Non-randomized Studies in Comparative Effectiveness Research; How Systematically Are They Identified by Existing Search Filters? Results from a Systematic Literature Review

Poster #MSR44

Grammati Sarri*[1], Marie Diamond [2], Stacy Grieve [3], Mihaela Musat [4], Maria Rizzo [1]

[1]Cytel, Inc., London, UK; [2]Cytel, Inc., Rotterdam, Netherlands; [3]Cytel, Inc., Toronto, ON, Canada; [4]Cytel, Inc., Waltham, MA, US

Background

- Health technology assessment (HTA) agencies, such as the National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) have issued guidance on the use of real-world data (RWD) to resolve or supplement evidence gaps in reimbursement submissions.
- Comparative effectiveness research (CER) aims to generate and synthesize evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care. Recently, real-world evidence (RWE) from non-randomized studies (NRS) has increasingly been used in CER.
- As with other types of evidence included in HTA submissions, reliably identifying evidence from NRS is critical to ensure the unbiased selection of evidence used in CER. However, systematically identifying such NRS evidence through database searches remains a challenge.
- Furthermore, limited research exists on developing and validating NRS search filters in CER for bibliographic databases.

Objective

- This study aimed to systematically identify and appraise existing NRS search filters to identify comparative studies of two or more different interventions and discuss their individual performance in identifying NRS for use in CER.

Methods

- A systematic literature review (SLR) was conducted to identify studies presenting or appraising NRS search filters, published between January 1, 2012, and July 18, 2022. A 10-year restriction was applied to reflect the use of RWD in HTA submissions and the evolving indexing of RWE search terms.
- MEDLINE, Embase, and the Cochrane Database of Systematic Reviews databases were searched via Ovid.
- Methods guidelines and other published material available from HTA agencies such as NICE, CADTH, or Germany's Institute for Quality and Efficiency in Healthcare were also manually searched.
- The eligibility criteria are detailed in Table 1. Primary studies and SLRs reporting on the development and validation of search filters for NRS were included.
- Given the limited research in this area, any studies reporting on search filters for observational studies more broadly were also considered.
- Results were synthesized qualitatively.

Table 1. Eligibility inclusion criteria

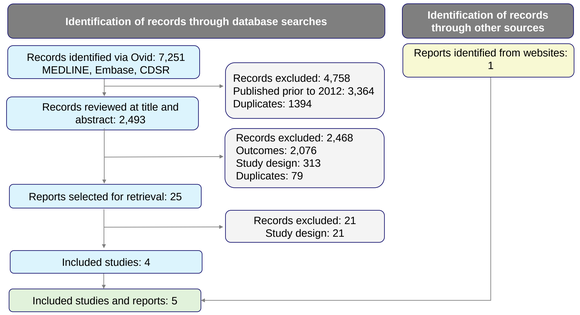
Eligibility criteria	
Population	Any population or disease indication
Intervention/comparator	All interventions or no intervention
Outcomes	NRS/observational search filters and any associated performance metrics (i.e., sensitivity, specificity, external validity)
Study design	• Studies that develop and validate a search filter and report the search terms and strategy • Systematic reviews of NRS search filters or reviews reporting NRS search strategies

Abbreviation: NRS, non-randomized study

Results

- In total, 7,251 records were retrieved from the database searches, of which 2,524 records were included for title/abstract review (after restricting to records published from 2012 onward and removing duplicates).
- Twenty-five publications were selected for full-text review and one reference (from CADTH Search Filters Database) was identified via hand-searching of HTA websites.
- Five publications (three primary studies and two SLRs) met the eligibility criteria and were included in the SLR (Figure 1).

Figure 1. PRISMA diagram



Abbreviation: CDSR, Cochrane Database of Systematic Reviews

- One study aimed to develop and validate a de novo search filter for retrieving NRS, one study aimed to translate and validate existing filters to different search platforms, and two SLRs reported search filters for different NRS study designs (some published before the search cutoff point). (Table 2) Since few search strategies were published after 2012, search strategies included in the identified SLRs were included.

Figure 2. Categories of filters identified in the SLR

Table 2. Studies identified in the SLR

Reference	Study type	Study description/objectives
Waffenschmidt 2020[1]	Search filter development and validation study	Develop a de novo search filter for retrieving interventional or observational NRS with a control group
Avau 2021[1]	Search filter development and validation study	Translate and validate filters for retrieving SLRs, interventional studies, and observational studies from MEDLINE and Embase via Ovid syntax to PubMed and Embase.com syntax
Hausner 2018[3]	SLR of NRS filters	Systematic review (in MEDLINE) and performance testing of NRS filters
Li 2019[4]	SLR of filters for observational studies	Cochrane review of search strategies to identify observational studies in MEDLINE and Embase
CADTH Search Filters Database[5]	Search filters for observational studies	Multi-database search filter (MEDLINE, Embase, PsycInfo) for observational studies

Abbreviation: CADTH, Canadian Agency for Drugs and Technologies in Health; NRS, non-randomized study; SLR, systematic literature review

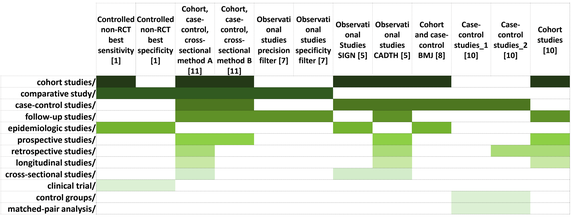
- Across these publications, 17 search filters were identified. (Table 3).
- The search filters proposed by CADTH were not formally validated and were developed for the internal reviews conducted by the agency.
- There was a high heterogeneity on the type of study design by database search across the identified filters. To allow a comparative analysis of the frequency of controlled vocabulary terms to describe NRS study design, the 12 filters considered in MEDLINE were selected (Figure 3).
- There was heterogeneity in the study design terms with more than 70 different text word searches identified; however, cohort, comparative, case control, and follow-up studies were the four most common study design terms used.

Table 3. Comparison of identified search filters

Study filters	Study types targeted	Sensitivity at development stage	Database for validation at development stage	Sensitivity at external validation
Filters identified in the present systematic review				
Best sensitivity filter Waffenschmidt 2020[1]	NRS with a control group	92.17% 92.42%	Ovid MEDLINE PubMed	NR
Best specificity filter Waffenschmidt 2020[1]	NRS with a control group	80.01% 80.89%	Ovid MEDLINE PubMed	NR
Avau 2021[2]	Observational	85% 47%	PubMed Embase	NR
CADTH[5]	Observational	NR	NR	Pragmatic validation
Filters published before 2012 identified in Hausner, 2018 and Li, 2019 systematic reviews				
Observational studies (SIGN)[6]	Observational	NR	NR	49%–90%*
MEDLINE precision (Fraser 2006)[7]	Observational	99.5%	Ovid MEDLINE	73%–88%*
MEDLINE specificity (Fraser 2006)[7]	Observational	99.5%	Ovid MEDLINE	85%–100%** 53%–85%*
MEDLINE cohort, case-control, and case series strategy (BMJ)[8]	Observational	NR	NR	55%–92%*
MEDLINE cohort, case-control, case series, and case study strategy (BMJ)[8]	Observational	NR	NR	61%–93%*
Search terms for non-RCTs (Royle 2003)◊, [9]	Non-RCT	NR	NR	46%–98%*
MEDLINE cohort study strategy (BMJ)[8]	Cohort	NR	NR	58%–69%*
Cohort studies (University of Texas)[10]	Cohort	NR	NR	52%–72%*
Case-control studies_1 (University of Texas)[10]	Case-control	NR	NR	78%*
Case-control studies_2 (University of Texas)[10]	Case-control	NR	NR	80%*
Medline cohort and case-control (BMJ)[8]	Cohort, case-control	NR	NR	61%–92%*
Fixed method A for (Furlan 2006)[11]	Comparative NRSs (cohort, case-control, cross-sectional)	48%–74% 81%–93% 76%–92%	MEDLINE Embase MEDLINE and Embase	49%–83%*
Fixed method B for (Furlan 2006)[11]	Comparative NRSs (Cohort, case-control, cross-sectional)	76%–93% 90%–100% 95%–100%	MEDLINE and Embase MEDLINE Embase	69%–85%*

*From Hausner 2018 (validation was done for MEDLINE)
**From Fraser 2006
◊search terms were provided but not in the context of a structured search strategy
Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; NR, not reported; NRS, non-randomized study; RCT, randomized controlled trial; SIGN, Scottish Intercollegiate Guidelines Network

Figure 3. Controlled vocabulary terms for study design used in at least two filters*



*Fifteen additional Medical Subject Headings (MeSH) terms were reported; eight were included in one search strategy each, while the CADTH filter included seven additional MeSH terms.

Discussion

- The SLR identified only one primary study aimed to develop and validate a search filter for NRS with a control group[1] and one more broadly for observational studies.[5]
- Among the filters identified, only one had adequate sensitivity (92%),[1] the minimum threshold required for comprehensive information retrieval.
- Among the search strategies available, there was a lack of consistency in Medical Subject Headings terms used across studies, likely due to different search filter aims (controlled NRS vs broader observational studies), and lack of standardized definition and labelling across NRS.
- Sensitivity of search strategies was affected by the overall study objective (observational, cohort, case-control) and the database (MEDLINE, Embase).
- A limitation to this study was the inclusion of search strategies published prior to 2012 based on published SLRs alone, with the assumption these SLRs were comprehensive.

Conclusions

- The optimal approach to search and identify NRS remains an under-researched topic.
- Published search filters lacked sensitivity and specificity or external validation for effective identification of NRS.
- There was limited choice among existing NRS search filters:
  - CADTH[5] recommended a search strategy [in electronic database] that is broad in scope with the largest range of controlled vocabulary (n=14 terms), but validation and performance of this strategy was not reported.
  - Waffenschmidt 2020[1] achieved adequate sensitivity (>92%) but was further limited to controlled NRS.
- Future research should focus on developing and validating NRS search filters using robust methods with reference sets outside the context of filter development to increase confidence in the optimal identification NRS. That will ultimately improve the unbiased selection of NRS in CER to be used in HTA submissions.

References: 1. Waffenschmidt et al, Res Synth Methods. 2020; 2. Avau et al, J Med Libr Assoc. 2021; 3. Hausner et al, BMC Med Res Meth, 2018; 4. Li et al, Cochrane DARE, 2019; 5. Observational Studies - MEDLINE, Embase, PsycInfo. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/36. 6. Scottish Intercollegiate Guidelines Network Observational studies: Medline http://www.sign.ac.uk/assets/search-filters-observational-studies.docx; 7. Fraser et al, BMC Med Res Methodol, 2006; 8. BMJ Publishing Group, 2012, https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/; 9. Royle et al, Health Technol Assess, 2003; 10. UTHealth School of Public Health. Search filters for various databases http://libguides.sph.uth.tmc.edu/ovid_medline_filters; 11. Furlan et al, J Clin Epidemiol, 2006.

Presented at ISPOR US | Boston, MA | May 7–10, 2023

Contact information: www.cytel.com