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Systematic Reviews in Health Research

Watch a recording of the session here

Jennifer Salerno

September 28th, 2021

Michael G. DeGroote SCHOOL OF MEDICINE

McMaster University

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Research Knowledge and Skill Builder Session: Systematic Reviews in Health Research

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Objectives

- To provide an overview of systematic review methodology in health research by introducing common approaches and frameworks.
- To share some tips and tools for conducting and evaluating systematic reviews.
- To highlight real-world examples that have used systematic review and meta-analysis methodology.

Systematic Reviews in Health Research

Cochrane Training

PRISMA

TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES

Purpose

- Provide a synthesis of the state of knowledge in a field from which future research priorities can be identified.

- PRISMA 2020 -

Defined

- A review that uses explicit systematic methods to collate and synthesize findings of studies that address a clearly formulated question.

- Cochrane Handbook of Systematic Reviews -

Typology of Reviews

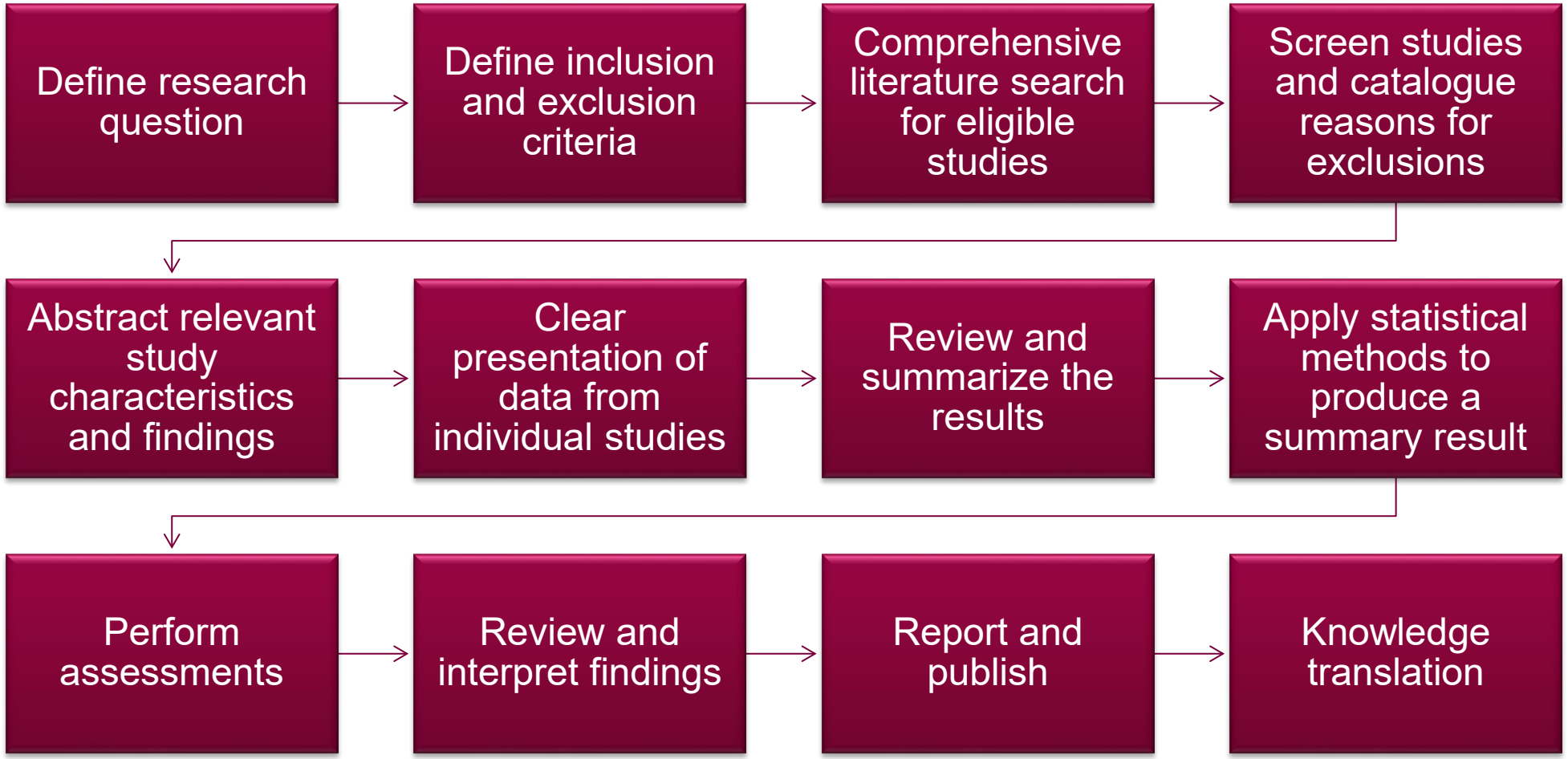
- Critical review
- Literature review
- Mapping review/systematic map
- Meta-analysis
- Mixed studies review/mixed methods review
- Overview
- Qualitative systematic review/qualitative evidence synthesis
- Rapid review
- Scoping review
- State-of-the-art review
- Systematic review
- Systematic search and review
- Systematized review
- Umbrella review

Grant et al. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Information and Libraries Journal. 2009;26:91-108.

Sutton et al. Meeting the review family: exploring review types and associated information retrieval requirements. Health Information & Libraries Journal. 2019;36:202–222.

…48 review types categorized into 7 broad groupings…

Overview: Components of a Systematic Review



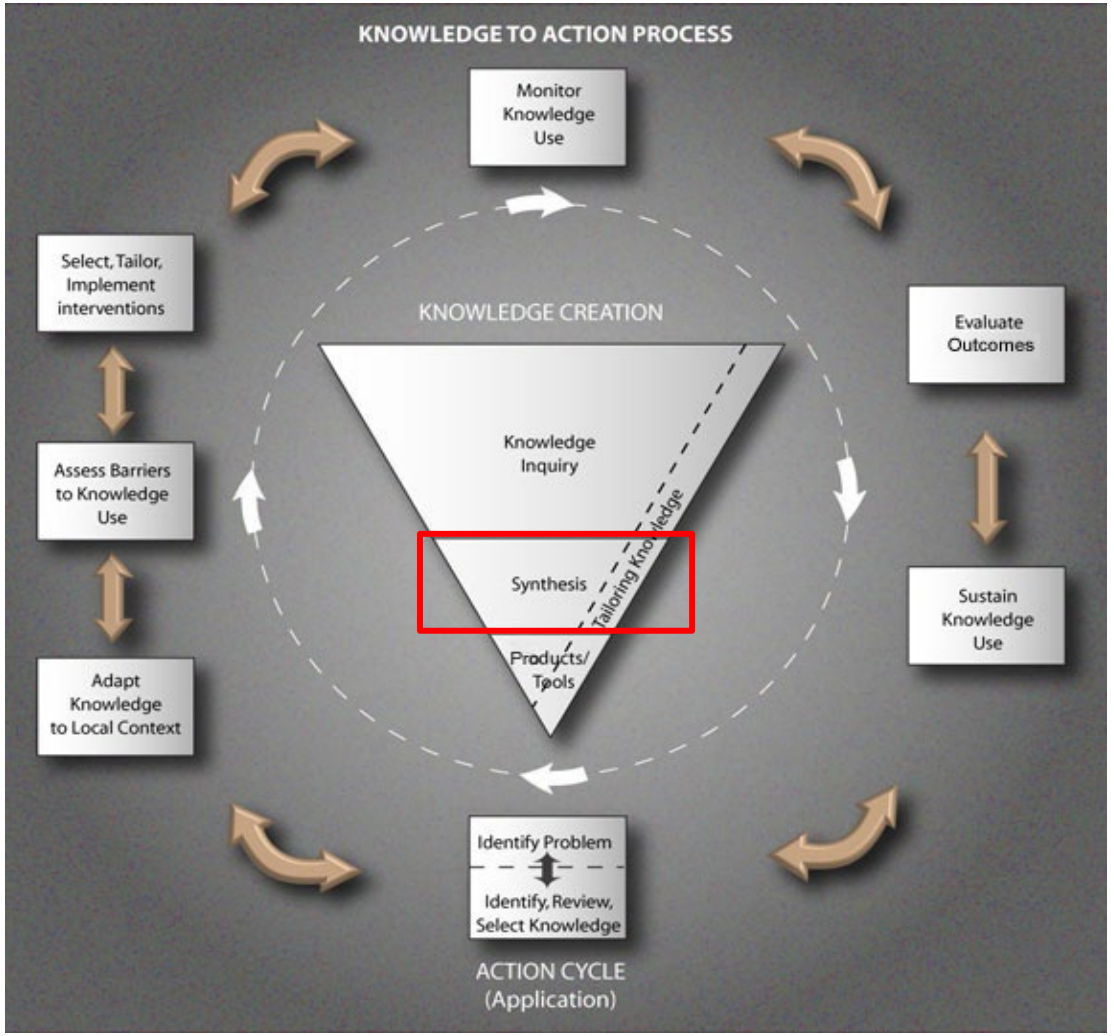
Developing Research Questions

- Where do good research questions come from?
- How do I take clinical experience and create a research question?
- **Highlight:** Six Aspects of Clinical Work

Richardson et al. The well-built clinical question: a key to evidence-based decisions. ACP Journal Club. 1995;Nov/Dec:A12-A-13.

Developing Research Questions

- How do you want your systematic review to be used?
- Various types of knowledge for different users
- **Highlight:** Knowledge-to-Action Framework (K2A)



Straus et al. Defining knowledge translation. CMAJ. 2009;181:3-4.

How to Get Started?

- ***PICO*** framework
- ***FINER*** criteria
  - *"Feasibility depends largely on the existence of a set of studies of the question"*
  - Broad questions: unmanageable
  - Narrow questions: empty review
- Iterative process initially
  - Clarify priorities and scope with end-users

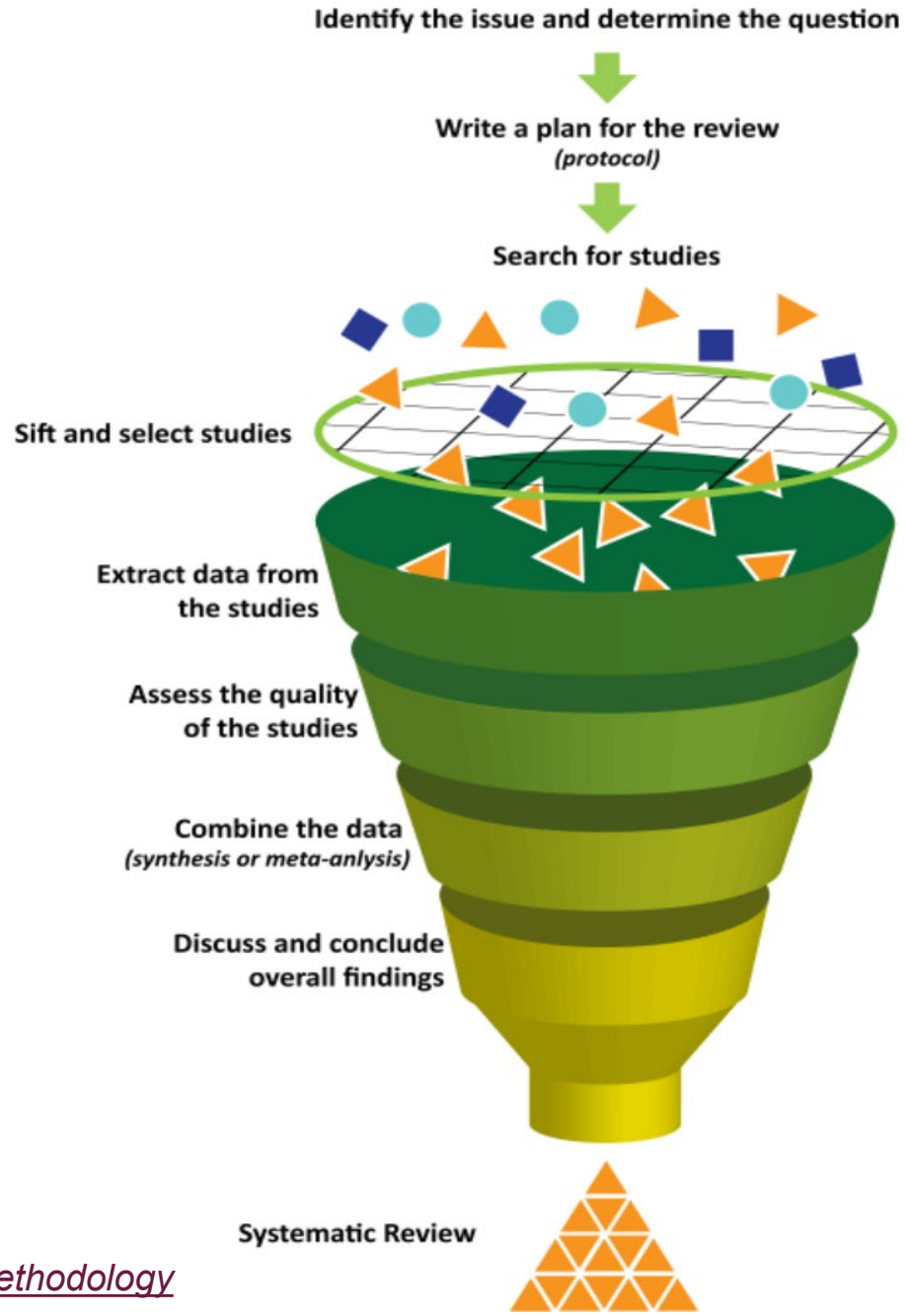


Figure: Mayo Clinic: https://libraryguides.mayo.edu/systematic-reviews/methodology

Preliminary Knowledge Synthesis

- Describes the background and significance
  - Why did you select this topic?
  - Magnitude of the problem?
- Outlines the key components of the systematic review
  - E.g., Research question, inclusion/exclusion criteria, key search terms, search dates etc.
- Summarizes findings from a preliminary literature search
  - E.g., Number of studies? Type of studies? Year of publication?

Preliminary Knowledge Synthesis

- Provides a clear rationale for choices
  - Change of clinical practice at a point in time?
  - Inclusion of key literature in search dates?
  - Study types: non-RCTs only?
  - Outcomes of interest?
- Engages your end-users for feedback and review
  - Inform feasibility
  - Opportunity for tailoring

Develop Systematic Review Protocol

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Define key components of the research question

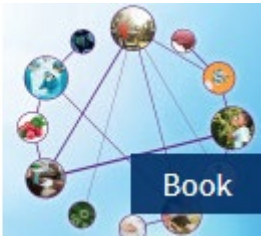
- PICO Framework, https://guides.lib.unc.edu/pico/about
  - P: population
  - I: intervention
  - C: comparator
  - O: outcome

UNC | UNIVERSITY LIBRARIES Health Sciences Library

Clearly articulate a detailed plan

- Cochrane online tool, https://training.cochrane.org/handbook/current
- Register protocol on PROSPERO, https://www.crd.york.ac.uk/prospero/

Cochrane Handbook for Systematic Reviews of Interventions



NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Consider *a priori* the criteria of what constitutes a high-quality systematic review

- Equator Network and PRISMA 2020 Reporting Guideline, https://www.equator-network.org/ and http://www.prisma-statement.org/
- Assessment of Quality: AMSTAR 2, https://amstar.ca/

PRISMA
TRANSPARENT REPORTING OF SYSTEMATIC REVIEWS AND META-ANALYSES

equator network

AMSTAR

Example #1

Ontario

Medical Advisory Secretariat
Ministry of Health and Long-Term Care

Systematic review question:

- What is the effectiveness of the Da Vinci Surgical System vs. laparoscopy and laparotomy for women undergoing any hysterectomy for the surgical treatment and management of their endometrial and cervical cancers?
- **What are the PICO elements?**
- **Can you recognize any built-in contingencies?**

Robotic-Assisted Minimally Invasive Surgery for Gynecologic and Urologic Oncology. Available: https://www.hqontario.ca/Portals/0/Documents/evidence/reports/rev_robotic_surgery_20101220.pdf

Defining Inclusion and Exclusion Criteria

- Study publication dates and language
- Publication types
- Study design(s)
- Study population
- Intervention
- Comparator or control group(s)
- Acceptable outcomes
- Other study design requirements

Example #2

Multiparametric magnetic resonance imaging for pre-treatment local staging of prostate cancer: A Cancer Care Ontario clinical practice guideline

Jennifer Salerno, PhD;[1] Antonio Finelli, MD;[2] Chris M... MD;[3] Nicholas Power, MD;[4] Nichola Schieda, MD;[5] Masoom A. Haider, MD[6]

Inclusi

Language

Publication dates

- Studies p...lished from Jan 1, 2008 to Feb 17, 2016.
- English language, humans, adults ≥18 years of age.

Study population

- Studies on pre-t... staging of prostate cancer.
- Studies o... with newly diagnosed biopsy-confirme... cer who are candidates for radical tr...

Intervention

- Studies using MRI of at least ... ± ER ± DCE, DWI, MRS.

Study design

- Studies that are systematic reviews, meta-analyses, randomized controlled trials, prospective or ...ve observational stu... ver the ...uestions of interest.

Other study design features

Acceptable outcomes

- ...porting at least one outcome of interest.
- Studies of a minimum size of 30 patients.

Exclusion criteria

Publication types

- Case reports (n=1), conference abstracts, in vitro, or animal studies.
- Studies of the technical aspects of MRI ± DCE, DWI, MRS.
- Studies of prostate cancer patients post-treatment (e.g., hormonal o... or surgery).

Intervention

- Studies pre-biops... ...osis/detection of prostate cancer.
- Studies of combined technologies (e.g., MR... guided TRUS biopsy in the diagnosis of prostate ca... positron emission tomography).

Study population

- Studies in which patients have been previously diagnosed and clinically staged and are under surveillance.

Other study design features

- Studies in which the study methods are not well-described or not clear.

Abbreviations: ER, endorectal coil, DCE, dynamic contrast-enhanced imaging; DWI: diffusion-weighted imaging; MRI, magnetic resonance imaging; MRS, proton magnetic resonance spectroscopic imaging; T, tesla; TRUS, transrectal ultrasonography.

Performing the Literature Search

- Specify all information sources (e.g., databases, reference lists) searched or consulted to identify studies
  - Specify the date range and the last search date
- Present the full search strategy for *all* databases, registers and websites, including any filters and limits used
- Specify the rules for updating
- Describe the results of the literature search and study selection process
  - E.g., number of records identified, exclusions and reasons, number of studies included in the review
  - Presented using a flow diagram

Example #2

- Search for Primary Literature
  - EBM Reviews
    - Cochrane Central Register of Controlled Trials
    - Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effects
    - Health Technology Assessment
  - OVID MEDLINE
  - EMBASE

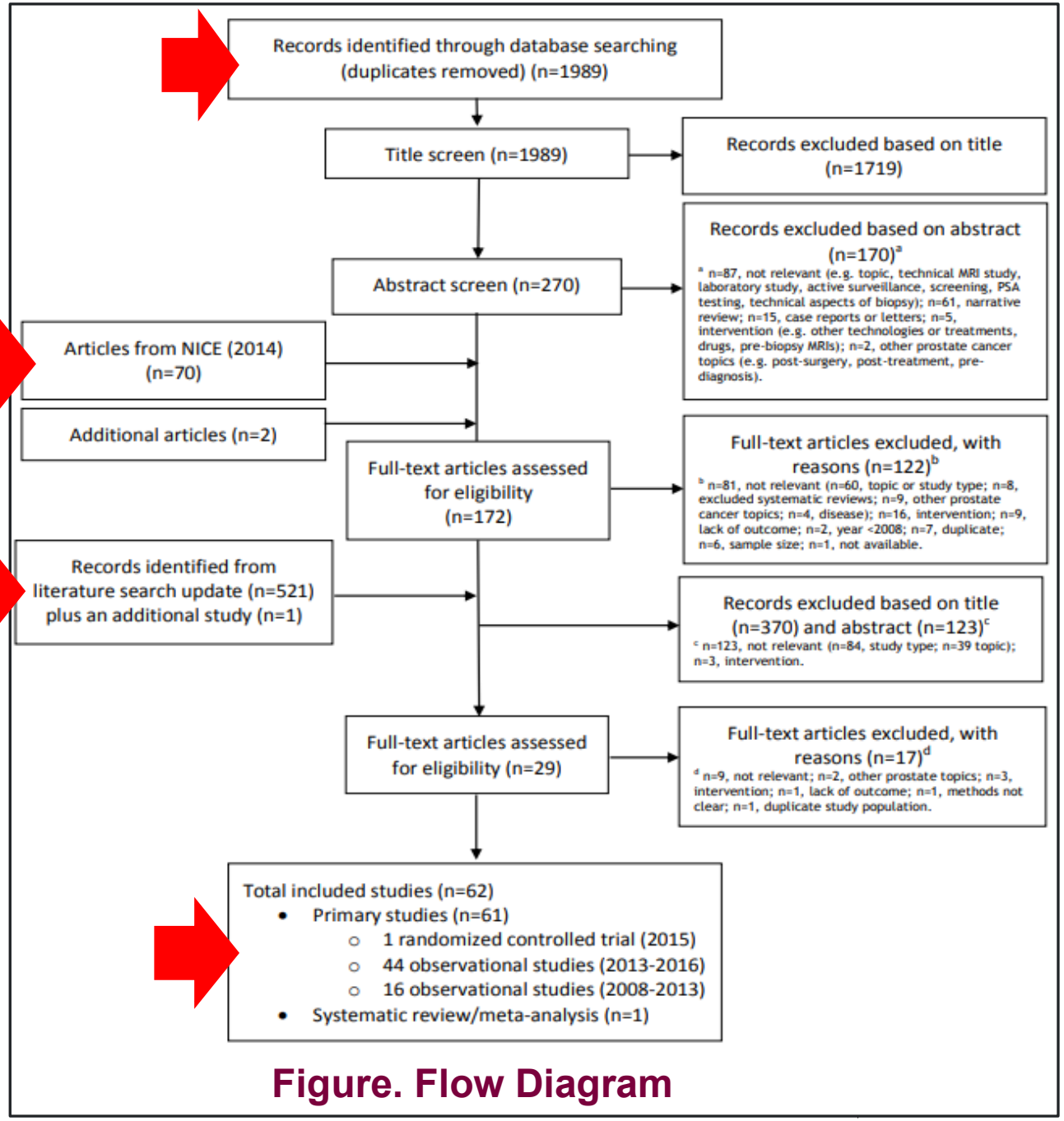


Figure. Flow Diagram

Magnetic Resonance Imaging for Pre-Treatment Local Staging of Prostate Cancer. Cancer Care Ontario Guideline (March 2016). Available: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/606.

Eligibility, Screening and Reviewing Studies

Title and abstract screening

- Endnote v. 20 for tracking
- Comparison of software management (U of T, Gerstein)
- Distiller software, https://www.evidencepartners.com/

Full-text review for eligible studies

- Apply the details of the inclusion and exclusion criteria

Data abstraction of study characteristics

- Key characteristics (e.g., author and publication date, study design features, characteristics of study population and intervention, results etc.)
- Look to inclusion and exclusion criteria for guidance
- Look to assessments (e.g., risk of bias, certainty/quality of evidence) for guidance
- Develop tables that will inform and 'tell the story'

Considerations:

- Develop forms and templates, with end-users
- Determine number of reviewers and any processes for working together and confirming data
  - ❖ Independent review
  - ❖ Uniformity
  - ❖ Unbiased

Meta-Analysis in Health Research

- **Purpose**
  - Systematically combine studies that have used comparable methods and produce a new summary estimate of effect.

- Berman et al., 2002 -

- **Defined**
  - A statistical technique used to synthesize results when study effect estimates and their variances are available, yielding a quantitative summary of results.

- Cochrane Handbook of Systematic Reviews -

Considerations for a Meta-Analysis

- Availability of data in published papers
- Nature of outcome
  - Categorical vs. continuous
- Type of analysis
  - Risk ratio / relative risk vs. (standardized) mean difference
- Benchmarks
  - Evaluation of heterogeneity, subgroup analysis, minimal important difference

Example #3

- Nurse-led and pharmacist-led care in the home for the management of heart failure reduced all-cause mortality and hospitalizations

Care in the Home for the Management of Chronic Heart Failure

Systematic Review and Cost-Effectiveness Analysis

Jennifer Fergenbaum, PhD; Sarah Bermingham, MSc; Murray Krahn, MD; David Alter, MD; Catherine Demers, MD

	CHM		UC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Brotons (2009)	60	144	75	139	26.7%	0.77 [0.60, 0.99]	
Iraurgui (2007)	62	137	75	142	25.8%	0.86 [0.67, 1.09]	
Inglis (2006)	130	149	135	148	47.5%	0.96 [0.88, 1.04]	
Total (95% CI)		430		429	100.0%	0.88 [0.80, 0.97]	
Total events	252		285				

Heterogeneity: $Chi^2 = 5.24$, $df = 2$ ($P = 0.07$); $I^2 = 62\%$

Test for overall effect: $Z = 2.59$ ($P = 0.010$)

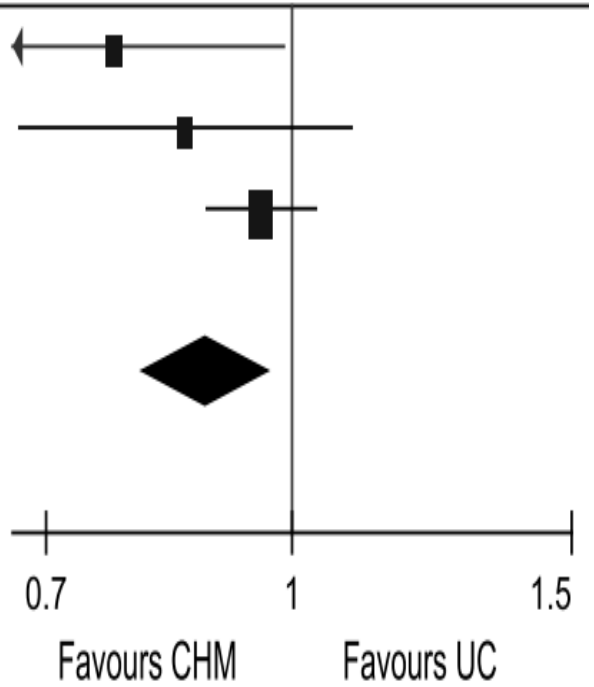


FIGURE 2. *Care in the home versus usual care for the outcome all-cause mortality and hospitalizations.*

Evaluating Risk of Bias – Individual Studies

- Critical appraisal by study design
  - Domains of evaluation based on a study's internal validity
  - Several different tools available (in-depth vs. nimble)
- Randomized Controlled Trials
  - **Cochrane Risk of Bias Tool (RoB 2.0)**
- Observational Studies
  - **Risk of Bias in Non-Randomized Studies - of Interventions Tool (ROBINS-I)**

Riskofbias.info, https://www.riskofbias.info/welcome; Summary of tools, U of T Gerstein Library: Available: *https://guides.library.utoronto.ca/c.php?g=713309&p=5121959*

Evaluating the Certainty of Evidence

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- GRADE approach to examine the body of evidence and summary estimate
- Group included studies by outcome
- Evaluate using the 5 pillars of GRADE:

1. **Study limitations**
   - ❖ Risk of bias for individual study design and execution
   - ❖ E.g., RoB, ROBINS-I critical appraisal tools
2. **Inconsistency**
   - ❖ Heterogeneity in the data (i.e., I^2 statistic, clinical or methodological reasons)
   - ❖ ICEMAN Tool: evaluation of subgroup analysis (Meta-analysis of RCTs)

GRADE Working Group, https://www.gradeworkinggroup.org/

Evaluating the Certainty of Evidence

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3. **Indirectness**
   - ❖ Alignment with defined PICO components
4. **Imprecision**
   - ❖ Small sample, few events and wide confidence intervals
5. **Publication bias**
   - ❖ Small studies, funded by industry

- Assess the extent of limitations for each
- Overall quality of evidence rating: very low, low, moderate, high

GRADE Working Group, https://www.gradeworkinggroup.org/

Example #3: GRADE Evidence Profile

GRADEpro GDT

https://gradepro.org/

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile for Comparison of In-Home Care and Usual Care: Mortality

No. Of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
All-cause mortality – heart failure patients							
5 (RCTs)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	Serious limitations (-1)[b]	Undetected	n/a	⊕⊕ Low
All-cause mortality – chronic disease							
1 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (-1)[b]	Undetected	n/a	⊕⊕⊕ Moderate
Combined all-cause mortality and hospitalizations							
3 (RCTs)	Serious limitations (–1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	n/a	⊕⊕⊕ Moderate
Cardiovascular-specific mortality							
2 (RCTs)	Serious limitations (–1)[c]	No serious limitations	No serious limitations	Serious limitations (-1)[b]	Undetected	n/a	⊕⊕ Low

In-Home Care for Optimizing Chronic Disease Management in the Community: An Evidence-Based Analysis. Vol 13, No. 5, 2013. MOHLTC. In: Optimizing Chronic Disease Management in the Community (Outpatient) Setting (Sept 2013). Available: https://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/Reviews-And-Recommendations/Optimizing-Chronic-Disease-Management-in-the-Community-Outpatient-Setting

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Evaluating Critical Domains of a Systematic Review

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

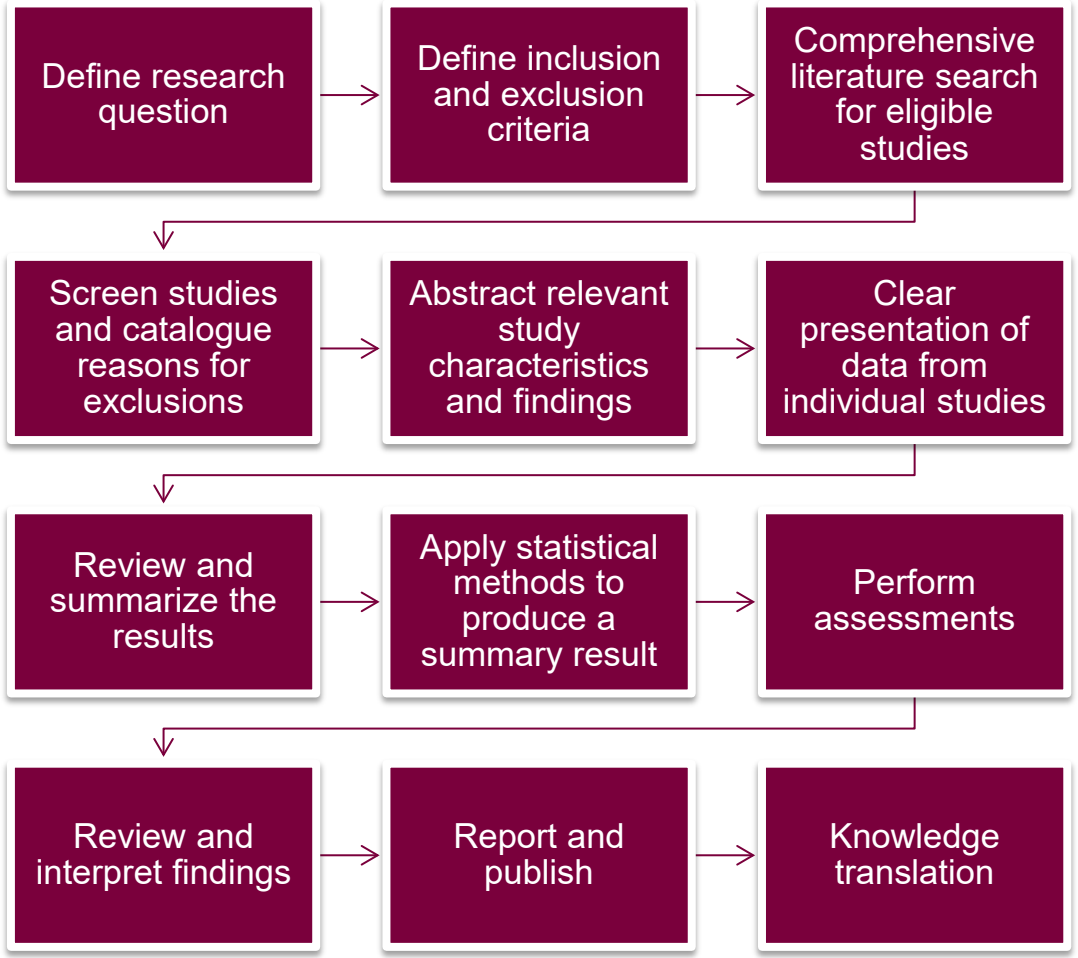
Beverley J Shea,[1,2,3] Barnaby C Reeves,[4] George Wells,[3,5] Micere Thuku1,[2] Candyce Hamel,[1] Julian Moran,[6] David Moher,[1,3] Peter Tugwell1,[2,3,7] Vivian Welch,[2,3] Elizabeth Kristjansson,[8] David A Henry[9,10,11]

thebmj

- ✓ Protocol registered before commencement of the review
- ✓ Adequacy of the literature search
- ✓ Justification for excluding individual studies
- ✓ Risk of bias from individual studies being included in the review
- ✓ Appropriateness of meta-analytical methods
- ✓ Consideration of risk of bias when interpreting the results of the review
- ✓ Assessment of presence and likely impact of publication bias

Assessment of Quality: AMSTAR 2, https://amstar.ca/

Summary: Systematic Review Approach



- Rigorous, well-designed approach
- Aims to minimize bias and provide transparency
- Comprehensive
- Systematic
- Others can replicate
- Specific methodology

Key Takeaways

- Research and clinical experiences can lead to a clearly defined research question
- Use preliminary work for topic refinement and tailoring
- Engage knowledge-users / end-users
- Clearly describe methods and perform a comprehensive literature search as it relates to your question of interest

Key Takeaways

- Perform critical appraisal and apply the appropriate risk of bias assessment tool to individual studies
- Evaluate the certainty of evidence using the GRADE approach for studies by outcome to support conclusions
- Several helpful online resources, handbooks, software, and reporting guidelines

“Not all reviews have to be systematic reviews, but all reviews should follow a system of injuiry”

- Sutton et al. 2019 -

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Thank you!

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