



# Designing and conducting systematic reviews and meta-analyses in ophthalmology

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## ABSTRACT

**Background:** Systematic reviews and meta-analyses represent the highest level of evidence in clinical research, yet their methodological quality in ophthalmology remains inconsistent despite a substantial increase in publication volume. The complexity of existing methodological guidance, such as comprehensive handbooks, may limit their practical use by clinicians and researchers. This study aims to provide a structured, field-specific guide to improve the design and execution of systematic reviews in ophthalmology.

**Methods:** This methodological review synthesizes established international standards and guidelines for systematic reviews, including protocol development, search strategy design, and study selection processes. Key methodological components were critically appraised and adapted to the context of ophthalmic research. The review focuses on the planning and execution phases prior to quantitative synthesis, outlining a stepwise framework encompassing question formulation, preliminary searching, protocol development and registration, database searching, screening, selection, and Risk of Bias (RoB) assessment.

**Results:** A comprehensive, step-by-step framework for conducting systematic reviews in ophthalmology is presented, structured into four phases and eleven key steps. The review highlights essential methodological considerations, including the formulation of focused research questions using structured frameworks (e.g., PICO and alternatives), the importance of preliminary searches, and the necessity of prospective protocol registration. It emphasizes transparent and reproducible search strategies using multiple databases and gray literature sources, as well as rigorous dual-reviewer screening and selection processes. Additionally, the appropriate application of RoB assessment tools based on study design is detailed. The findings underscore common methodological limitations in ophthalmology reviews, particularly low rates of protocol registration and adherence to reporting standards.

**Conclusions:** This review provides a practical and structured guide to enhance the methodological quality of systematic reviews in ophthalmology. By translating established methodological standards into a field-specific framework, it aims to improve transparency, reproducibility, and overall research quality. Adoption of these recommendations may address existing gaps in methodological rigor and support the generation of high-quality evidence in ophthalmic research.

## KEYWORDS

systematic literature review, meta analysis as topic, ophthalmology, ocular surgery, research methodology, evidence based medicine

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## INTRODUCTION

Systematic reviews and meta-analyses produce the highest level of evidence among study designs and hierarchy of evidence [1–3]. Bibliometric assessments have shown that in 2019 alone, almost 80 systematic review articles were published each day, and during the first two decades of the twenty-first century the publication of this class of articles increased by over twenty-fold [4]. The rapid expansion of therapeutic approaches, preventive strategies, diagnostic methods, and prognostic markers over the past two decades, alongside the growth of corresponding primary research, have given rise to a clear need for the design, execution, and dissemination of systematic reviews and meta-analyses, as there are systematic review and meta-analysis categories addressing each entity [5–7]. Along with other fields of clinical science, the field of ophthalmology has also witnessed a marked increase in the publication of systematic reviews and meta-analyses. In a recent ophthalmology bibliometric study, the average annual growth rate of systematic review and meta-analysis publications between 2000 and 2020 exceeded 20% [8].

The Cochrane Collaboration first developed a guideline for the design and execution of interventional systematic reviews in the early 1990s [9], and since then has continuously updated this resource. The current edition of the handbook for designing and conducting systematic reviews and meta-analyses of interventional studies exceeds 800 pages [10]. Unfortunately, most clinical specialists and even many clinical researchers are unable to make use of this source efficiently. For this reason, practical guidelines tailored for specialists and researchers in various clinical fields have been published across most disciplines of clinical science [11–15].

The aim of this methodological review is to present a step-by-step guide for ophthalmologists on how to design and conduct a systematic review and meta-analysis. The article is divided into two parts: Part I outlines the steps involved in planning and conducting a systematic review, and Part II describes the stages of conducting a meta-analysis.

### Steps for Designing and Conducting Systematic Reviews and Meta-Analyses:

Methodologically, systematic reviews are structured and transparent review studies that follow a set of predefined, specific steps [16]. The entire process is categorized into four phases comprising eleven steps (see [Figure 1](#)).

#### *Step 1: Developing a Systematic Review Question*

An essential and foundational step in designing a systematic review is defining the *systematic review question* [17]. In contrast to the research question in narrative reviews or scoping reviews, the question in a systematic review must be focused and highly specific [18]. A systematic review question must be *a priori* (pre-specified), and once the protocol has been registered should not be altered [19]. Typically, the question should follow a structured and formulated format. One of the most common and important frameworks for developing systematic review questions is the PICO model, which is frequently used in interventional systematic reviews [20]. The PICO structure describes the systematic review question by specifying its four components: P (Participants), I (Intervention), C (Comparison/Control), and O (Outcome)—for example: *Anti-vascular endothelial growth factor (Anti-VEGF) injections vs. panretinal photocoagulation laser therapy in patients with proliferative diabetic retinopathy for improving best-corrected visual acuity (BCVA)* [21].

A critical point for researchers to keep in mind when formulating a systematic review question is that the PICO framework is not suitable for all types of systematic reviews. Various alternative structures and question formats tailored to other widely used systematic review types such as prevalence, relational, and diagnostic accuracy systematic reviews as well as interventional ones have been described [19]. [Table 1](#) summarizes several common categories of systematic reviews along with their corresponding question formats and an example from the field of ophthalmology.

#### *Step 2: Preliminary Search*

A preliminary search refers to the phase of searching information sources or academic databases to obtain a rapid, initial assessment of the existence of any relevant studies. This assessment enables the researcher to finalize the systematic review question [13]. Considering how rapidly systematic reviews and meta-analyses are published across most clinical subspecialties in the current academic environment [4], formulating a single preliminary systematic review question is insufficient to consider it definitive and proceed directly to protocol development. Since most components of the protocol, including the systematic review question, cannot be modified after protocol registration [19], it seems reasonable to examine all aspects of the topic in greater depth. This step allows addressing the following questions:

- Do published systematic reviews or meta-analyses exist that are similar to the proposed systematic review question? If so, is there a need to update the existing review?
- Are the search terms and keywords for the predetermined systematic review questions appropriate, or do they require refinement?
- Are there any existing systematic review protocols or protocol articles whose title is similar or related to the proposed systematic review question?
- If no systematic review or meta-analysis aligned with the predetermined question exists, is there a sufficient number of eligible primary studies to warrant conducting this systematic review?

Although the guidelines for systematic reviews and meta-analyses do not provide explicit recommendations regarding the number of databases suitable for this step, we recommend that, for systematic reviews in ophthalmology (and indeed in most clinical fields), at minimum PubMed, PROSPERO [26], and Epistemonikas [27] be searched and their outputs assessed.

**Table 1. Summary of common categories of systematic reviews, their corresponding question formats, and examples from ophthalmology**

SR/MA type	Style of SR question	Example from ophthalmology
<b>Prevalence</b>	<b>POLIS</b> P: Population, Participants O: Outcome, disease L: Location, country, ... I: Indicator (prevalence, ...) S: Study design	Global prevalence of retinopathy in prediabetic patients [22].
<b>Associational or Causational</b>	<b>PECO</b> P: Participants E: Exposure, risk factor C: Control group O: Outcome	Association between triglyceride glucose index and diabetic retinopathy in type 2 diabetes [23].
<b>Interventional</b>	<b>PICO</b> P: Participants I: Intervention C: Control. comparison O: Outcome	Efficacy and safety of Rebamipide ophthalmic suspension in patients with dry eye disease [24].
<b>Diagnostic</b>	<b>PIRT</b> P: Participants I: Index test R: Reference test T: Target condition	Diagnostic accuracy of Optical Coherence Tomography Angiography (OCTA) for diagnosis and classification of diabetic retinopathy [25].

**Table 2. Guidance on selecting appropriate Risk of Bias (RoB) checklists according to study design and type of systematic review.**

SR/MA type	Types of Primary Studies	Different checklist(s) for RoB
<b>Prevalence</b>	Cross-sectional; descriptive Cross-sectional; descriptive-analytical	Hoy et al. [61] Joanna Briggs Institute (JBI)* checklist for prevalence studies
<b>Associational or Causational</b>	Cross-sectional (CS); analytical Case control (CC) Cohort (longitudinal) (CH)	Newcastle Ottawa Scale (NOS); for CC & CH [62], adapted for CS [63]. JBI checklists for all types of observational studies (analytical cross-sectional, case control and cohort)
<b>Interventional</b>	Trial (randomized or non-randomized) Experimental (true or quasi) Non-randomized studies (observational)	Cochrane RoB-1 [60] Cochrane RoB-2 [64] JBI checklists for two types of interventional studies (RCT** and quasi-experimental) ROBINS-I [65]
<b>Diagnostic</b>	Diagnostic test studies; Cross-sectional, Cohort or Case control design	QUADAS-1 [66] QUADAS-2 [67] JBI checklist for diagnostic test accuracy studies

\*: the collection of JBI checklists are named "Critical Appraisal Tools", accessible for different study designs [68]; \*\*: randomized controlled trial.

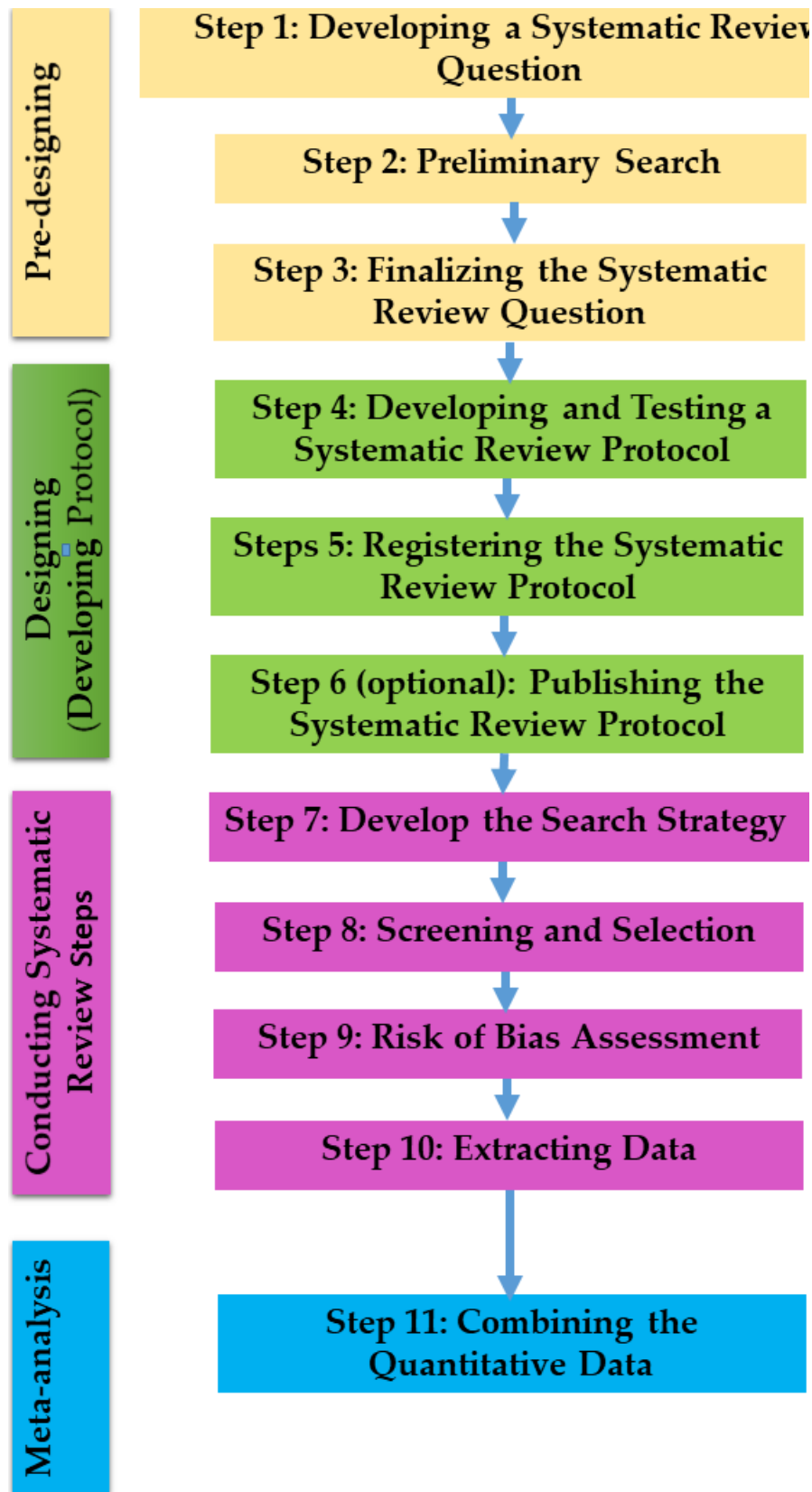


Figure 1. Steps of systematic reviews and meta-analyses in ophthalmology and other clinical medicine disciplines.

**Step 3: Finalizing the Systematic Review Question**

After completing the preliminary search and reviewing the documents identified in this step, researchers may find it necessary to revise or refine the initial systematic review question, so the authors are able to proceed to the next phase, designing the systematic review more confidently. One type of revision available to authors is the use of a narrowing strategy [28–30]. Through this approach, authors may restrict their inclusion criteria [30]. For example, if the initial plan was to include all patients affected by a particular health condition, a review of previously published studies may lead them to refine the population to a specific subgroup—such as adults or children. Experience gained from peer reviewing and assessing numerous systematic review articles across various clinical fields indicates that one of the main sources of difficulty encountered by systematic review researchers is lack of attention to this step [31].

**Execution Phase of a Systematic Review****Step 4: Developing and Testing a Systematic Review Protocol**

A systematic review protocol is a written document that describes, in a transparent and structured manner, the methodology of a systematic review. It must be developed prospectively and subsequently registered. When properly prepared, a systematic review protocol enhances methodological transparency, reduces bias, and prevents duplicate or similar systematic reviews [13, 32].

Prospective registration of systematic review protocols means that the following components must be pre-specified within the protocol and should not be amended during the execution, statistical analysis, or manuscript preparation stages:

- The systematic review question
- Eligibility criteria
- Methodological quality assessment or Risk of Bias (RoB) assessment
- Statistical analysis plan or quantitative synthesis strategy [13]

Aside from the items listed above, we strongly recommend clarifying the search strategy components plus the screening and selection processes in the protocol [33]. The largest registry for systematic review and meta-analysis protocols is PROSPERO [34], which has registered biomedical systematic review protocols since 2011 [35]. Other platforms also register systematic review protocols prospectively, including the Registries section within the Open Science Framework (OSF Registries) and INPLASY [32]. The most commonly used template for writing a protocol is the structure adopted by PROSPERO [36].

As systematic review protocol registration must be prospective, authors should ensure the validity and accuracy of all key methodological components before registration, particularly the two critical elements of eligibility criteria and search strategy. The process of evaluating these components is called protocol piloting or pilot testing of the systematic review. Pilot testing can also be applied to other components of a systematic review, such as selecting an appropriate RoB tool or designing a data extraction form [37].

**Steps 5 and 6: Registering and Publishing the Systematic Review Protocol**

Prospective registration of a systematic review protocol refers to the process of entering the components of the protocol document into a registry (such as PROSPERO or the other platforms noted above) before commencement of any operational steps of the review [32]. According to PROSPERO's stated criteria, data extraction for a systematic review must not begin prior to the completion of protocol registration [38].

Although publishing a protocol paper derived from a systematic review protocol is an optional step, a comparative assessment of systematic reviews with and without a published protocol article demonstrated superior quality and transparency in reporting of reviews accompanied by a published protocol [39]. Fortunately, for authors who wish to publish a protocol paper, an extension of the PRISMA reporting guideline, known as PRISMA-P, is available [40].

**Step 7: Developing the Search Strategy**

One of the most critical steps in conducting a systematic review is the development and execution of the search strategy. Regrettably, in many published systematic reviews the reporting of the search strategy lacks sufficient transparency and therefore fails to meet standards for reproducibility [41]. A search strategy is typically developed by addressing the following questions:

- Which sources will be searched?

The primary source for identifying eligible studies in systematic reviews is bibliographic databases. Importantly, no single database can provide a comprehensive output for a systematic review, hence systematic reviews must always use a combination of databases. Searching at least four to five databases is generally considered an acceptable approach [42]. In ophthalmology and in most clinical specialties, a suitable combination includes PubMed/MEDLINE, Scopus, Web of Science, EMBASE, and Google Scholar.

To increase the comprehensiveness of identifying eligible primary studies and to reduce publication bias, unofficial literature (gray literature) searches are also encouraged for systematic reviews [43]. Recommended categories of gray literature include theses, conference proceedings, research reports, organizational reports, and ongoing studies (in particular, recently completed clinical trials that can be identified through protocol registration platforms) [44].

- What will be the timeframe of the search?

It is recommended that the timeframe for searching both bibliographic databases and gray literature sources be explicitly defined. This is important because many systematic review questions are time-dependent (e.g., introduction of a drug, specific intervention, diagnostic technique, biomarker) and because databases differ in their archival start dates. Moreover, many guidance documents for search strategy development such as PRISMA-S emphasize the need to report search dates [45].

- Which terms or keywords will be used?

The starting point for determining search terms is to identify the components of the systematic review question. In interventional systematic reviews using the PICO framework, the Cochrane Handbook recommends building the search strategy around three elements: P (Participants), I (Intervention), and S (Study Design). However, experts generally recommend not incorporating study design into the search strategy because most primary studies do not report their study design in the abstract section of their article. Once the components have been specified, synonyms for each component must also be identified. To this end, MeSH, Emtree, or expert consultation may be used [46].

- What is the search syntax for each database?

After defining the components and their synonyms, the search syntax can be constructed using the Boolean operators OR (between synonyms of each component) and AND (between components), thereby forming the initial structure of the systematic review search [46]. Additionally, most databases allow the use of tags (fields) to specify where terms must appear in an article (e.g., title, title/abstract, full text) [46]. In most situations, the “title/abstract” field is sufficient. Further techniques such as exact phrase searching (quotation marks) and truncation [47] can substantially improve the precision and comprehensiveness of the search.

Because syntax conventions differ across databases, once the search strategy is finalized for the first database it must be adapted for all other databases. The PRISMA 2020 reporting guideline (the latest standard for systematic review reporting) recommends providing the full search syntax for every database used [48].

- Which sources will require manual searching?

Beyond electronic databases and searchable platforms (e.g., clinical trial registries), many sources of gray literature—such as conference proceedings or reference lists of relevant articles—require manual searching [49–51].

- What restrictions will be applied to the search?

Some systematic reviews may impose restrictions, for example using only English-language sources, applying geographical constraints (common in prevalence reviews with a regional or national focus), or excluding certain study designs. When such restrictions are applied, authors must provide justification and explicitly report them in the search strategy [52].

- Is an updated search necessary?

In some systematic reviews, an updated search or re-run may be needed [53], for instance when the time interval between conducting the original search and the publication of the review becomes prolonged.

### ***Step 8: Screening and Selection***

Selection of eligible primary studies is carried out according to the eligibility criteria specified in the systematic review protocol. This step consists of two processes: screening and selection. Screening refers to evaluating the titles and abstracts of all records retrieved from the search. Ideally, this process should be performed independently by two

reviewers, after which any discrepancies should be resolved either through discussion/consensus or by consulting a third expert reviewer [46].

We recommend that, to minimize errors in identifying eligible studies—particularly false-negative errors (which means exclusion of relevant articles)—the screening output be classified into three categories: included, excluded, and probable (uncertain) [54, 55]. This approach helps ensure that potentially relevant studies are not overlooked when the abstract alone does not provide sufficient clarity about eligibility.

The selection process follows screening and is conducted on studies classified into the included and probable groups. These studies undergo full-text assessment against eligibility criteria. Similarly, to the screening phase, it is recommended that the selection be carried out independently by at least two reviewers to minimize errors in including eligible studies [56].

According to the Cochrane Handbook, these two processes (screening and selection) must be documented using two components:

1. The PRISMA flow diagram, which reports number of studies retrieved from all information sources, number of duplicates removed, number of records screened and selected, and number of excluded records at each stage.
2. A list of excluded studies, based on full-text assessment, along with reasons for exclusion, enabling transparent evaluation and helping prevent false-negative errors [46].

As in the screening stage, disagreements in the selection process should be resolved through consensus or consultation with a third expert reviewer [57].

#### ***Step 9: Risk of Bias (RoB) assessment***

Once the list of eligible primary studies is finalized, steps 9 and 10 must be performed on these studies. Step 9 focuses on identifying the major sources of bias within the included studies. A systematic review may be subject to two broad types of bias:

1. Publication bias, arising from incomplete access to all available data from primary studies;
2. Study-level bias, which may vary according to the type and design of the primary studies included [58, 59].

There is considerable experimental evidence regarding the impact of bias in primary studies on their results. Therefore, tools or relevant RoB checklists are used to evaluate the level of effect of important biases. It is noteworthy that in the past, “assessment of methodological quality” was used to evaluate the internal validity of primary studies. After the first edition of the Cochrane RoB-1 checklist in 2011, the phrase Risk of Bias was suggested and became widely used [60].

Based on the type of primary study, different checklist-based tools should be used to assess the RoB. Table 2 provides guidance on selecting appropriate RoB checklists by study design and systematic review type.

After selecting the appropriate RoB tool or checklist, depending on the type of systematic review and included primary studies it is recommended to involve researchers who are familiar with the design and execution of primary studies and their biases (ideally they should be methodologists). Some guidelines for the design and execution of systematic reviews suggest that assessment and completion of RoB checklists be carried out independently by two reviewers [69]. In these circumstances, disagreements on completed checklists in each included study should be resolved through consultation with a third expert reviewer or consensus.

This methodological review presents a structured, field-specific framework tailored to ophthalmology, translating complex international guidelines into a practical, stepwise approach that enhances accessibility for clinicians and researchers. A key strength lies in the integration of established standards—including protocol registration, search strategy development, and RoB assessment—with discipline-specific considerations. However, as a narrative review it does not incorporate a formal systematic evaluation of methodological studies, which may limit its comprehensiveness. Furthermore, the recommendations may require adaptation across different ophthalmic subspecialties. Future research should aim to empirically assess the impact of such tailored guidance on the quality of published systematic reviews and to develop standardized training tools and checklists specific to ophthalmic research. The forthcoming Part II will address data extraction and quantitative synthesis in greater detail.

## **CONCLUSIONS**

In this paper, we present the first part of the design and execution guidelines for systematic reviews and meta-analyses in clinical fields, with a focus on ophthalmology. Given the expanding growth of publications of systematic reviews and meta-

analyses, the proportion of these articles in clinical journals, including ophthalmology journals, is expected to increase considerably. Unfortunately, the methodological quality of systematic reviews and meta-analyses in the ophthalmology field in terms of two criteria—pre-registration (a priori registration) and adherence to reporting guidelines (e.g. PRISMA, MOOSE)—was 5.6% and 36.5%, respectively. In ophthalmology journals, these indices were significantly lower than in journals in other fields. As a result, a specific instruction for design and execution of systematic reviews and meta-analyses for ophthalmologists and ophthalmic researchers appears to be necessary. In Part II of this series of articles, we will discuss data extraction from primary studies; data synthesis or meta-analyses; and their subset steps.

### ETHICAL DECLARATIONS

**Ethical approval:** No ethical approval was required.

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