A Systematic Literature Review Assessing the Role of Systematic Literature Reviews in Clinical Trial Design

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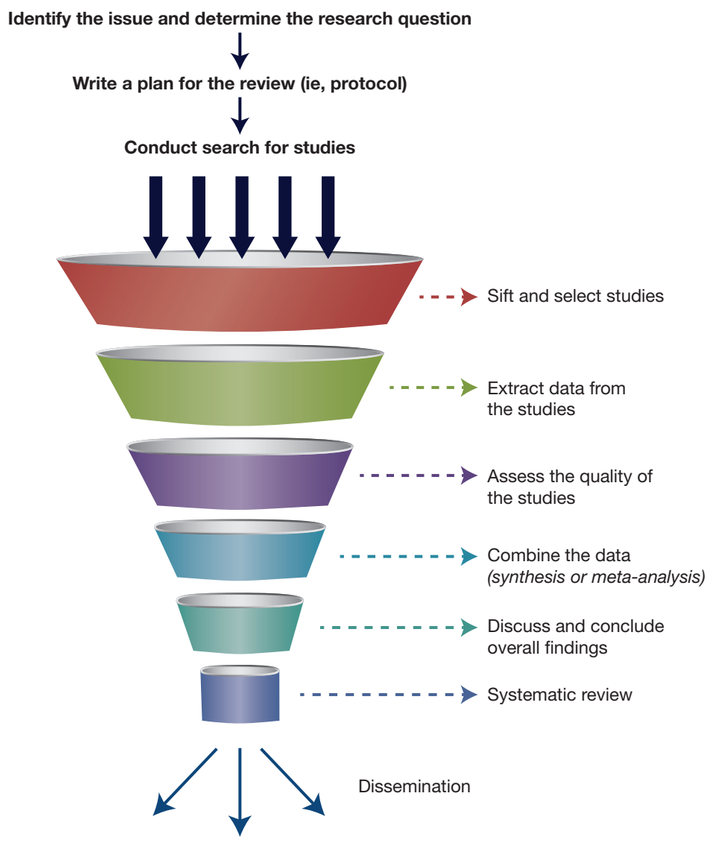
Introduction

Systematic Literature Reviews

- Systematic literature reviews (SLRs) are a key component in the evidence-based assessment of healthcare interventions.
- In contrast to the traditional or narrative literature review, SLRs use a more rigorous and well-defined approach to reviewing the literature in a specific subject area.
- Based on the utilization of a predefined structured methodology designed to identify all available research prior to the development of the study hypothesis, SLRs have become valuable resource in the critical impact analysis of therapeutic interventions across multiple research studies.
- Existing as standalone evidence, SLRs are designed to address broader clinical questions than single empirical studies, enabling such reviews to be prioritized above other research designs in the "hierarchy of evidence" due to the potential to provide practical evidence-based conclusions.[1]
- Specifically, SLRs employ a prespecified and transparent approach for searching and assessing the literature to provide greater clinical insights (**Figure 1**).

Figure 1. Process Map of Conducting a Systematic Literature Review



Clinical Trial Protocols

- Central to the implementation of clinical trials is the development of a clinical trial protocol, a document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project.
- The International Congress on Harmonization (ICH) Good Clinical Practice Guidelines identify specific topics that should generally be included in a clinical trial protocol, including background to the disease state, goals and objectives of the study, and a proposed study hypothesis.[2]
- In a similar, but abbreviated manner, each clinical trial protocol must be approved by an institutional review board (IRB), independent ethics committee (IEC), ethical review board (ERB), or research ethics board (REB), who reviewing the study hypothesis and methods proposed for research to ensure there are no ethical violations.

Potential Role of Systematic Literature Review in Clinical Trial Development

- It has been proposed that one reason for the failure of clinical trials may be due to an inaccurate study hypothesis, or the development of a clinical trial protocol that is designed to answer a different question.[3-7]
- Utilizing an SLR as part of the discovery phase may assist in identifying the full scope of scientific information available regarding a potential clinical trial design, providing valuable guidance to the development of the overall study hypothesis.
- The current use of SLRs in the development of clinical trial protocols is unknown.

Systemic Limitations for SLRs to Support Clinical Trials

- The main source of information for the IRBs, IECs, ERBs, and REBs for approving a clinical trial protocol is the investigator's brochure, which is a comprehensive document containing all of the preclinical and clinical information regarding an investigational product for the risk-benefit assessment to justify its use in humans.
  - For early-phase human trials (phase 1/2), the investigator's brochure should provide a detailed summary of all the available evidence regarding the nonclinical pharmacology, toxicology, pharmacokinetics, and metabolism of an investigational product, as well as any corresponding evidence in humans, if available.[8]
  - The summary of nonclinical pharmacology should incorporate studies assessing potential therapeutic activity and safety, including preclinical pharmacodynamics studies that evaluate efficacy in animal models.[8]
  - Recent studies of investigator's brochures, preclinical efficacy publications, and risk–benefit assessments have demonstrated significant deficits in the study design and reporting of preclinical efficacy studies,[9] as well as publication biases in both the investigator's brochures and peer-reviewed journals.[10]
  - Issues with the conduct and reporting of preclinical efficacy may be a leading cause of the poor probably of success for clinical trials in many therapeutic fields.[11,12]

Hypothesis

- There is poor utilization of SLRs in the development of clinical trial protocols.

Methods

- Authors conducted a systematic literature search of all National Library of Medicine databases to determine if study investigators are conducting an SLR when designing the protocol for phase 2/3 clinical trials.

Protocol

- A brief overview of the protocol developed and used to identify SLRs conducted as part of trial protocol development can be found in **Table 1**.

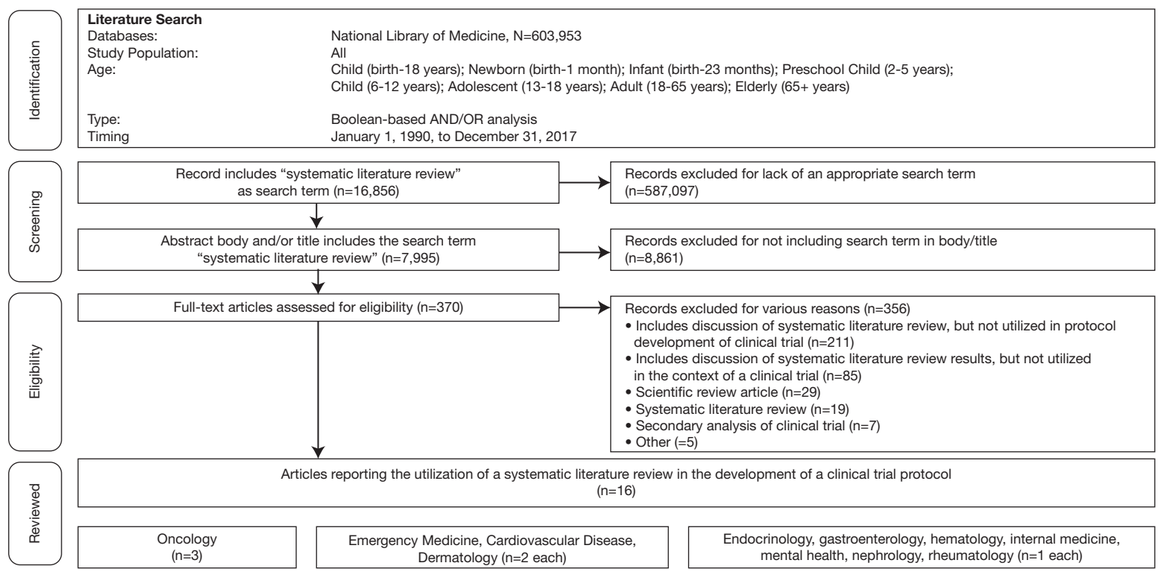
Table 1. Abridged SLR Protocol

Literature Database	National Library of Medicine
Search Type	Boolean-based AND/OR analysis
Search Terms	• Systematic Literature Review – Systematic Literature Review; Systematic Review • Clinical Trial – Clinical Trial; Clinical Trial, Phase II; Clinical Trial, Phase III; Comparative Study; Controlled Clinical Trial; Multicenter Study; Observational Study; Randomized Controlled Trial • Study Protocol – Protocol; Study Protocol; Trial Protocol
MeSH Headings	All
Study Population	All
Age	All
Ethnicity	All
Species	Human
Language	English
Publication Type	All
Journal Category	All
Timeframe	January 1, 1990, to December 31, 2017
Search Exclusions	• Clinical Trial – Clinical Trial, Phase I; Preclinical • Publication Type – (Non-systematic) Literature Review; Case Studies; Secondary Analysis • Search Terms – None • Population – None

Results

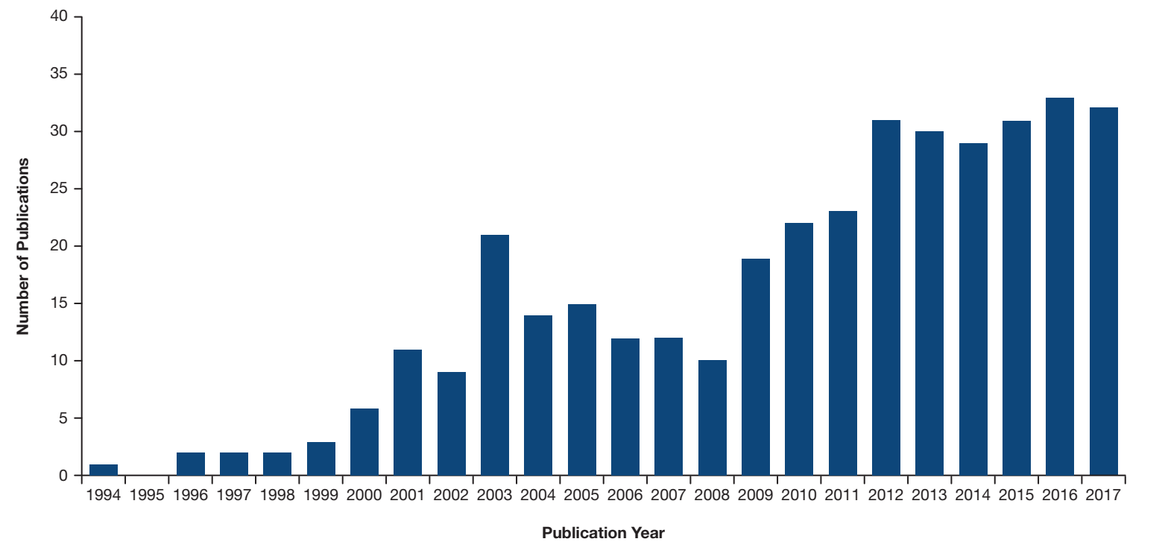
- The flowchart for the results of the SLR is presented in **Figure 2**.

Figure 2. SLR Flow Chart



- A total of 603,953 publications were identified under the protocol for the search terms "clinical trials" and "study protocols."
- With the addition of the "systematic literature review" term, the search identified a total of 16,856 publications.
- Of the 16,856 publications, a total of 7,995 utilized the terms "systematic literature review" or "systematic review" in the title or abstract body.
- Analysis of these 7,995 publications identified that only 370 discussed systematic evidence and clinical trial design within the context of the overall article.
  - Over time there has been an increase in these types of publications, though the overall total number is still relatively low (**Figure 3**).

Figure 3. Publication Timeline for Peer-reviewed Publications Meeting Search Criteria (N=370)



- Retrieval of 370 articles was conducted to challenge the study hypothesis that there is poor utilization of SLRs in the development of clinical trial protocols.
- Of the 370 articles identified for in-depth review, only 16 publications reported the results of an SLR that was conducted as part of the design of an interventional clinical trial.
  - Oncology: n=3
  - Emergency medicine, cardiovascular disease, dermatology: n=2 each
  - Endocrinology, gastroenterology, hematology, internal medicine, mental health, nephrology, rheumatology: n=1 each, with 7 focusing on a therapeutic intervention.
- The primary purpose of the 16 SLRs was to justify the unmet need asked as part of the development of the clinical trial hypothesis.
- For perspective, as of April 1, 2018, there are 14,684 phase 2 and 7,689 phase 3 clinical trials registered on the *ClinicalTrials.gov* database that are currently recruiting, enrolling by invitation, or active but not recruiting.

Conclusions

- This SLR supports the study hypothesis, indicating that SLRs are substantially underutilized in the development of clinical trial protocols, in line with other analyses.[13,14]
- Despite the well-documented importance of SLRs in evidence-based medicine and clinical practice decision-making, there is limited evidence to support the hypothesis that SLRs are being utilized when designing clinical trial protocols.
- A greater awareness of the potential role of SLRs in the design of clinical trial protocols is warranted.

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Further Readings

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