SLRs could benefit from a new approach to study identification: a case study

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Poster No. SA105

Background

- Systematic literature reviews (SLRs) that adhere to gold-standard guidelines, as prescribed by HTA bodies, remain a vital but time-consuming exercise. Current practice usually involves a single step in which study registries and databases are searched and screened simultaneously.[1,2] This conventional approach results in concurrent screening of study registry records and study reports.
- Researchers and companies alike could benefit from an initial, indicative early SLR output that maps the study landscape, ahead of the conclusion of the review, to reduce initial uncertainties and aid in early synthesis planning.
- Cooper *et al*. 2024,[3] proposed a new method of study identification for reviews of RCTs of medical interventions, which separates the identification of unique studies from study reports into separate phases (**Table 1**). This method accelerates the process of compiling a list of eligible studies and therefore permits early synthesis planning.
- A key feature of this method involves the use of a 'Living Table' (**Table 2**), which provides the reviewers with a clear record of included studies and associated study reports as the review evolves.

Objectives

- In an SLR conducted to identify efficacy and safety data of 17 interventions for the prophylactic and on-demand treatment of hereditary angioedema, the new method of study identification was implemented and evaluated.
- **The objectives of this case study were to:**
  - Assess the useability of the new process method for study identification;
  - Evaluate the advantages and disadvantages of using the new process method, relative to the conventional approach.

Methods

- The new method recommends three sequential phases of searching and screening to identify eligible studies and eligible study reports. A 'Living Table' was created during Phase 1 as suggested by Cooper *et al.*[3] and the records identified at each stage were added (example depicted in **Table 2**).
  - **Phase 1:** trial registries (clinicaltrials.gov and WHO ICTRP) were searched and screened against the PICOS, allowing the identification of unique, registered studies. The SLR protocol was finalised based on the study mapping results to permit inclusion of trial information in the search strategy.
  - **Phase 2:** study names/IDs and numbers of unique studies identified during Phase 1 were added to the search strategy employed for database searching, to increase the sensitivity of the search. Phase 2 identified study reports of the studies previously identified during Phase 1, as well as study reports of any unregistered studies.
  - **Phase 3:** additional searching of conference and HTA websites was employed, in addition to citation searching of reports previously identified at earlier phases, to identify reports of previously identified or unregistered studies.

Results

- **Table 1** presents each phase of searching and screening, and the results of each phase.
- **Phase 1** identified 70 unique studies comprising a treatment landscape of 26 RCTs of relevant interventions. These became the focus at subsequent phases.
- **Phase 2** identified 45 study reports of the 26 previously identified RCTs, and one additional report of an unregistered trial, taking the total to 27 RCTs.
- **Phase 3** identified 59 study reports of the previously identified RCTs, inclusive of 34 conference abstracts and 23 HTA/regulatory reports.

Table 1: Process of searching and study identification by Phase

Phase	Phase 1	Phase 2	Phase 3
	Unique studies were identified via searching and screening of the study registries.	Study names/ID and trial numbers identified during Phase 1 were added to the search strategy. Study reports and unregistered studies were identified via searching and screening of the databases.	Study reports and unregistered studies in the form of conference abstracts/posters and HTA documents were identified via searching and screening of conference and HTA websites. Included study reports from Phase 2 were used for citation searching.
Resources searched	**Registries:** • clinicaltrials.gov • WHO ICTRP	**Databases:** • MEDLINE (MEDALL) • Embase • Cochrane CENTRAL • CINAHL	**Conferences:** • CPCI-S • Embase conference search • AAAAI • ACAAI • EAACI **Websites:** • INAHTA • NICE • SMC • EMA • ICER • CADTH • PBAC • HAS • TLV • NMA • HILA
n screened	**n=389**	**n=5,509**	**n=696**; **n=69**
n included	**n=70** unique studies comprising **n=26** RCTs	**n=45** study reports of 26 previously identified RCTs **n=1** study report of an unregistered study	**n=59** study reports of previously identified RCTs, inclusive of **n=34** conference abstracts/posters and **n=23** HTA/regulatory reports

Table 2: Example of the 'Living Table'

Study Name/ID	Primary report	Other reports
FAST-2 (NCT00500656)	**Identified during Phase 2:** Cicardi, M *et al.* Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. New England journal of medicine. 2010; 363(6): 532-541.	**Trial registry records identified during Phase 1:** • NCT00500656. Subcutaneous Treatment With Icatibant for Acute Attacks of Hereditary Angioedema (HAE). • EUCTR2004-001540-71. Randomised, double blind, controlled, parallel group, multicentre study of a subcutaneous formulation of Icatibant vs. oral Tranexamic acid for the treatment of hereditary angioedema (HAE). **Full text publications identified during Phase 2:** • Bas, M. *et al*. Repeat treatment with icatibant for multiple hereditary angioedema attacks: FAST-2 open-label study. Allergy. 2013; 68(11): 1452-1459. **Conference/HTA records identified during Phase 3:** • AWMSG. Icatibant (Firazyr®). 2012 • AWMSG. Icatibant acetate (Firazyr®) for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency). 2008 • EMA. Icatibant Accord (icatibant). 2021 • EMA. Firazyr® (icatibant). 2023 • HAS. Firazyr® (icatibant (acetate)). 2019 • SMC. Icatibant acetate (Firazyr®). 2012

- An example of the Living Table is shown in **Table 2.**
  - This RCT was identified during **Phase 1**, via two trials register records, and added to the Living Table .
  - During **Phase 2**, the primary study report was identified, along with one additional full text publication.
  - Finally, **Phase 3** yielded an additional six HTA/ regulatory records associated with the trial.
- The Living Table was populated at each phase, allowing reviewers to initially view the trial landscape and subsequently see the study reports associated with each RCT.

Discussion

- The new method proposed by Cooper *et al*.[3] was successfully implemented and a number of advantages identified by reviewers, when reflecting on the relative benefits *versus* The Conventional Approach.
- The early overview of RCTs, delivered by Phase 1, facilitated refinement of the search strategy via the inclusion of trial information to increase sensitivity of the search.
- The early view of studies at Phase 1 rapidly informed reviewers of the nature of RCT design which served as an early indicator of the need for complex statistical synthesis as well as highlighting any requirement for PICOS amendments, before the bulk of searching and screening ensued.
- Reviewers found screening of trials registry records in an initial step, prior to screening other record types, more straight-forward and time efficient compared to the conventional approach.
- Use of the living table provided a real-time overview of the evidence base at all stages, rather than waiting for screening to complete and compiling records on completion of screening.
- An early view of the comparator RCT landscape was also of benefit to the company commissioning the review.

Conclusions

The new model of study identification, which separates out the identification of studies from the identification of reports relating to studies, offered multiple benefits to both researchers and sponsor, relative to the conventional approach. The most significant advantage was an early view of the scope for synthesis, indicating the need for advanced statistical comparisons such as network meta-analysis.

Abbreviations: AAAAI, American Academy of Allergy, Asthma & Immunology; ACAAI, American College of Allergy, Asthma & Immunology; CADTH, Canadian Agency for Drugs and Technologies in Health; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CPCI-S, Conference Proceedings Citation Index; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; HAS, Haute Autorité de Santé; HILA, Pharmaceuticals Pricing Board; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; INAHTA, International HTA database; NICE, National Institute for Health and Care Excellence; NOMA, The Norwegian Medicines Agency; PBAC, Pharmaceutical Benefits Advisory Committee; RCT, Randomised Controlled Trial; SMC, Scottish Medicines Consortium; SLR, Systematic Literature Review; TLV, The Swedish Dental and Pharmaceutical; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Presented at ISPOR Europe, November 2024, Barcelona, Spain

References:

1. Cooper C, Booth A, Varley-Campbell J, Britten N, Garside R. Defining the process to literature searching in systematic reviews: a literature review of guidance and supporting studies. BMC Medical Research Methodology 2018;18(1):85.

2. Cooper C, Booth A, Husk K, Lovell R, Frost J, Schauberger U, et al. A Tailored Approach: A model for literature searching in complex systematic reviews. Journal of Information Science 2022; 50(4):1030-1062.

3. Cooper C, Premji Z, Worsley C, Tomlinson E, Dawson S, Prentice, E. A New Process Model for Study Identification in Systematic Review: Separating Studies From Reports. Presented at ISPOR Europe 2024; Poster number: SA80, Abstract number 145742.