restrictions will be applied. We will screen the reference lists of included studies for additional eligible studies not retrieved by our search. The searches will be re-run just before the final analyses to retrieve the most recent studies eligible for inclusion.

### 17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, an electronic file could be supplied which will be linked to from the Register record. This will be

made publicly available from the published record immediately, or it can be held in confidence until the review has been completed, at which time it will be made publicly available.

**Example:** <http://www.biomedcentral.com/1756-0500/3/250>

### 18. Human disease modelled.

This is a mandatory field

Give a short description of the disease, condition or healthcare domain being modelled.

This could include health and wellbeing outcomes.

**Example:** Type 2 diabetes; Myocardial infarction; Physical activity in the elderly.

### 19. Animals/population.

This is a mandatory field

Give summary criteria for the animals being studied by the review, e.g. species, sex, details of disease model. Please include details of both inclusion and exclusion criteria.

**Example:** Inclusion criteria: all animal models with experimental cancer in which metastasis can develop (all species, all sexes). Exclusion criteria: animals with co-morbidities; ex vivo, in vitro and in silico models; experimental cancer without metastasis

### 20. Intervention(s), exposure(s).

This is a mandatory field

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed (e.g. dosage, timing, frequency). Please include details of both inclusion and exclusion criteria.

For reviews of pre-clinical animal studies, the intervention would be e.g. treatment with a drug, or a therapeutic intervention such as exercise. For reviews of animal exposure studies, e.g. in toxicology, the intervention would be exposure to a certain compound. For reviews aiming to provide an overview of animal models for a certain health problem or disease, this would be the intervention(s) used to induce the disease model (e.g. high-fat diet to induce obesity, or transverse aortic constriction to induce heart failure). See also Field #30 for additional information on review types.

**Example:** Inclusion criteria: analgesic treatment with compounds registered for use in clinical practice, including pre-treatment of tumor cells with analgesics before injection. All timings, frequencies and dosages of treatment are eligible for inclusion. Exclusion criteria: treatment with analgesics not registered for use in clinical practice.

### 21. Comparator(s)/control.

This is a mandatory field

Where relevant, give details of the type(s) of control interventions against which the experimental condition(s) will be compared (e.g. another intervention or a non-exposed control group). Please include details of both inclusion and exclusion criteria.

Control or comparison interventions should be described in as much detail as the intervention being reviewed. A "control group" may refer to vehicle-treated animals, sham-treated animals, animals undergoing no treatment at all, baseline measurements, etc. Indicate which of these control conditions are eligible for inclusion.

If the review aims to provide an overview of available animal models for a certain health problem / disease (animal model review, see Field #30), the comparator would generally be a healthy, naive animal".

**Example:** Inclusion criteria: vehicle-treated control animals. Exclusion criteria: all other control conditions (e.g. no treatment, saline-treated if vehicle is not saline).

### 22. Study designs to be included.

This is a mandatory field

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should



be stated. Please include details of both inclusion and exclusion criteria.

**Example:** Inclusion criteria: controlled studies with a separate control group. Exclusion criteria: case studies, cross-over studies, studies without a separate control group.

### 23. Other selection criteria or limitations applied.

Give details of any other inclusion and exclusion criteria (e.g. publication date or language restrictions).

**Examples:** Inclusion criteria: all languages, all publication dates. Exclusion criteria: none.

### 24. Outcome measure(s).

This is a mandatory field

Give details of the outcome measures to be considered for inclusion in the review. Please include details of both inclusion and exclusion criteria.

**Example:** Inclusion criteria: tumor number and/or tumor incidence reported. Exclusion criteria: no relevant outcomes reported (e.g. tumor weight only).

### 25. N/A.

This question does not apply to systematic reviews of animal studies for human health submissions

### 26. Study selection and data extraction.

This is a mandatory field

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.

Other relevant details could include whether study selection and/or data extraction will be blinded (researchers unaware of author/journal details) and whether and how authors of eligible studies will be contacted to provide missing or additional data.

For reviews of individual participant data, this field should include the data to be sought and how this will be collected.

A description of any other manipulation or transformation of the extracted data that is planned may be included.

**Example:** Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer.

A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement; indicators of acceptability to users; suggested mechanisms of intervention action; information for assessment of the risk of bias. Two review authors will extract data independently, discrepancies will be identified and resolved through discussion (with a third author where necessary). Missing data will be requested from study authors.

**Example for IPD:** Those responsible for the included studies will be asked to supply line by line individual participant data comprising: de-identified patient reference; allocated treatment, date of randomisation; date of birth, gender, tumour stage, tumour histology, survival status, date of last follow up or death.

### 27. Risk of bias and/or quality assessment.

This is a mandatory field

State whether and how risk of bias and/or study quality will be assessed. Assessment tools specific for pre-clinical animal studies include [SYRCLE's risk of bias tool](#) and the [CAMARADES](#) checklist for study quality.

[SYRCLE's risk of bias tool](#) is used to perform an assessment of internal validity, addressing selection, performance, detection, attrition, and other types of bias. The [CAMARADES](#) checklist is used to perform a combined assessment of the reporting of a number of measures to reduce bias, and several indicators of

external validity and study quality. Both tools may be adapted by adding or removing items. If this is planned, specify which adaptations have been made. "No risk of bias and/or quality assessment planned" is acceptable only if the aim of the review is limited to providing an overview of available animal models, without presenting any outcome data.

## 28. Strategy for data synthesis.

This is a mandatory field

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Where appropriate, the planned analytical approaches (e.g. Bayesian or frequentist (classical), fixed or random effects; categorising studies within a narrative synthesis) should be outlined. Whether and how statistical heterogeneity will be explored and how any observed heterogeneity will impact on or modify the planned approach to analysis should be stated, along with any planned sensitivity analyses.

**Example:** We will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, type of outcome and intervention content. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes).

We anticipate that there will be limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing trials. However, where studies have used the same type of intervention and comparator, with the same outcome measure, we will pool the results using a random-effects meta-analysis, with standardised mean differences for continuous outcomes and risk ratios for binary outcomes, and calculate 95% confidence intervals and two sided P values for each outcome. In studies where the effects of clustering have not been taken into account, we will adjust the standard deviations for the design effect. Heterogeneity between the studies in effect measures will be assessed using both the  $\tau^2$  test and the  $I^2$  statistic. We will consider an  $I^2$  value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on study quality. We will use stratified meta-analyses to explore heterogeneity in effect estimates according to: study quality; study populations; the logistics of intervention provision; and intervention content. We will also assess evidence of publication bias.

**Example for IPD:** Individual data from all randomised participants will be included in the analyses, which will be performed on an intention to treat basis. A two-stage approach to synthesis will be used. For time to event outcomes, the individual times to event will be used in the stratified (by trial) logrank test to produce hazard ratio estimates of the effect of treatment for individual trials. These hazard ratios will then be combined across studies using a fixed effect model to give combined hazard ratios. For dichotomous outcomes, the number of events and the number of patients will be used to calculate Peto odds ratio estimates of treatment effect. These will be generated for individual trials and then combined across trials using a fixed effect model. For all outcomes, trial results will also be combined using a random effects model to test robustness to model choice.

## 29. Analysis of subgroups or subsets.

This is a mandatory field

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

The approach to be taken should be stated, e.g. whether subgroup analyses, meta-regression or modelling of covariates is planned and, where appropriate, details of categorisation (e.g. BMI <25, 25-30, >30) should be given. Where it is not possible or appropriate to specify subgroups or subsets in advance, for example in a qualitative synthesis, please make a statement to this effect.

**Example:** If the necessary data are available, subgroup analyses will be done for people with stage I and stage II disease separately. Within each stage, and overall, we also plan to do a subgroup analysis by age (<20, 20-30, 30-40, >40 years).

This is a qualitative synthesis and while subgroup analyses may be undertaken it is not possible to specify the groups in advance

### 30. Review type.

This is a mandatory field

Pre-clinical animal intervention reviews have a review question in the PICO format and concern pre-clinical testing of intervention(s) in animal models of disease. Animal model reviews aim to provide an overview of animal models for a certain health problem or disease (area) and do not investigate the efficacy of treatment. They may still have a PICO review question where the intervention is the induction of a disease model. Experimental animal exposure reviews have a review question in PECO format and concern the effect of exposure to certain compounds in experimental animals, e.g. safety studies in toxicology.

### 31. Language.

Select each country individually to add it to the list below, use the bin icon to remove any added in error. The entry will default to English if no other selection is made. For languages other than English, registrants are asked to indicate whether a summary or abstract will be made available in English.

### 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.

### 33. Other registration details.

List other places where the systematic review protocol is registered. The name of the organisation and any unique identification number assigned to the review by that organisation should be included.

**Example:** All Wales Systematic Review Register (AWSRR2 Sciaticax)

### 34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one. This may be to an external site such as a journal or organisational website. Alternatively an unpublished protocol may be deposited with CRD in pdf format. A link to this will be automatically added.

**Example:** G.P.J. van Hout, S.J. Jansen of Lorkeers, K.E. Wever, E.S. Sena, W.W. van Solinge, P.A. Doevendans, G. Pasterkamp, S.A.J. Chamuleau and I.E. Hofer. Anti-inflammatory compounds to reduce infarct size in large-animal models of myocardial infarction: A meta-analysis (pages 4–10). Version of Record online: 20 JAN 2015 | DOI: 10.1002/ebm2.4

### 35. Dissemination plans.

This is a mandatory field

Give brief details of plans for communicating essential messages from the review to the appropriate audiences. Any knowledge transfer or implementation activities beyond publication of the final report that are planned should be included.

**Example:** In addition to producing a report for the funders of this review, which will be made available free of charge on their website, a paper will be submitted to a leading journal in this field. Furthermore, should the findings of the review warrant a change in practice, a one page summary report will be prepared and sent to lead clinicians and healthcare professionals in the National Health Service.

### 36. Keywords.

This is a mandatory field

Give words or phrases that best describe the review. Keywords will help users find the review in the Register. Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Information specialists at the Centre for Reviews and Dissemination (CRD) will assign MeSH terms. When the review is published, NLM assigned MeSH terms will be added where these are available.

**Example:** Systematic review; meta-analysis; recurrence; survival; radiation; resectable; soft-tissue; sarcoma.

### 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.

**Example:** This is an update of our earlier systematic review and is being undertaken in the light of the publication of significant new research. The citation for the existing review is Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis. Van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR. Brain. 2007 Dec;130(Pt 12):3063-74.

### 38. Current review status.

This is a mandatory field

Review status should be updated when the review is completed and when it is published

Select from drop down list to indicate the current status of the review:

Use the free text box to provide an explanation of the status of the review.

**Example:** Discontinued: This review has been abandoned as we have been unable to secure adequate funding to proceed.

### 39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

**Example:** This review is being undertaken as part of the planning for a randomised trial to compare all different types of radiotherapy for localised, resectable soft-tissue sarcoma.

### 40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint.

Give the full citation for the preprint or final report or publication of the systematic review, including the URL where available.

This field may also be used to record the availability of an un-published final report, summary results etc.

**Example:** This review is being undertaken as part of the planning for a randomised trial to compare all different types of radiotherapy for localised, resectable soft-tissue sarcoma.