**Protocol Template for Systematic Reviews and Meta-analyses**

*\*Indicates that a field is required*

*Note: It is recommended to answer optional fields for the review to be ready for publication, but may not be required if the results are not intended for publication*

1. **Consider registering the protocol on PROSPERO**

*If proceeding with PROSPERO registration, the following sections can be skipped. If time permits, PROSPERO registration is highly recommended since improves the credibility of a review.*

1. **Review title**

*Give the official title of the review. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.*

1. **Study coordinator/corresponding author**

*Give the title, first name, last name, and the organizational affiliations of the study coordinator or corresponding author of the review.*

1. **Review team members’ and their organizational affiliations**

*Give the title, first name, last name, and the organizational affiliations of each member of the review team. Affiliation refers to groups or organizations to which review team members belong. Review team members will be listed ‘manuscript’ style in the order entered in this list.*

1. **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. Include any unique identification numbers assigned to the review by the individuals or bodies listed.*

1. **Conflicts of interest**

*List any conditions that could lead to actual or perceived undue influence on judgments 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.*

1. **Research Question, Purpose Statement, and/or Hypothesis\***

*State the question, purpose, and/or hypothesis of the review clearly and precisely. It may be appropriate to break very broad questions/hypotheses down into a series of related more specific questions/hypotheses. Questions may be framed or refined using PI(E)COS where relevant.*

*Note: A systematic review should be highly specific and targeted on a clearly focused problem. Most reviews should only target a single research question, but multiple related questions may be given.*

1. **Background/Context**

*Describe the historical/clinical background that frames the scientific problem. Things to consider include but are not limited to:*

* 1. *Brief background about the disease, treatments, etc.*
  2. *Why is this review interesting/needed?*
  3. *What have other authors said on this topic?*
  4. *Has a similar review been conducted? How is this one different?*
  5. *How will this review impact the targeted field of research field?*

1. **Search strategy\***

Give details of the sources to be searched. The full search including the search terms is not required since that will be found elsewhere in the nest, but the following should be considered:

* 1. *Will a previous systematic review be used to define the search strategy/search terms? If so, include a reference to that review*
  2. *Who will design the search strategy?*
  3. *How will the search strategy be designed?*
  4. *Are cutoff search dates chosen? If so, why were these dates chosen?*
  5. *Which databases are chosen? How might this impact the comprehensiveness of the search?*
  6. *Were field experts consulted for additional studies that meet eligibility requirements?*

*Note: For publications in medicine Embase, MEDLINE, Web of Science, and Google Scholar at a minimum are recommended to ensure adequate/efficient coverage. PsycINFO and CINAHL databases should be searched if the research question is related to the field of psychiatry, psychology and/or to nursing and allied health.*

1. **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. For comparative efficacy studies, it is critical to guarantee that all participants could in principle be randomized to the treatments included in the review.*

*Things to consider include but are not limited to:*

1. *Patient characteristics/demographics (age, sex, etc.)*
   1. Adults
2. *Comorbidities (diabetes, heart failure, etc.)*
   1. Should we include patient with terminal illness?
   2. *Should we include patients with chronic pain?*
   3. *Should we include patients with SUD? YES.*
   4. *Should we include patients with PTSD?*
3. *Treatment eligibility requirements*
4. *Concomitant and rescue treatments*
5. **Intervention(s), exposure(s)\***

*Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed. This is particularly important for reviews of complex interventions (interventions involving the interaction of several elements). If appropriate, an operational definition describing the content and delivery of the intervention should be given.*

*Ideally, an intervention should be reported in enough detail that others could reproduce it or assess its applicability to their own setting. The preferred format includes details of both inclusion and exclusion criteria.*

*Things to consider include but are not limited to:*

*Intervention(s)*

1. *The type of treatment/therapy (if applicable, including details about the specific drug label or device used)*
2. *Treatment dose (e.g., 100mg/kg)*
3. *Dose schedule/timing of treatments (twice a day, weekly, etc.)*
4. *Route of administration (intravenous, subcutaneous, etc.)*
5. *If relevant, other important procedural details that may impact outcome assessments (anesthesia, pain medications, imaging modality used, etc.)*
6. *Concomitant therapies/rescue therapies*

*Exposure(s)*

* 1. *Patient characteristic/disease state (being specific with definitions and any coding systems used)*
  2. *Severity of disease state and how severity is measured*
  3. *Concomitant diseases/conditions*
  4. *Other important characteristics that may impact outcome assessments*

1. **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). The preferred format includes details of both inclusion and exclusion criteria. Control or comparison interventions should be described in as much detail as the intervention being reviewed. If the comparator is ‘treatment as usual’ or ‘standard care’, this should be described, with attention being paid to whether it is ‘standard care’ at the time that an eligible study was done, or at the time the review is done. Systematic reviews of qualitative studies rarely have a comparator or control; stating ‘Not applicable’ is therefore acceptable.*

1. **Types of studies to be included in the review\***

*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.*

*The preferred format includes details of both inclusion and exclusion criteria. If different study designs are needed for different parts of the review, this should be made clear. Where qualitative evidence will be incorporated in or alongside a review of quantitative data, this should be stated.*

1. **Primary outcome(s) \***

*Give the pre-specified primary (most important) outcomes of the review. Things to consider include:*

1. *The definition of the outcome.*
2. *Indicate whether the outcome is a part of the inclusion criteria of the review.*
3. *The nature of the variable, taking into account:*
   1. *Variable type: dichotomous, ordinal, nominal, continuous, etc.*
   2. *Time dependency: Time-to-event, change from baseline, repeated measures data, etc.*
   3. *Competing events (e.g., time to hospital discharge with competing risk of death before discharge)*
   4. *Composite outcomes (e.g., non-fatal heart attack or cardiovascular death) and how each component is measured and included in the composite result (weighted, unweighted, etc.)*
   5. *Units (minutes, mg/L, etc.)*
4. *Follow-up/timeframe of study and when/how often measurements are made*
5. *Any scales/clinical scoring systems used for measuring the outcome, including links/citations of the scales/scoring systems*
6. *If applicable, include details about how the outcome is adjudicated (e.g., independent safety review committee blinded to treatment group)*
7. *How do you expect the outcome to be most commonly reported? Will measures be taken to combine outcome data that are not reported according to this expected method of reporting (contacting authors, data transformations, etc.)?*

*Including a table like the one below is recommended*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Definition | Synonym | Antonym | Variable Type | NOTES |
| Mortality | All-cause mortality at 90-day follow-up. Excluding 1) all studies/patients that had the outcome at baseline (e.g., case-control studies identifying characteristics associated with a mortality population) and 2) studies that failed to include at least 90-day follow-up | * Died * Expired * Deceased * modified Rankin Scale (mRS) score = 6 | * Survived * Survival * Alive * modified Rankin Scale (mRS) score = 0, 1, 2, 3, 4, or 5 | Binary | * Give separate columns for events (n) and sample size (N) * Sample (N) = Total sample – number of subjects with missing data * Remove events with follow-up <90 days * Events recorded as 0 or 1 * 0=Survived; 1=Died |
| Time-to-recanalization | The time elapsed from first baseline angiogram to achievement of modified treatment in cerebral infarction (mTICI) score ≥2b or, if not obtained, to the final angiogram | * Puncture to recanalization * Time to reperfusion * Recanalization time * Reperfusion time * Procedure time * Procedure duration | N/A | Continuous (positive) | * Give separate columns for sample size (N), mean, standard deviation (SD), median, first quartile (Q1), and third quartile (Q3) * Sample (N) = Total sample – number of subjects with missing data * Convert units as appropriate; reference unit = minutes * Decimals given to one place greater than the original data * No censoring of times * Lower value is more favorable |

*Note: It is usually recommended to include only one primary outcome and it should be the most important/definitive measure of success. In a meta-analysis of RCTs, it is often a good idea to match the primary outcome with the most common primary endpoints of the RCTs.*

1. **Secondary outcomes \***

*List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review.*

1. **Data extraction (selection and coding)\***

*Give the procedure for selecting studies for the review and extracting data. Things to consider include:*

* 1. *Will studies be dual screened?* 
     1. *If yes, who will screen studies and who will adjudicate differences? How will differences be adjudicated (blinded assessments, third-party adjudication with discussion of disagreements with independent gatherers, etc.)?*
     2. *If no, who will screen studies?*
  2. *Will dual data gathering be performed?*
     1. *If yes, who will gather data from studies and who will adjudicate differences? How will differences be adjudicated (blinded assessments, third-party adjudication with discussion of disagreements with the independent gatherers, etc.)?*
     2. *If no, who will screen studies?*
  3. *Provide a list of the data to be extracted, being descriptive with definitions and variable types.*
  4. *Will authors be contacted for deidentified datasets or missing data? How will this be performed?*
  5. *Will multiple sources of the study results be checked for data availability (for example, extracting study results from clinicaltrials.gov or secondary reports)? Describe.*
  6. *Will any variable manipulation/transformation procedures be used? Describe.*
  7. *Will images be used for obtaining data? Describe.*

1. **Risk of bias (quality) assessment**

*State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis. Things to consider include:*

1. *Will risk of bias be performed?*
2. *Which risk of bias form will be used?*
3. *Who will perform the risk of bias?*
4. *Will dual gathering with third party adjudication be performed?*
5. *How will results of the risk of bias assessment be presented?*
6. *Will any studies be excluded on the basis of risk of bias results?*
7. *Will the results of the risk of bias assessment be incorporated in the statistical analysis?*
8. **Strategy for data synthesis \***

*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, fixed or random effects; categorizing 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. What assumptions do the statistical models make? How will these assumptions be assessed?*

*Note: an important underlying assumption of meta-analysis is exchangeability (*i.e., all studies measure the same underlying relative treatment effects, and any observed differences are due to chance*) and transitivity (in the setting of a network meta-analysis, the assumption that we can combine direct evidence to deduce a related comparison via an indirect path, given that the effect being measured is sufficiently similar/exchangeable among the included studies). Statistical procedures can be used to evaluate potential violations of these assumptions, but nothing can replace expert knowledge of the subject matter. In general, an expert with clinical background about the topic should assess whether it is sensible to combine the results of the studies, given information about the study/patient characteristics within and across studies. According to Salanti, there are at least three main assumptions to justify in order to combine results: 1) whether participants included in the network could in principle be randomized to any of the treatments, 2) whether studies are comparable in terms of the distribution of covariates and important effect modifiers, and 3) whether the direct and indirect treatment effects are in statistical agreement. The statistician will typically need input from the field expert to evaluate the first two assumptions.*

1. **Analysis of subgroups and/or moderators\***

*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. randomized or non-randomized).*

*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 categorization (e.g. BMI 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.*

1. **Limitations**

*Review the study protocol and list out any limitations associated with the review. Are any of these limitations avoidable? If so, consider refining the protocol as needed. If applicable, what future research could be conducted to mitigate or resolve these limitations?*

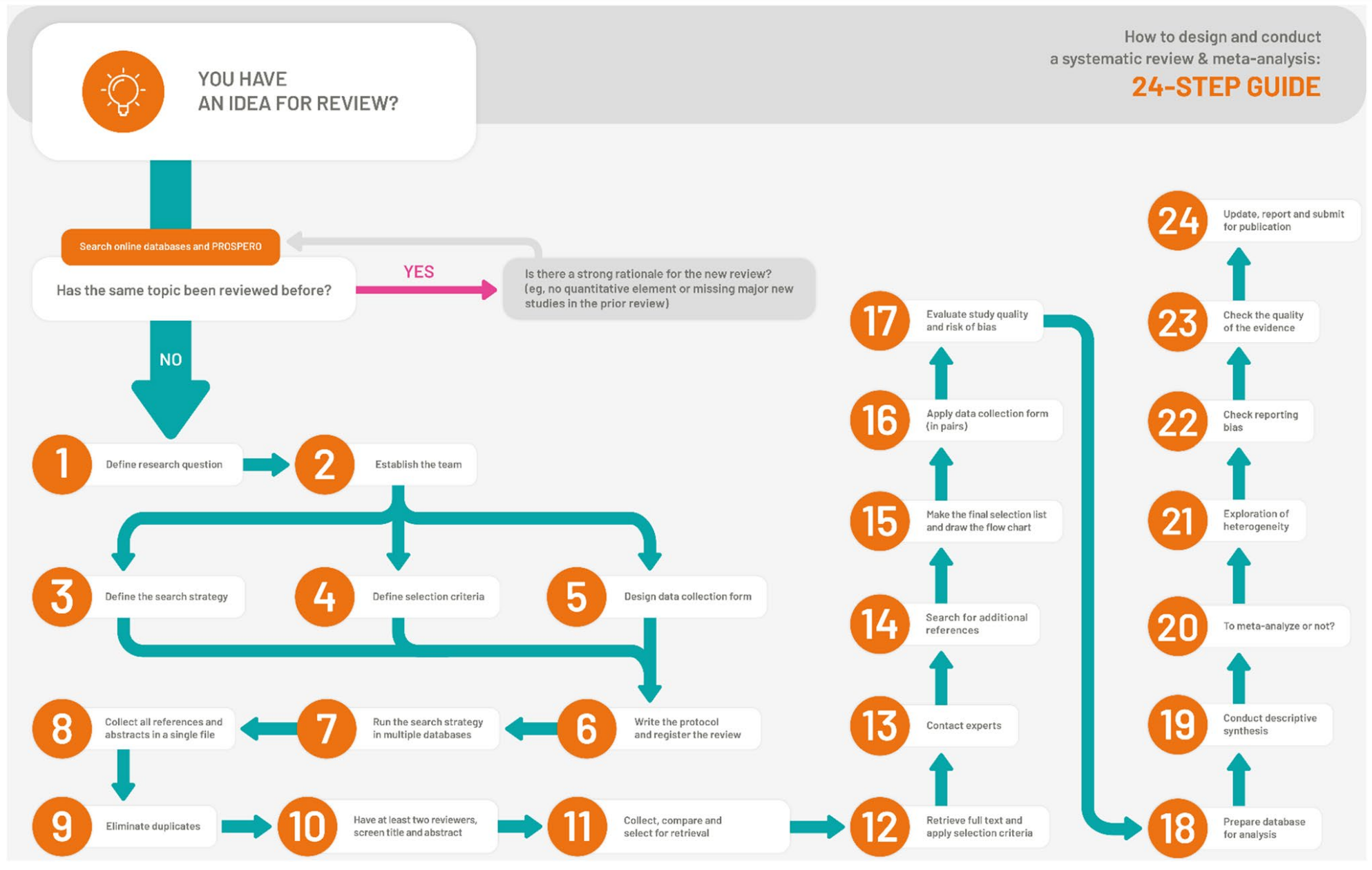
1. **Additional information**

*Provide any other information that is relevant to the review.*

**Overall Process:**

*The flowchart below summarizes the typical steps to take when conducting a systematic review. Please also see the source article for an excellent guide for conducting systematic reviews and meta-analyses:*

[*https://pubmed.ncbi.nlm.nih.gov/31720912/*](https://pubmed.ncbi.nlm.nih.gov/31720912/)

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