Introduction and course overview

Lecture #1

CHSC 7362
Systematic reviews and meta-analysis

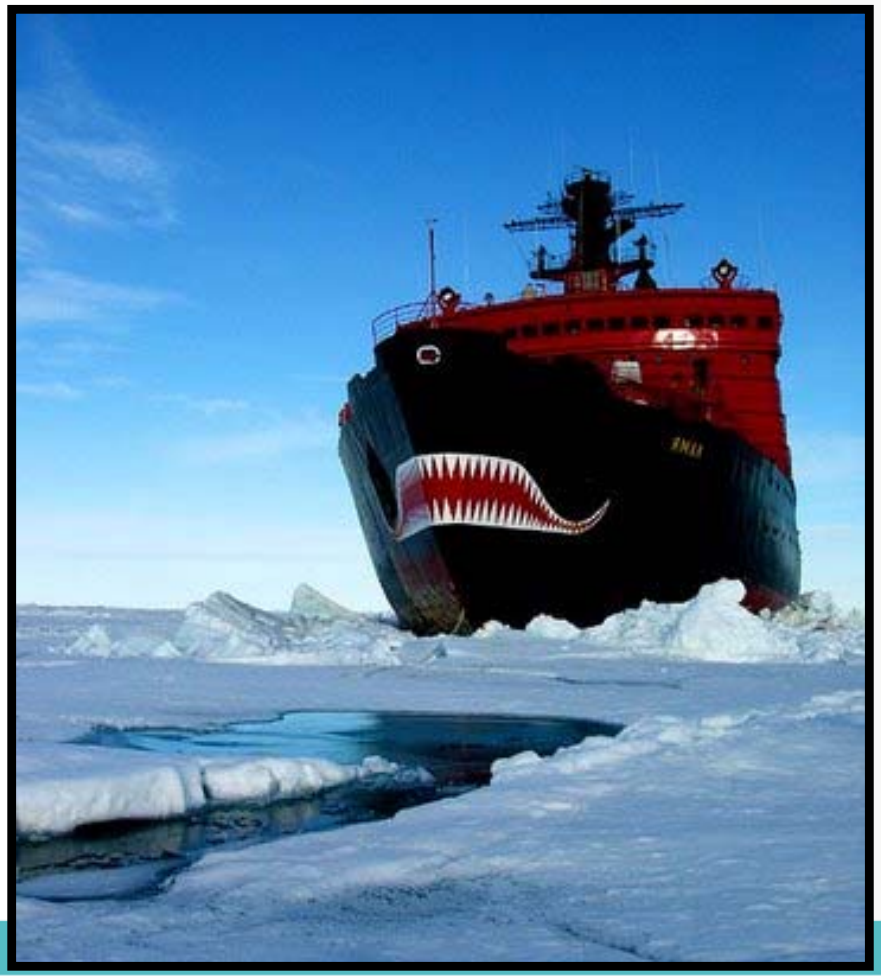
Lecture 1: Objectives

- Introductions
- Course structure
- Assignments and course evaluation scheme
- Primary course resources (textbook, readings, software)

- Lecture 1:
  - What is a systematic review?
  - Purpose and function of systematic reviews
  - Types of systematic reviews
  - Steps required to complete a systematic review
  - Forming systematic review questions
  - Completing and registering systematic review protocols


BRACE YOURSELF
THE ICE BREAKERS ARE COMING
makeameme.org

Ice Breaker! Tell us…



- What's your academic background?
- What is your past exposure to epidemiology? (courses, work experience)
- What exposure you'd had to SR/MA?
- Specific goals you hope to achieve by taking this course?
- Something interesting about you

Course Structure

- 12 x 3-hr seminars, including class presentations
  - Mix of lectures
  - Exercises and practical experiences
  - Reviewing published systematic reviews
  - Solving challenges regarding your own systematic review
- All seminars will be in held virtually over Zoom until end of February
- In-person seminars planned to be live-streamed over Zoom

Zoom details

- Topic: Systematic reviews and meta-analysis course
- Time: Thursdays, 1:00 – 3:50 PM

- Join Zoom Meeting: https://us02web.zoom.us/j/8398046440?pwd=TXM5NWM0VDdRZFhuQjR3VVFxc0tqZz09
- Meeting ID: 839 804 6440
- Passcode: 12345
- One tap mobile: 8557038985,,8398046440# Canada Toll-free
- Dial by your location: 855 703 8985 Canada Toll-free
- Find your local number: https://us02web.zoom.us/u/keymjOLKsc

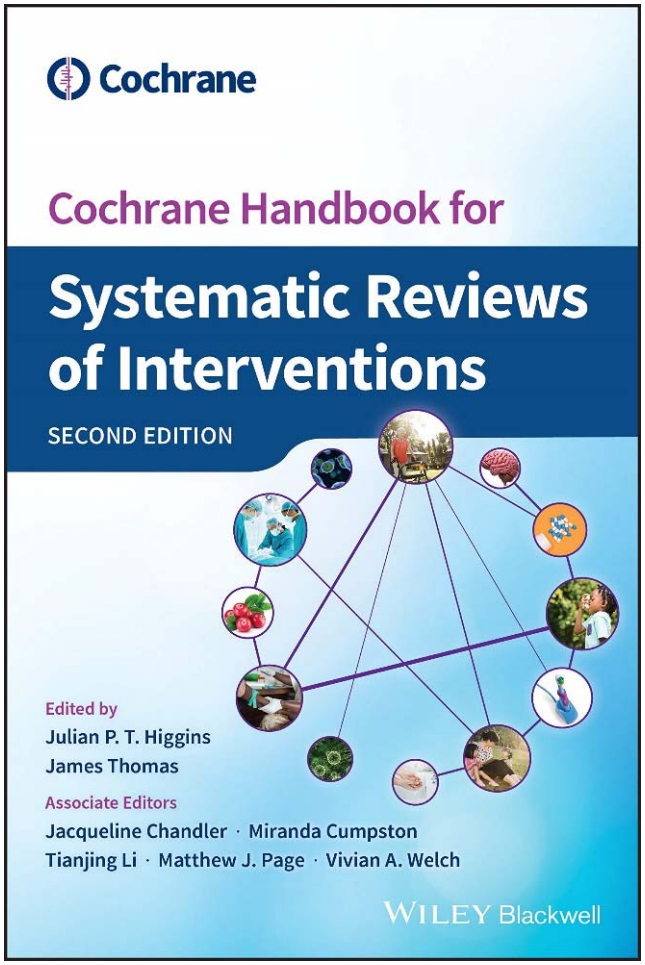
Office hours / Contacting the instructors

- Contact the specific profs/ instructors to arrange a time to meet
- Meetings will take place over Zoom or in-person
- We are here to help!

Evaluation and Grades

You will receive a letter grade based on the following:

- Systematic review question development — 10% (Feb 17)
  - PICOS style – template to be provided
- Protocol — 25% (Mar 17)
  - 10 - 12 pages – template to be provided
- Final full report — 55% (Apr 28)
  - ~20 - 25 pages – template to be provided
- Class participation and presentations — 10%
  - SR review question (5 min, Max of 5 ppt slides) (Feb 10)
  - Your SR/MA (10 min, Max of 12 ppt slides) (Apr 21)



Course Requirements

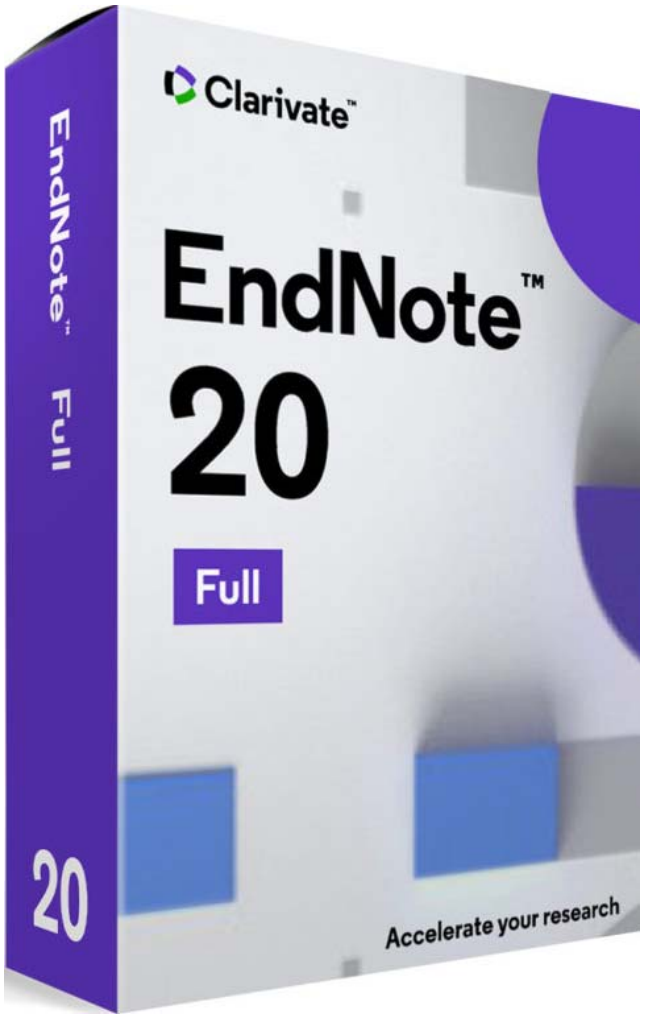
Cochrane Handbook for Systematic Reviews of Interventions version 6.2

https://training.cochrane.org/handbook/current

Review Manager (RevMan) 5

https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download/download-and-installation

Cochrane RevMan



Course Requirements

Endnote 20

https://libguides.lib.umanitoba.ca/citationmanagers/endnote

The University of Manitoba Libraries **does not** offer a site license for EndNote.

EndNote can be **purchased** from the University Bookstore for $149.99 for students.

Members of the University of Manitoba community have **free access to EndNote Web**, a web-based version of EndNote which is intended to be used with EndNote Desktop.

Additional items

Readings (via drop box)

- Additional readings (optional)
- Lecture slides
- Recorded Zoom sessions

Overall course objectives

- To recognize what a systematic review is, the types of systematic reviews and their purpose, and how systematic reviews are used in health-care decision making.
- To learn how to plan, conduct and report a systematic review and meta-analysis.
- To complete a systematic review including preparing a protocol, conducting the review, meta-analysing data, and reporting the results orally and in a manuscript.

** Focus will be on SR/MA of randomized trials **

Course Schedule

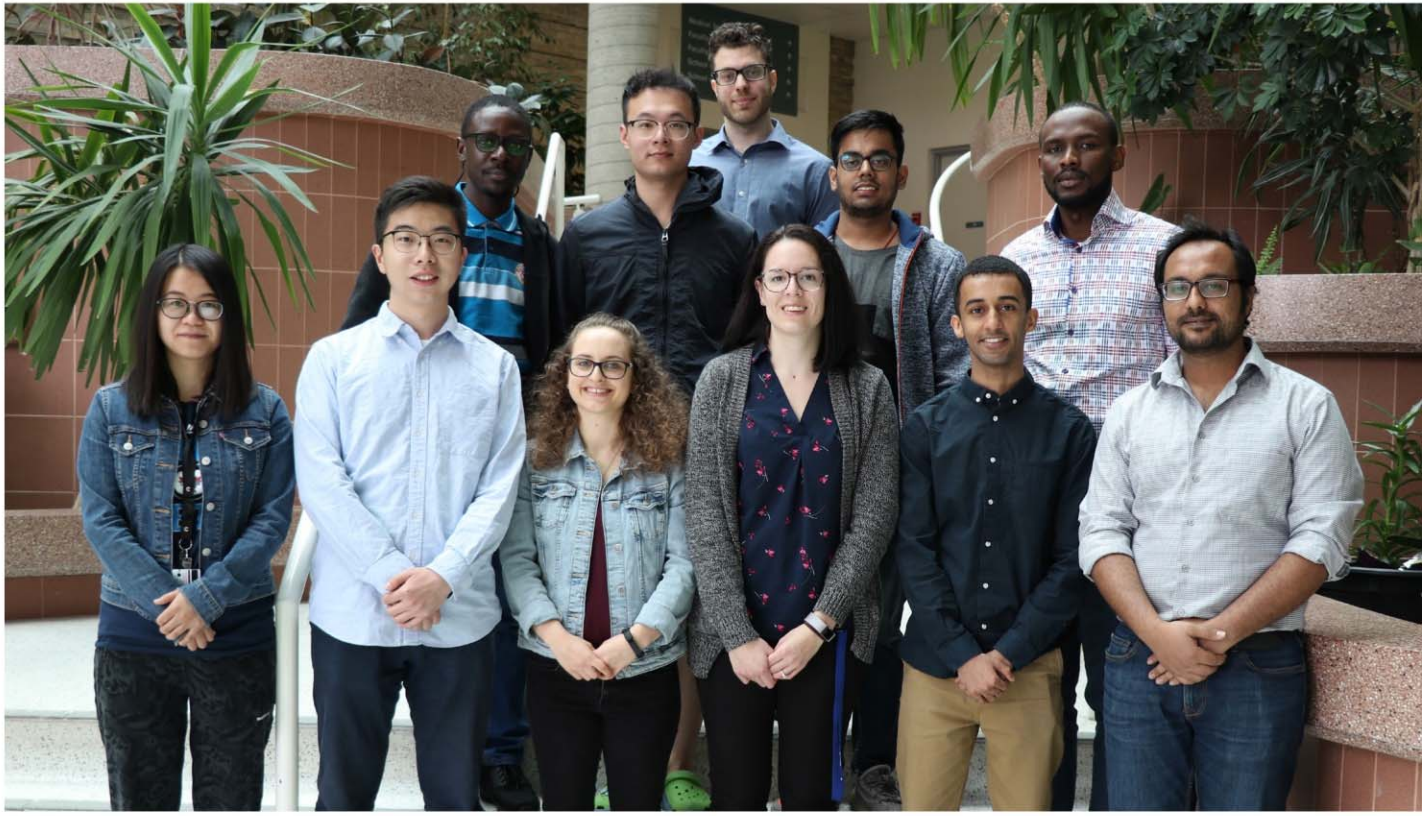
- See Course syllabus (in drop box)

How will you succeed in this course?

- Stay on top of the material – fast paced course
  - You can not complete a SR in a few weeks
  - High level of interactivity
  - Ask questions when concepts are unclear and share your experience and opinions frequently. Lecture content should prompt discussion.
  - 10% of the grade is allocated to participation and presentations.
  - Share your experiences with us and with each other.
- Use the templates provided when creating your own protocol and manuscript; complete all sections.

Primus Focus of the Course:

- Systematic reviews of efficacy and safety based on **Randomized Controlled Trials (RCTs)**
- We will only introduce concepts related to systematic reviews that incorporate 'other' study designs



An assembly of students who have recently worked at CHI. From left (front): Qian Liu, Zhongyuan Zhang, Allison Feely, Stephanie Monkman, Saeed Al-Azazi, Mohammed Rashidul Anwar, ***(middle)*** Oluwagbenga Fakanye, Shuo Jia, Rishabh Saraf, Olawale Ayilara, ***(back)*** Matthew Love

SUPPORTING STUDENTS & JUNIOR RESEARCHERS IN CONDUCTING AND PUBLISHING HIGH-QUALITY RESEARCH

Goal

The Strategy for Patient Oriented Research (SPOR) Capacity Development Framework acknowledges the need to "effectively support training and career development in patient-oriented research."

Building on that framework, one of the Knowledge Synthesis (KS) platform's goals is to support students in not only learning the fundamentals of knowledge synthesis research, but actively engaging and leading their own research. As such, we have been offering regular training opportunities in the form of organized workshops and courses, as well as individualized supports for students and junior researchers.

Even after their training is complete, several students have continued to use the skillsets they have acquired and are developing successful track records in completing and publishing their work. For example, a former student and new investigator recently published a systematic review that was not only published in the Canadian Medical Association Journal, but was also the 33rd most cited, discussed, and shared work among over three million articles published in 2017 (https://cmaj.altmetric.com/details/21993583).

More and more students are turning to the KS platform for training, and are keen to develop their research agendas.

Since **2015**…

Over 75 students, residents/ fellows and junior investigators

Most are published or actively pursuing publication

Rady Faculty of Health Sciences | UM

Introduction to Systematic Reviews, Meta-Analyses & other Knowledge Synthesis products

Rady Faculty of Health Sciences | UM

Goals

At the end of the presentation, you should have a better idea about:

- What a systematic review is and how is differs from a traditional 'narrative review' or 'literature search'
- Why we prefer to 'systematically review' the evidence
- Different types and approaches to systematic reviews
- Meta-analysis: when, why, and how
- Different ways of presenting the resulting information to multiple audiences, including *clinicians*, *consumers*, and *policy-makers*
- Some of the major challenges in conducting systematic reviews

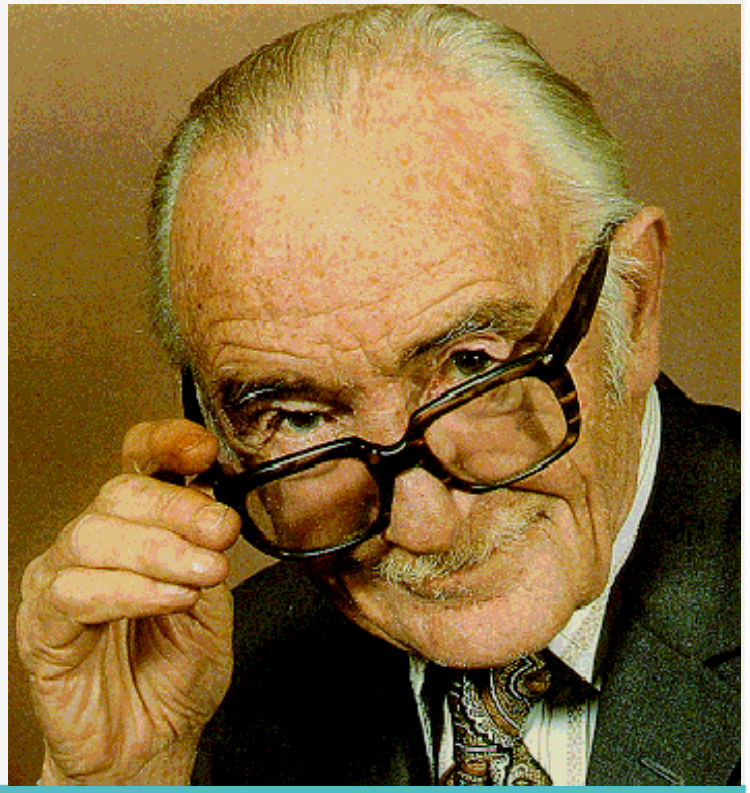
Archie Cochrane

In 1979 stated that “it is surely a great criticism of our profession that we have not

1) organised a critical summary,

2) by specialty or subspecialty,

3) adapted periodically, of all relevant randomised controlled trials”



What is Knowledge Synthesis?

Knowledge Synthesis…

"The contextualization and integration of research findings of individual research studies within the larger body of knowledge on the topic."

"A synthesis must be reproducible and transparent in its methods, using quantitative and/ or qualitative methods."

Canadian Institutes of Health Research

Example of Knowledge Synthesis

- Systematic reviews
- Realist syntheses
- Narrative syntheses
- Meta-analyses
- Meta-syntheses
- Practice guidelines
- Consensus conference or expert panel

What is a Literature Review?

Literature Review…

‘an overview of research on a given topic and answers to related research questions’

Literature Review…

- Key characteristics:
  - *Organizes* the literature (make sense of it all… connect the dots)
  - *Evaluates* the literature (high quality to low quality)
  - *Identifies patterns and trends* in the literature
  - *Synthesises* the literature (high quality to low quality)

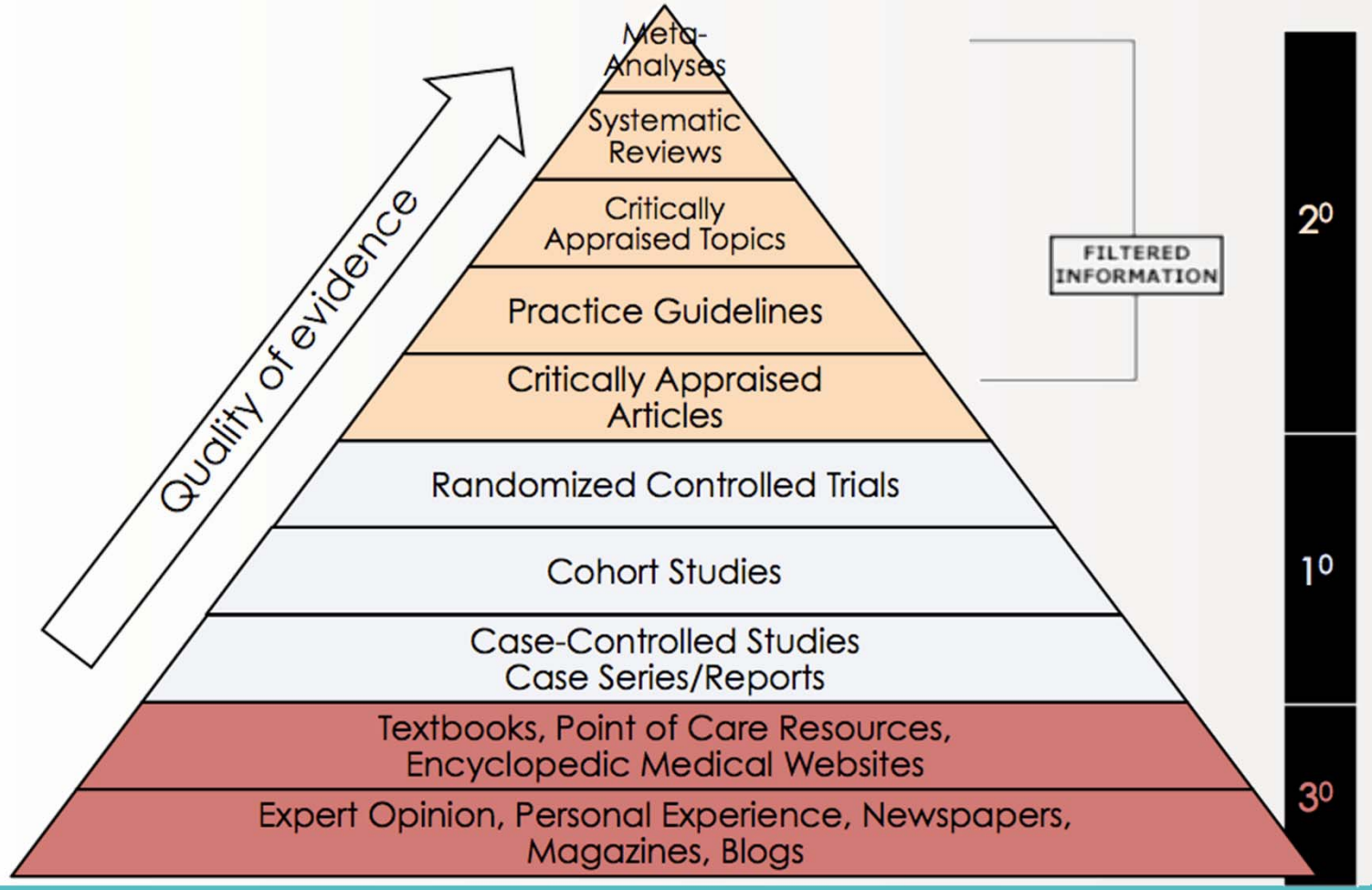
- But it's not:
  - *Annotated Bibliography*
  - *One-stop shop* for everything related to a topic
  - *Book review*

What is a Systematic Review?

Systematic Review…

‘an attempt to gather all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research or clinical question through a reproducible, transparent process’

Evidence informed decision making



Proposed new evidence-based medicine pyramid

M Hassan Murad et al. Evid Based Med 2016;21:125-127

What is a Meta-Analysis?

Meta-Analysis…

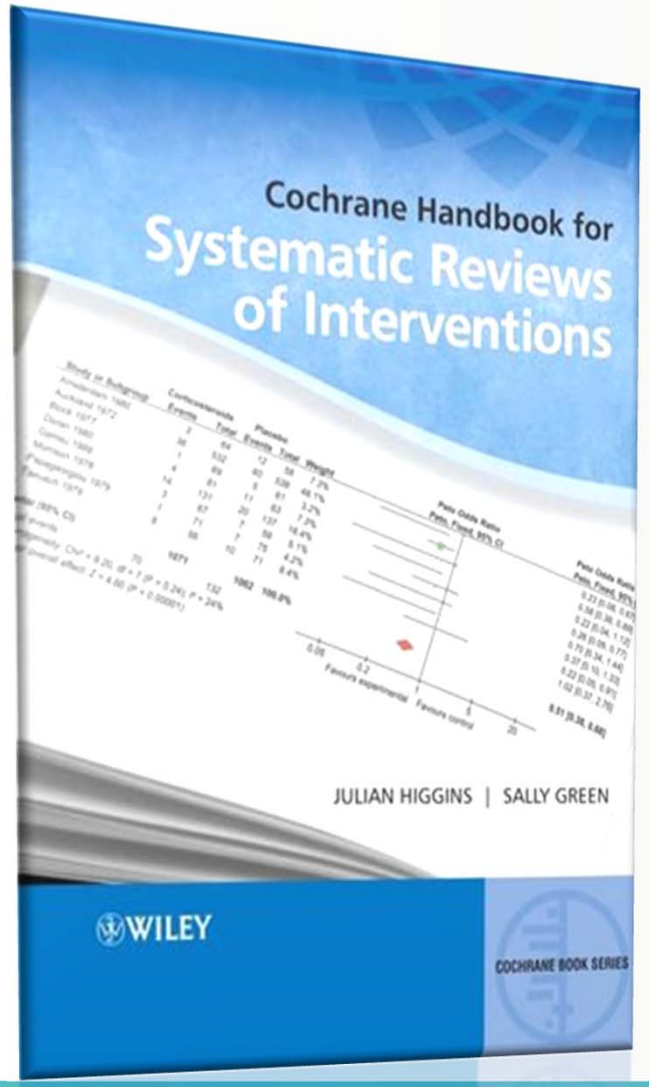
- A **statistical technique** for combining data from separate analyses… hence ‘meta’
- Produces a **weighted average** across relevant analyses
- A meta-analysis may, or may not, be a component of a systematic review
- A meta-analysis can be performed independent of a systematic review

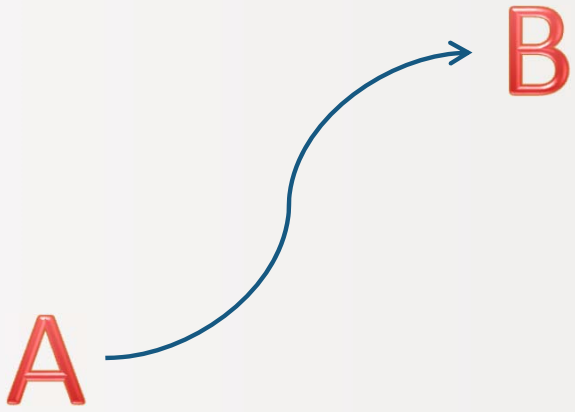
Qualitative Analyses?

Qualitative Analyses…

- Predominantly aggregative or 'integrative', where findings from individual primary qualitative studies are summarised to address specific questions
- Aim is to develop theory or models from conceptual literature (e.g., grounded theory and meta-ethnography)

‘Traditional’ systematic review





Advantages

- Reduce bias – by gathering 'all' evidence
- Transparent
- Replicable
- Resolves controversy between conflicting studies
- Identifies gaps in current research
- Can be basis of cost-effectiveness analyses and knowledge translation projects
- Provides a reliable basis for decision making

Characteristics

- Key characteristics:
  - *Clearly stated set of objectives* with pre-defined eligibility criteria
  - Explicit, *reproducible methodology*
  - Systematic search that *attempts to identify all the studies* that meet the eligibility criteria
  - *Assessment of the validity* of the findings
- Additional characteristics:
  - May use *statistical methods (meta-analysis)* to summarize the results coming from different trials
  - If data is meta-analyzed, then *biases* (e.g., publication bias) and homogeneity among studies *can be evaluated*

Systematic vs. Literature Review

Feature	Lit. Review	Systematic
Clinical Question	Broad	Focused
Search strategy/ sources of information	Not usually specified	Comprehensive/ explicit search strategy
Selection criteria		Criterion-based selection; uniformly applied
Quality assessment		Rigorous critical appraisal
Synthesis	Qualitative summary	Quantitative summary (usually)
Conclusions	Based on a sample of the evidence	Based on all available evidence
Grading	Sometimes performed	Strength of Evidence is Graded

Common Types of Reviews

- **Intervention Review (most common)**
  - Evidence about the effects of a healthcare intervention

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  - Evidence around diagnostic accuracy of different screening tests

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- **Intervention Review (most common)**
  - Evidence about the effects of a healthcare intervention
- **Diagnostic Accuracy Review**
  - Evidence around diagnostic accuracy of different screening tests
- **Prognostic Review**
  - Evidence of models or predictors of patient outcomes

Other Types

- **Overviews of reviews**
  - Evidence from already published systematic reviews for a given topic or disciplinary area

Other Types

- **Overviews of reviews**
  - Evidence from already published systematic reviews for a given topic or disciplinary area
- **Scoping reviews**
  - Map out previous primary research and systematic reviews for a given topic or disciplinary area
- **Rapid reviews**
  - Rapidly assess (usually ≤6 weeks) the evidence about the effects of a healthcare intervention

Other Types

- **Realist reviews**
  - Deal with complex 'system' issues and attempt to provide explanation rather than judgment (e.g., answer questions like 'how', 'why', and for 'whom')

Why Should We Care?

- Primary research is often false and/ or biased

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

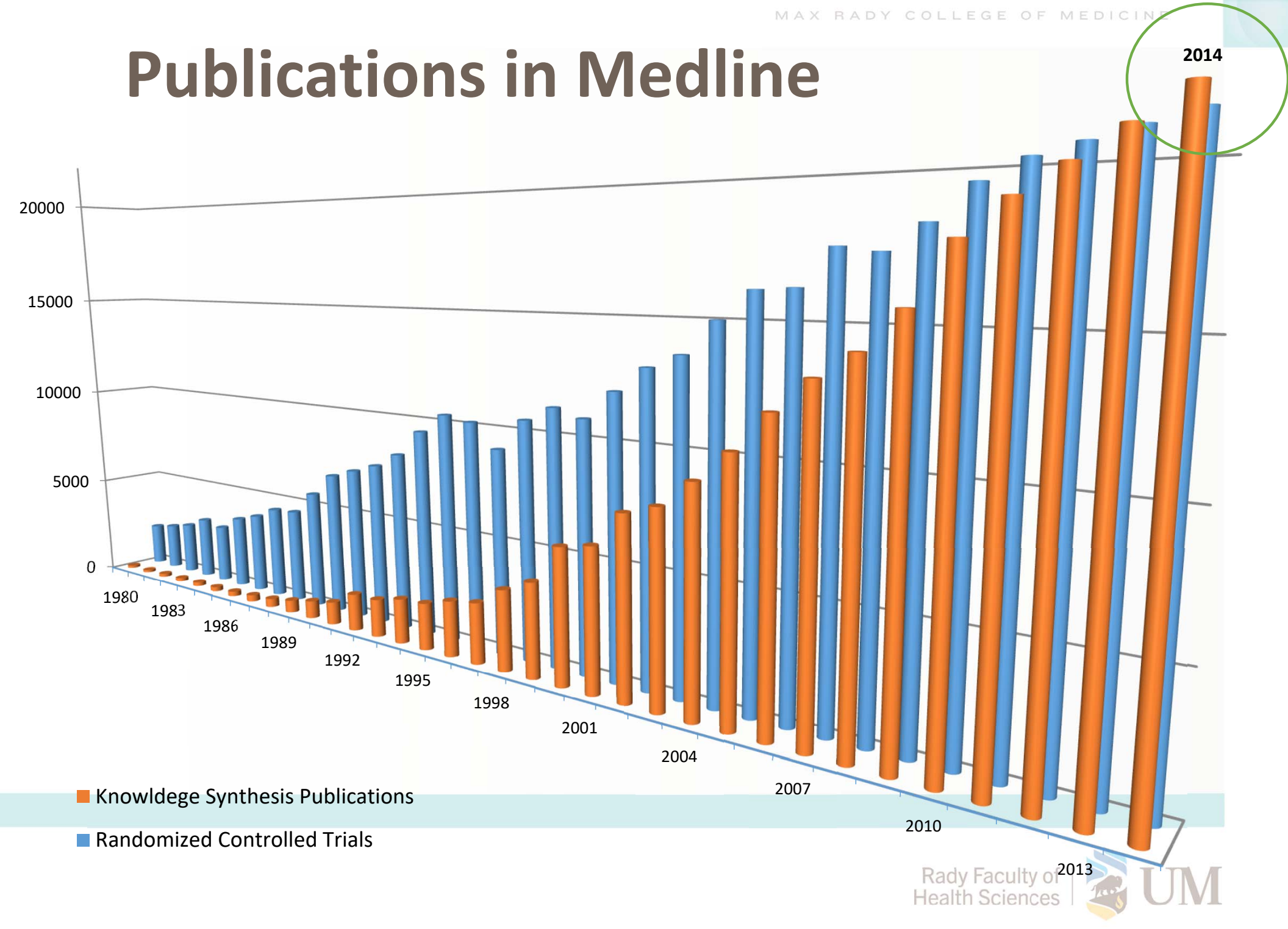
It can be proven that most claimed research findings are false.

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful. is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2

Why Should We Care?

- Primary research is often false and/ or biased
- Systematic reviews are highly publishable (even with negative findings)
- Governments/ funding agencies understand the need for systematic reviews and are willing to fund them
- Most major grants for clinical trials will not be accepted without a systematic review showing the need for primary research

Publications in Medline



Identify knowledge gaps

Ref #	Year of Publication	# Pts
6	Dec-87	22
7	Mar-89	99
8	Apr-89	175
9	Sep-90	219
10	Oct-90	257
11	Dec-90	296
12	Jun-91	376
13	Sep-91	396
14	Dec-91	455
15	Apr-92	486
16	Jun-92	601
17	Jun-92	2385
18	Jun-92	2445
19	Nov-92	2495
20	Dec-92	2664
21	Jan-93	2754
22	Jul-93	2795
23	Aug-93	3005
24	Dec-93	3044
25	Jan-94	3146
26a	Feb-94	3201
26b	Feb-94	3342
27	Feb-94	3396
28	Apr-94	3475
29	Jul-94	3575
30	Aug-94	3668
31	Aug-94	3724
32	Oct-94	3822
33	Oct-94	3854
34	Dec-94	3882
35	Dec-94	4047
36	Feb-95	4147
37	Feb-95	4210
38	Feb-95	4240
39	Apr-95	4338
40	Jun-95	4382
41	Jun-95	4420
42	Sep-95	4450
43	Oct-95	4548
44	Oct-95	4578
45	Oct-95	4832
46	May-96	4882
47	Jul-96	4975
48	Aug-96	5023
49	Aug-96	5135
50	Oct-96	5326
51	Dec-96	5970
52	Jan-97	6008
53	Jan-97	6060
54	Aug-97	6227
55	Sep-97	6333
56	Dec-97	6376
57a	Oct-98	6442
57b	Oct-98	6507
58	Nov-98	7303
59	Aug-99	7360
60	Sep-99	7510
61	Mar-00	7593
62	Dec-00	7677
63	Dec-00	7697
64	Jan-01	7897
65	Sep-01	7952
66	Sep-01	8011
67	Jun-02	8040

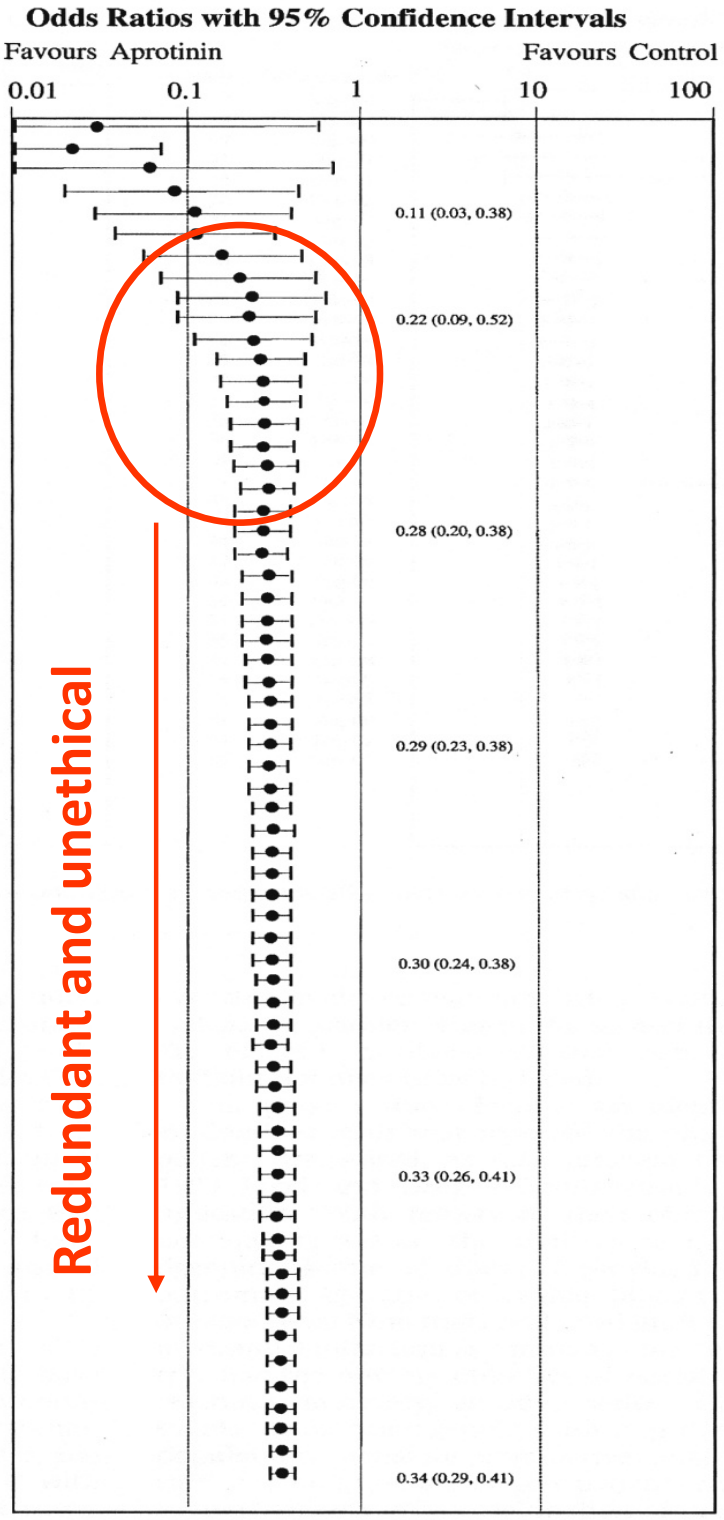
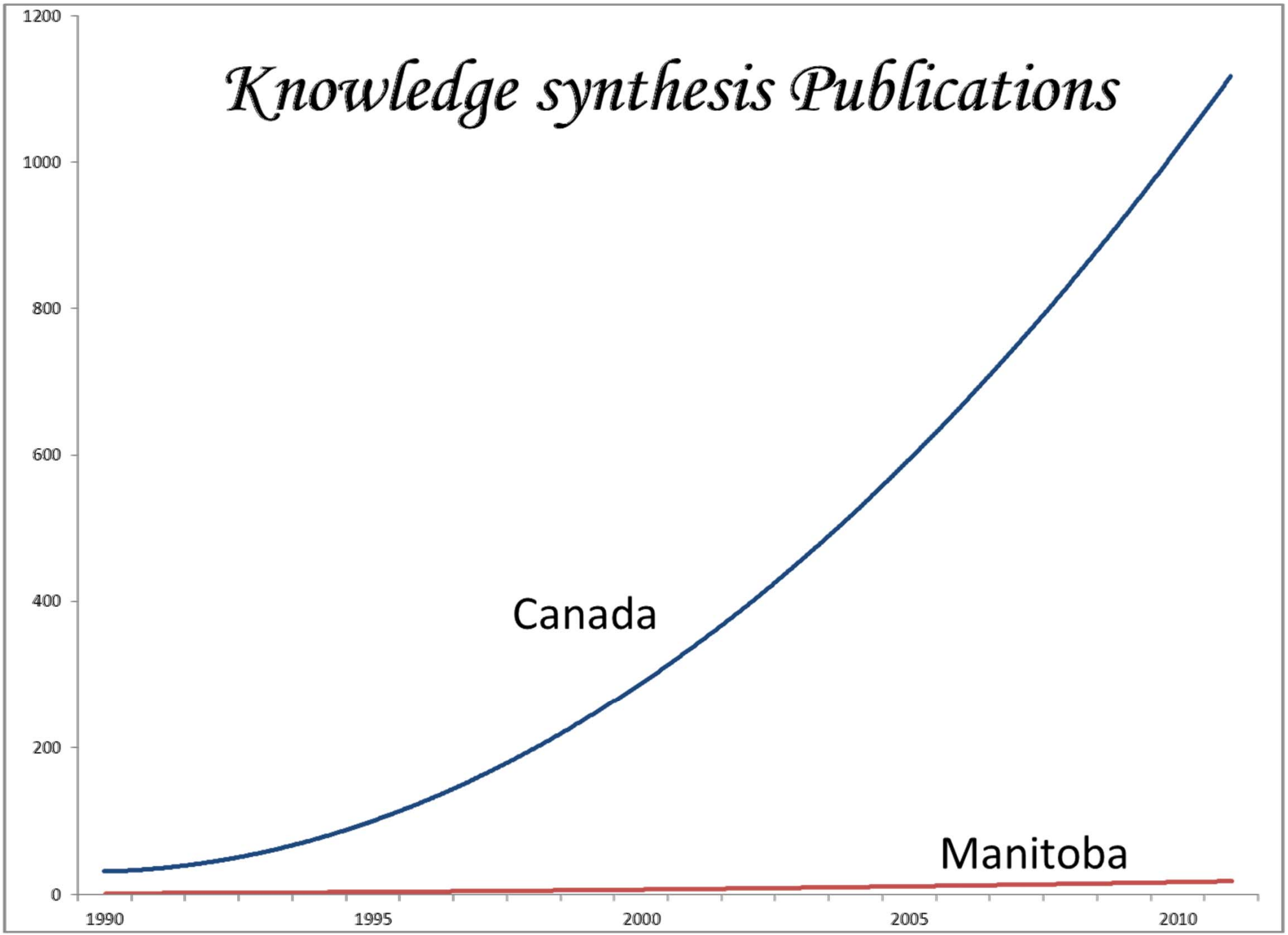


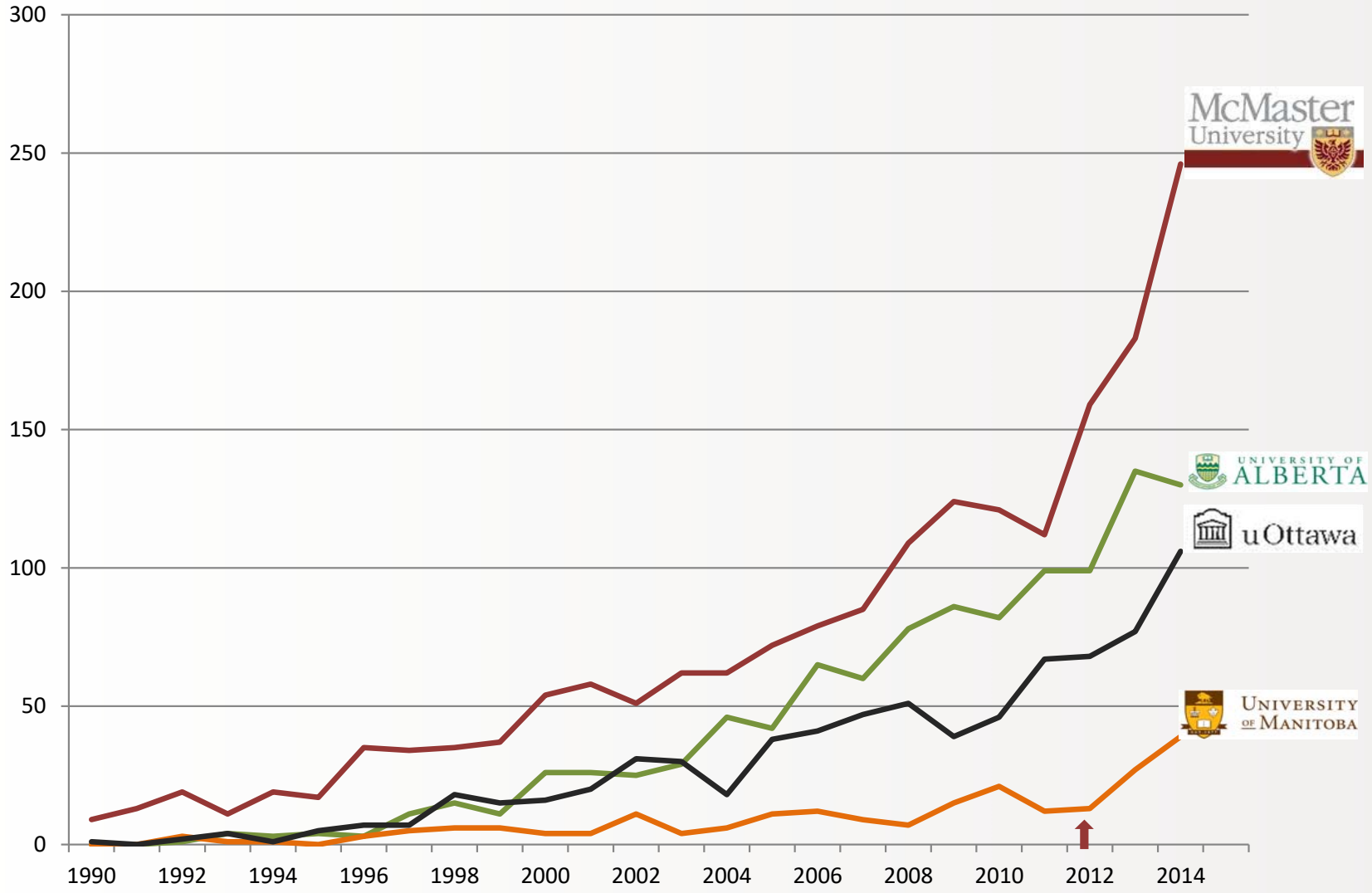
Figure 3 Cumulative meta-analysis of all RCTs.


Knowledge synthesis Publications
1200
1000
800
600
400
200
0
1990
1995
2000
2005
2010
Canada
Manitoba

Why do you think Manitoba has been lagging behind the rest of Canada?

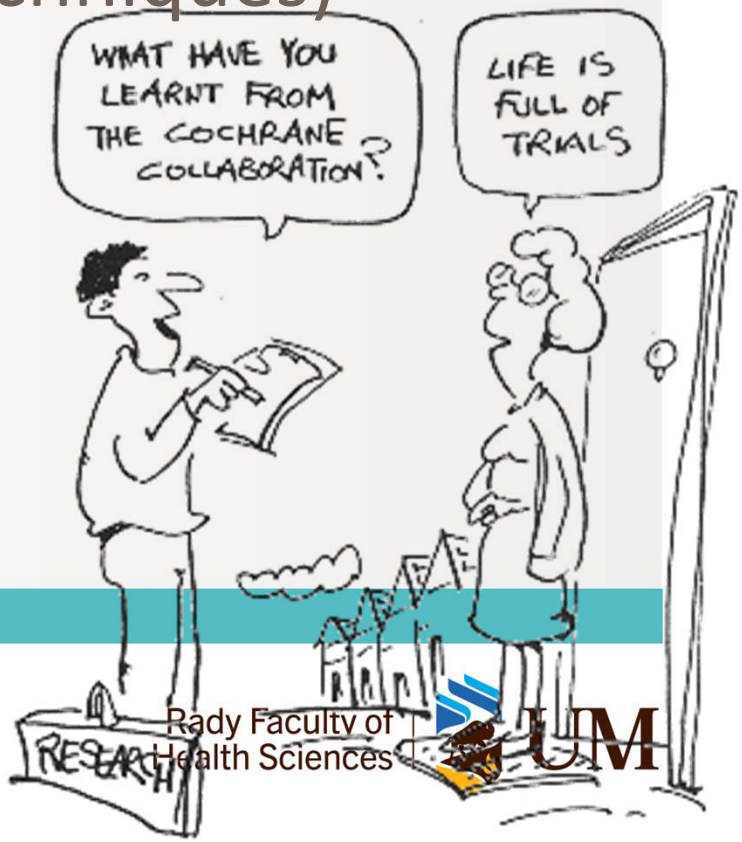

MOVIECLIPS.COM

KS Publications (1990 – 2014)



Barriers

- **Requires a complex team:**
  - Clinical epidemiologists
  - Clinicians/ content experts/ patient advocates
  - Statisticians (meta-analytic techniques)
  - Search strategy coordinators
  - Research assistants
  - Database managers
  - Project coordinators

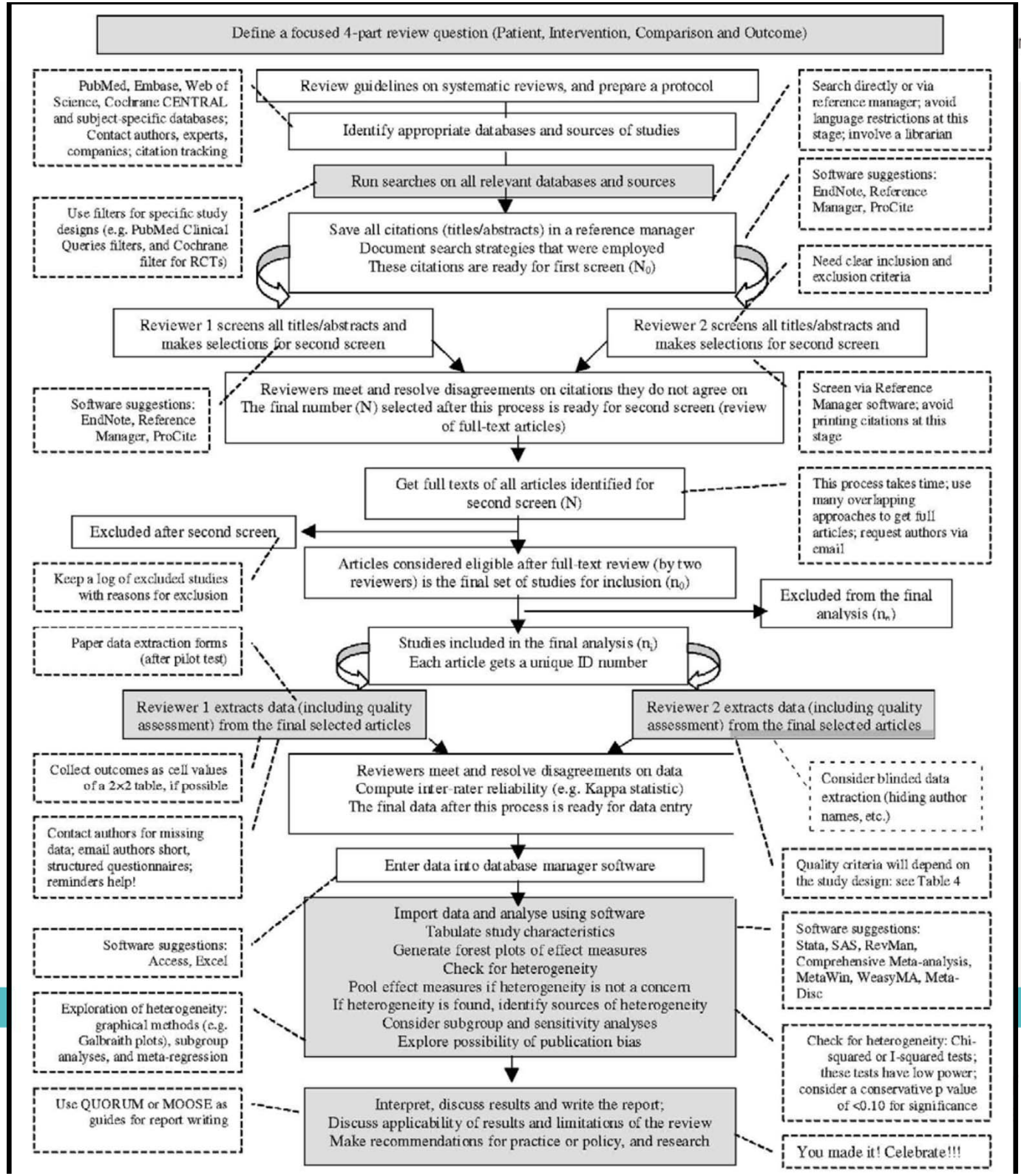


Barriers

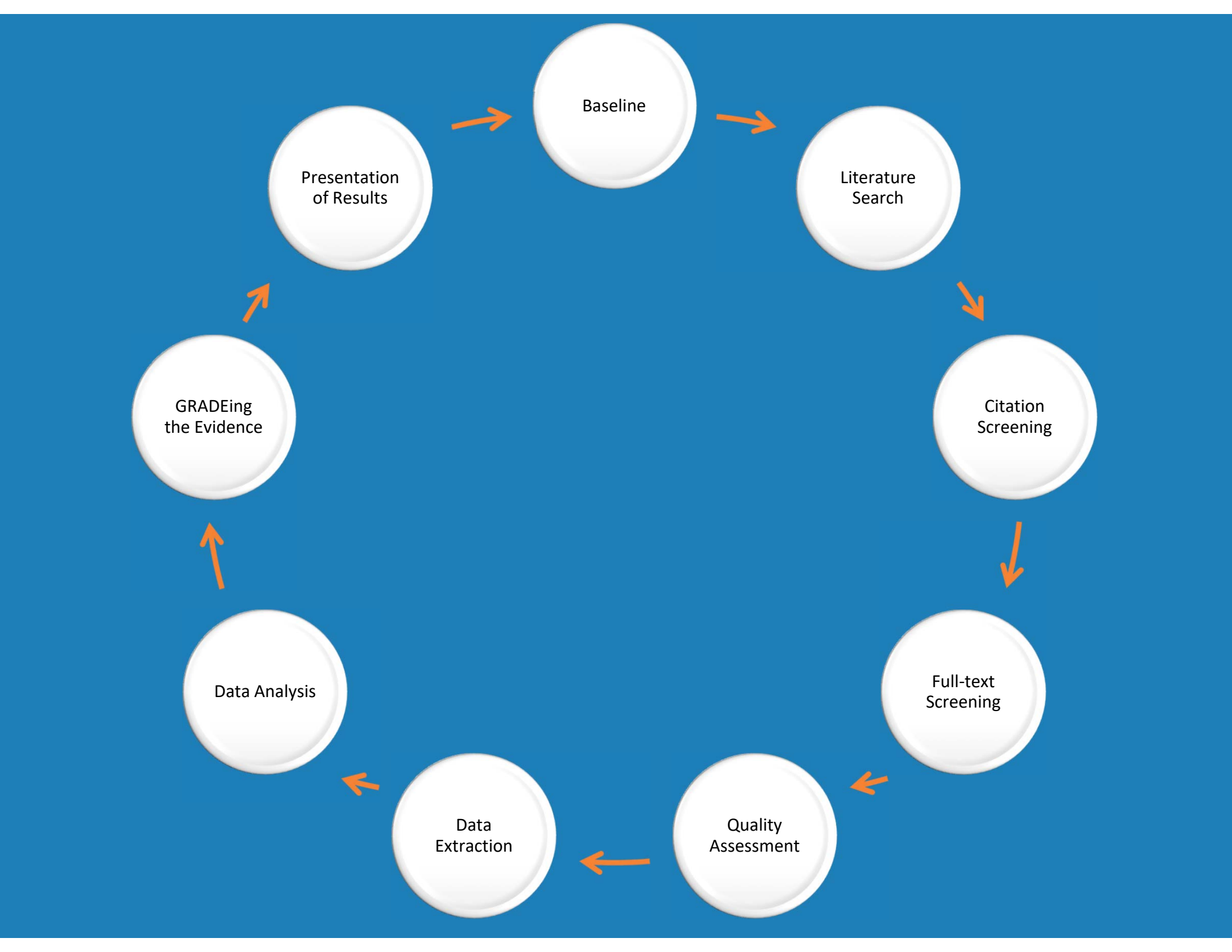
- **Time:**
  - Full review: 6 to 8 months
  - Rapid review: 4 to 6 weeks
  - Other review types: variable

- **Cost:**
  - Full review: $25,000 to over $500,000
  - Rapid review: $5,000 to $25,000
  - Other review types: variable

Barriers



Pai et al. Natl Med J India. 2004;17(2):86-95


Baseline
Literature Search
Citation Screening
Full-text Screening
Quality Assessment
Data Extraction
Data Analysis
GRADEing the Evidence
Presentation of Results

WinnipegHealthRegion.ca

News and Information from the Winnipeg Regional Health Authority

- About the Region
- Hospitals & Facilities
- Community Health
- Long Term Care
- Programs

preparing for Pandemic Influenza

INSIDE THIS SECTION

- Pandemic Influenza Home
- Weekly Influenza Surveillance Update
- Fact Sheets & Resources
- Related Links

UM

Limitations

- Empty reviews: no studies/ evidence available
- Negative findings: no conclusive results
- Biased results: Studies are often poor quality or at unclear to high risk of bias
- Limited answer to complex questions: results limited to specific clinical question
- Results not directly linked to practice change

Questions

Theoretical case study

- A friend's grandmother fell and broke her hip
- She is fine but had to have immediate surgery
- When you visit her in the hospital, she is drowsy, confused and seems to be in some pain
- The nurse tells you that this is 'normal' for her age… but you are not convinced
- So… you decide to search for information on managing pain in hip fracture patients

Theoretical case study

Questions we need to answer…

What's the question (again)???

What are we looking for???

Where should we search???

Can we 'trust' what is being said???

What if we find lots of 'reports'???

What if these 'reports' are conflicting???

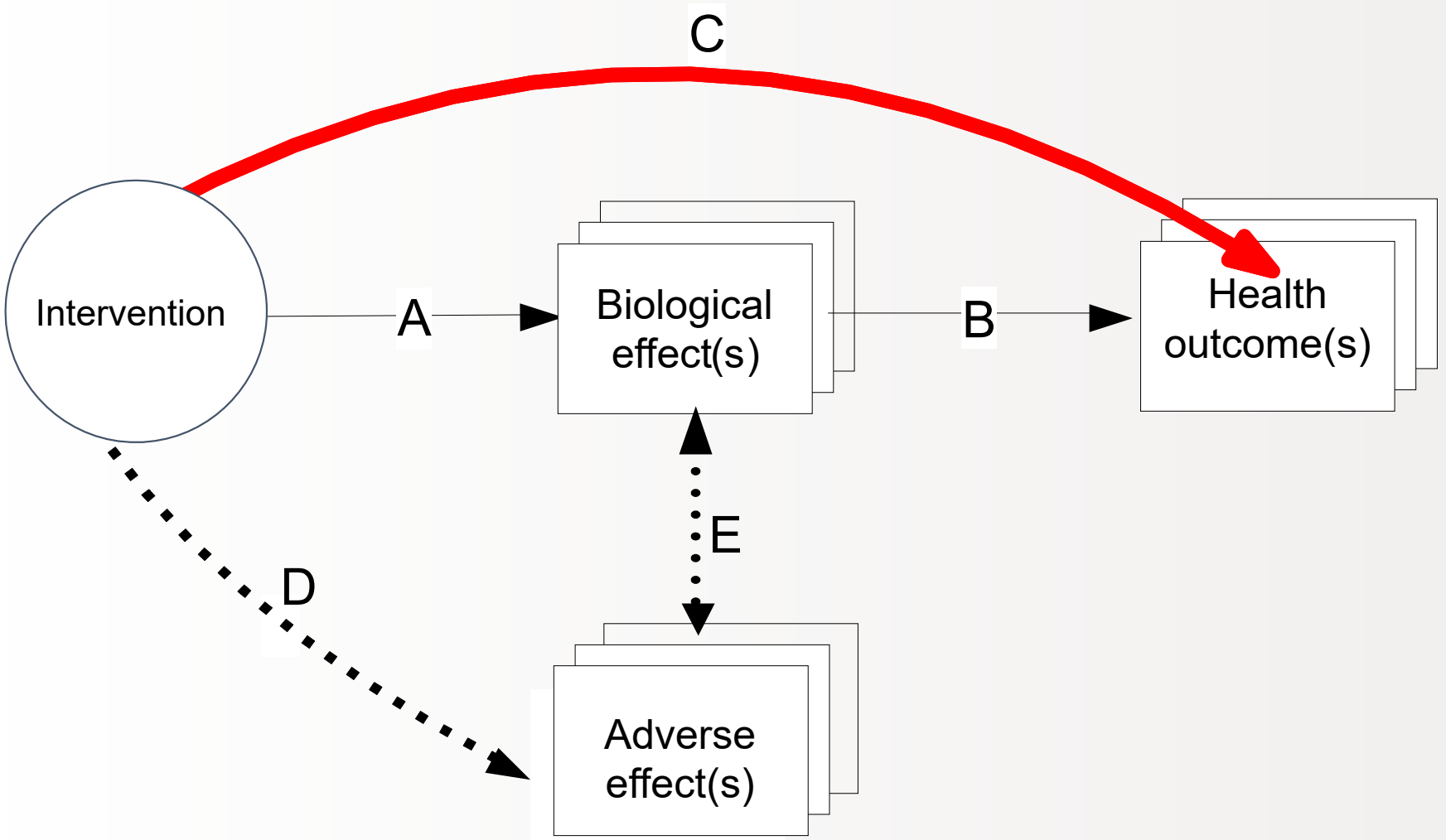
How do we 'tell' others what we found???

What's the question (again)???

What's the question (again)???

- The question will determine the inclusion and exclusion criteria (PICOTS format):
  - Population of interest
  - Interventions and Comparators
  - Outcomes of interest

Simplified Evidence Model



What's the question (again)???

- The question will determine the inclusion and exclusion criteria (PICOTS format):
  - Population of interest
  - Interventions and Comparators
  - Outcomes of interest
  - Timing (duration)
  - Appropriate Settings
  - Appropriate Study designs

What's the question (again)???

- Poorly formulated question:

  What drugs best manage pain?

- Well formulated question:

  In older adults (≥50 years) admitted to the hospital following acute hip fracture, what is the effectiveness of pharmacologic and/ or non-pharmacologic pain management interventions for controlling acute (up to 30 days post-fracture) and chronic pain (up to 1 year post-fracture) compared with usual care or other interventions in all settings?

What are we looking for???

What are we looking for???

- Inclusion/ Exclusion criteria
  - Must be defined a priori
  - Allows inclusion/ exclusion of studies based on objective criteria

	Inclusion criteria	Exclusion criteria
Study design	Randomized controlled trials, nonrandomized controlled trials (e.g., quasi-randomized trials), cohort studies (prospective or retrospective), case-control studies	Observational study designs with no comparison group (case reports, case series, cross-sectional studies)
Participants	Older adults (≥50 years old) of either sex admitted to hospital with acute hip fracture due to low energy trauma	Majority (>80%) of participants <50 years; acute hip fractures due to high energy trauma
Interventions	Pharmacological and/or nonpharmacological pain management monotherapy or combination therapy, regardless of mode of administration or time point during the care pathway	Interventions directly related to surgical/nonsurgical treatment of the hip fracture and not a pain management intervention
Comparator	Usual care (as defined by study authors) or another intervention(s) for pain management, administered as monotherapy or combination therapy	Initial care for patients is substantially different than the current practices in North America (e.g., based on time to discharge from acute care to subacute care)
Outcomes	Primary: Acute and chronic pain Secondary: Mortality, functional status, pain med. Use Adverse events: mental status, quality of life, length of stay	None of the aforementioned outcomes were available from the trial report or through communication with the study's corresponding author
Timing	From time of trauma leading to acute hip fracture and thereafter	
Setting	All settings	

Where should we search???

Where should we search???

- Common general medical citation databases:
  - Medline
  - PubMed
  - Embase
  - Scopus
  - Web of Knowledge
  - MedRxiv (pre-prints)
- Specialty citations also available:
  - CINAHL: nursing literature
  - PsycInfo: psychology and psychiatry literature
  - LILACS: Spanish and Portuguese literature
  - Disease-specific: LitCovid, Cochrane Covid

Database Overlap

OIR
32,1

18

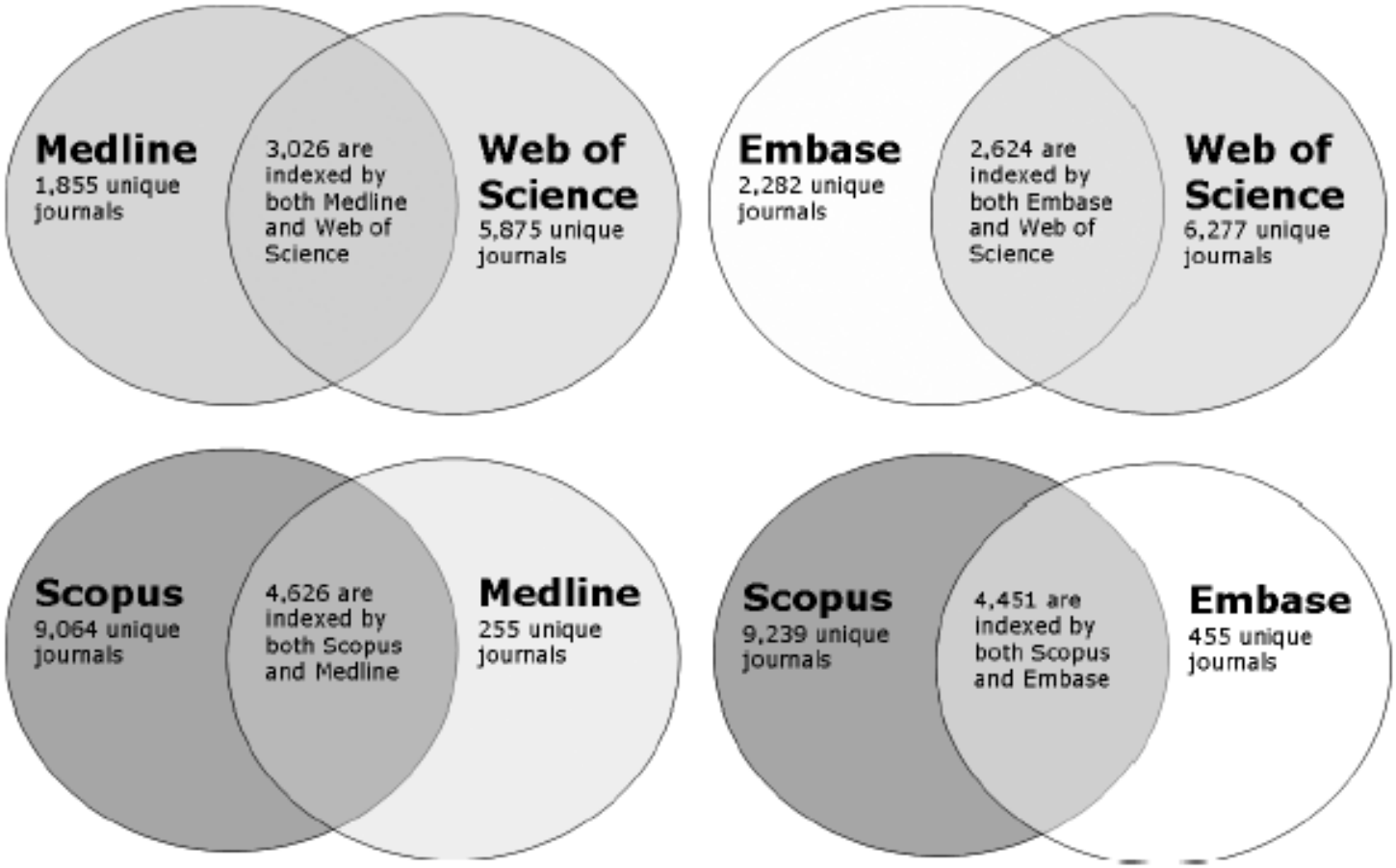


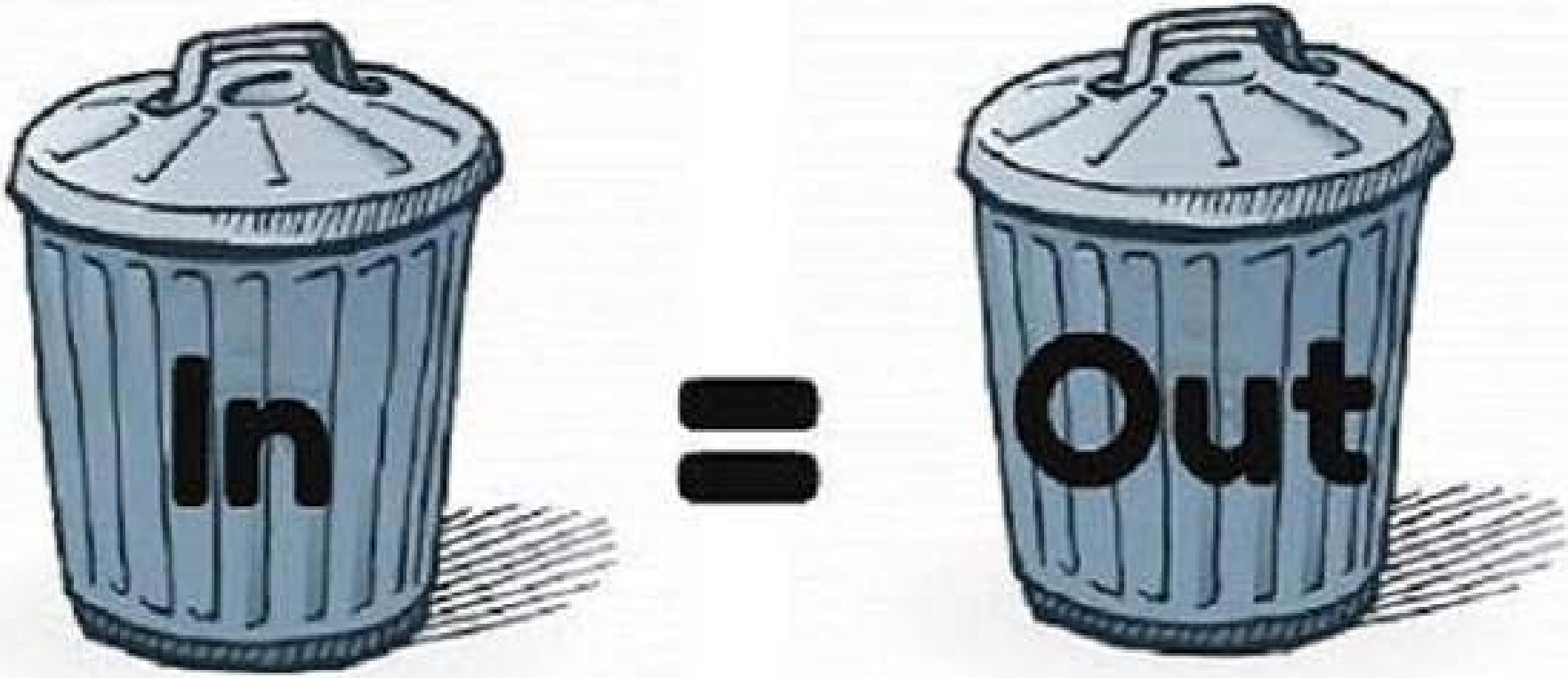
Figure 2.
Overlap of active titles (source type "Journal" only) between the citation databases and the medical databases

Gavel Y, Iselid L. Web of Science and Scopus: A journal title overlap study. Online Information Review. 2008;32(1):8-21.

Sources for pre-synthesized evidence

- **Cochrane Library** http://www.thecochranelibrary.com
- **AHRQ** (Agency for Healthcare Research & Quality http://www.ahrq.gov
- **Centre for Reviews and Dissemination** http://www.york.ac.uk/inst/crd/
  - DARE - Database of Abstracts and reviews of Effects
  - NHS EED – NHS Economic Evaluation Database
  - HTA – Heath Technology Assessment Database
- **Trip database** http://www.tripdatabase.com
- **MEDLINE/EMBASE**
  - Use appropriate filters or MeSH/EMTREE headings
- **Up-to-date**
- **SR review protocol registries:** PROSPERO & Cochrane

Can we 'trust' what is being said???


In
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Out


SO IF YOU DON'T HAVE THE CUSTOMER'S BIRTH DATE, JUST FILL IN ANYTHING – IT'S A MANDATORY FIELD. AND WE PUT INTERNATIONAL PHONE #S IN THE SHOE SIZE FIELD BECAUSE THAT'S THE ONLY PLACE IT LETS US.
DOESN'T THAT CAUSE PROBLEMS LATER?
YES. ANY OTHER QUESTIONS?

Can we 'trust' what is being said???

- Internal validity of included studies:

  SR validity ~ validity of primary studies

- Internal validity of included studies need to be assessed
- Common tools include:
  - Cochrane Risk of bias tool (randomized trials)
  - ROBINS-I (non-randomized trials)
  - New-Castle – Ottawa Scale (cohorts/ case controls)
  - AMSTAR 2/ ROBIS (Systematic reviews)

Can we 'trust' what is being said???

- Risk of Bias/ Quality assessment:
  - Randomized trials are (usually) more rigorous than observational studies
  - Systematic reviews based on well-designed trials will likely be more valid and accurate

Don’t believe everything you….

Hear

Read

See

Think

What if we find lots of 'reports'???

What if we find lots of 'reports'???

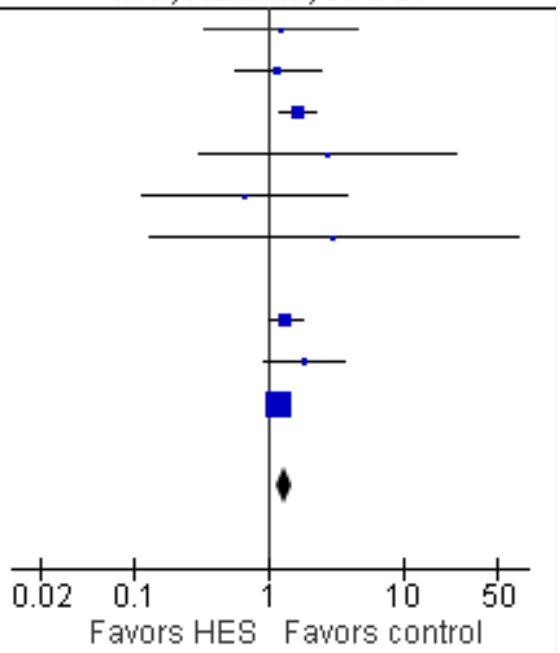
- Meta-analysis:
  - Combining data from different trials to get a summary effect estimate
  - Assumes clinical homogeneity between individual trial PICOTS
  - Assumes a 'reasonable' amount of statistical homogeneity between individual trials

Forest Plot

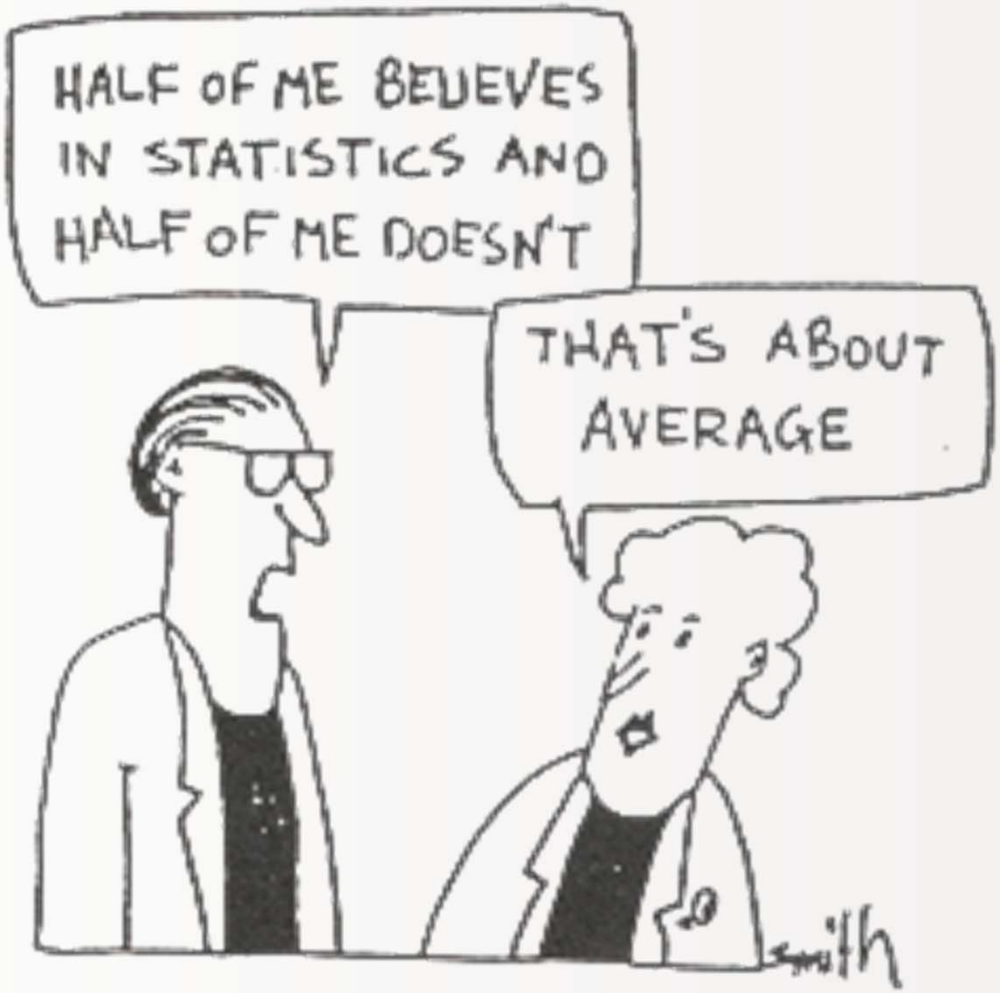
Study or Subgroup	HES Events	HES Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Berard 1995	5	155	4	152	1.0%	1.23 [0.34, 4.48]	1995
Schortgen 2001	13	65	11	64	3.3%	1.16 [0.56, 2.40]	2001
Brunkhorst 2008	81	297	51	303	18.0%	1.62 [1.19, 2.21]	2008
McIntyre 2008	3	21	1	19	0.4%	2.71 [0.31, 23.93]	2008
James 2011	2	58	3	57	0.6%	0.66 [0.11, 3.78]	2010
Du 2011	1	21	0	21	0.2%	3.00 [0.13, 69.70]	2010
Vlachou 2010	0	12	0	17		Not estimable	2011
Perner 2012	87	400	65	400	20.8%	1.34 [1.00, 1.79]	2012
Guidet 2012	21	100	11	96	3.9%	1.83 [0.93, 3.59]	2012
Myburgh 2012	235	3500	196	3500	51.8%	1.20 [1.00, 1.44]	2012
Total (95% CI)		**4629**		**4629**	**100.0%**	**1.32 [1.15, 1.50]**	
Total events	448		342				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.07$, $df = 8$ ($P = 0.75$); $I^2 = 0\%$

Test for overall effect: $Z = 4.08$ ($P < 0.0001$)



What if we find conflicting 'reports'??



What if we find conflicting ‘reports’??

How do you present the results???

RESEARCH

Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies

Meghan B. Azad PhD, Ahmed M. Abou-Setta MD PhD, Bhupendrasinh F. Chauhan MPharm PhD, Rasheda Rabbani PhD, Justin Lys MD, Leslie Copstein MD, Amrinder Mann MD, Maya M. Jeyaraman MD PhD, Ashleigh E. Reid MPAS, Michelle Fiander MLIS, Dylan S. MacKay PhD, Jon McGavock PhD, Brandy Wicklow MD MSc, Ryan Zarychanski MD MSc

Cite as: *CMAJ* 2017 July 17;189:E929-39. doi: 10.1503/cmaj.161390

ABSTRACT

BACKGROUND: Nonnutritive sweeteners, such as aspartame, sucralose and stevioside, are widely consumed, yet their long-term health impact is uncer-

outcomes included weight, obesity and other cardiometabolic end points.

RESULTS: From 11 774 citations, we

secondary outcomes. In the cohort studies, consumption of nonnutritive sweeteners was associated with increases in weight and waist circumfer-

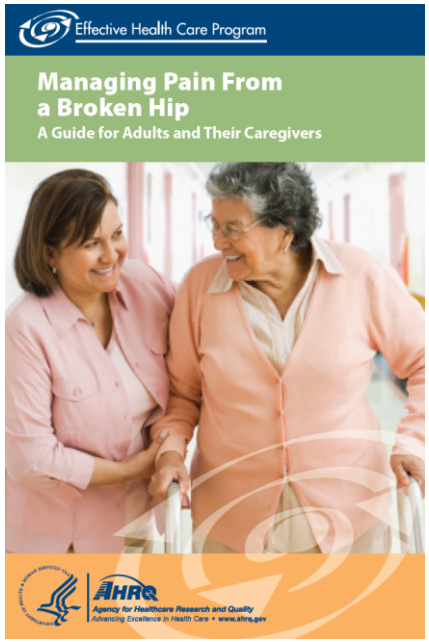
Online video (Reuters Health)

Annals of Internal Medicine

Established in 1927 by the American College of Physicians

U.S. Government Report

AHRQ Advancing Excellence in Health Care



Patient guide (English)

Clinical guide

Patient guide (Spanish)

Online video (Reuters Health)

Questions

Systematic Review Protocols

Every good scientific study starts with a protocol

Why publish systematic review protocols?

- Systematic reviews can represent the highest level of evidence
- Mitigating bias is CENTRAL to the systematic review process
- Protocols must be transparent, reproducible, robust, and free from bias as possible
- Researchers must adhere to this pre-specified plan to avoid bias

(Stewart L. Systematic Reviews 2012, 1:7)

But data manipulation only happens in industry…Right??

Outcome reporting bias in randomized trials funded by CIHR

(Chan A. CMAJ 2004;171:735)

- Reporting of RCTs is inconsistent with study protocols
- Compared 48 trials funded by CIHR from 1990 to 1998
  - 31% of outcomes of efficacy were incompletely reported
  - 59% of outcomes related to harm were incompletely reported
  - Statistically significant outcomes had a higher odds of being completely reported
- Primary outcomes differed between protocols and publications in 40% of trials

What about data manipulation in Systematic Reviews?

Published manuscripts of systematic reviews: Comparing what was done to what was planned

(Silagy CA. JAMA 2002;287:2831)

- Compared published Cochrane reviews to their protocols
- 68% of reviews had undergone a major methods change

Comparison of protocols and registry entries to published reports for RCTs

(Dwan K. Cochrane Database Syst Rev 2011,1)

- 20% of Cochrane reviews changed at least 1 outcome when compared to the protocol
- Changed outcomes were more likely to be 'significant.'

Protocol Registration

- Guard against outcome and other reporting biases
- Maintain a permanent public record of study elements
- Can be tool to mitigate publication bias
- Can prevent duplication of effort
- When should you register your review?
- Will this be effective?

Who will use/benefit from SR protocol registration?

- Researchers
- Funding organizations
- Guideline developers
- Journal editors
- Peer Reviewers

Where to publish your SR protocol?

- PROSPERO http://www.crd.york.ac.uk/PROSPERO/
- Cochrane – For Cochrane Reviews
- AHRQ – Comparative effectiveness reviews
- Pre-print servers (e.g., Medrxiv, OSF)
- Peer-reviewed journal (e.g. Systematic Reviews)

Elements of a systematic Review protocol?

- Cover Page
  - Title
  - Review team & author order
  - Funding
  - Conflicts of interest
- Background
  - What's the problem?
  - What's known? Other SRs?
  - What are the knowledge gaps and why is a systematic review needed?
- Objective
- Structured PICO question
  - Consider a rationale for outcomes
- Eligibility criteria
- Role of review team members
- Methods
  - Search strategy + Medline search
  - Data extraction
  - Data management
  - Assessment of methodological quality/bias
  - Analytic plan
  - Subgroup / sensitivity analysis
- References
- Appendices (search strategy, data extraction form?, quality assessment tools?)

Examples of systematic review protocols

Managing your Systematic Review

Folder structure

01 - Administration

02 - Protocol

03 - Literature Search

04 - Level I Screening

05 - Article Retrieval

06 - Level II Screening

07 - Data Extraction

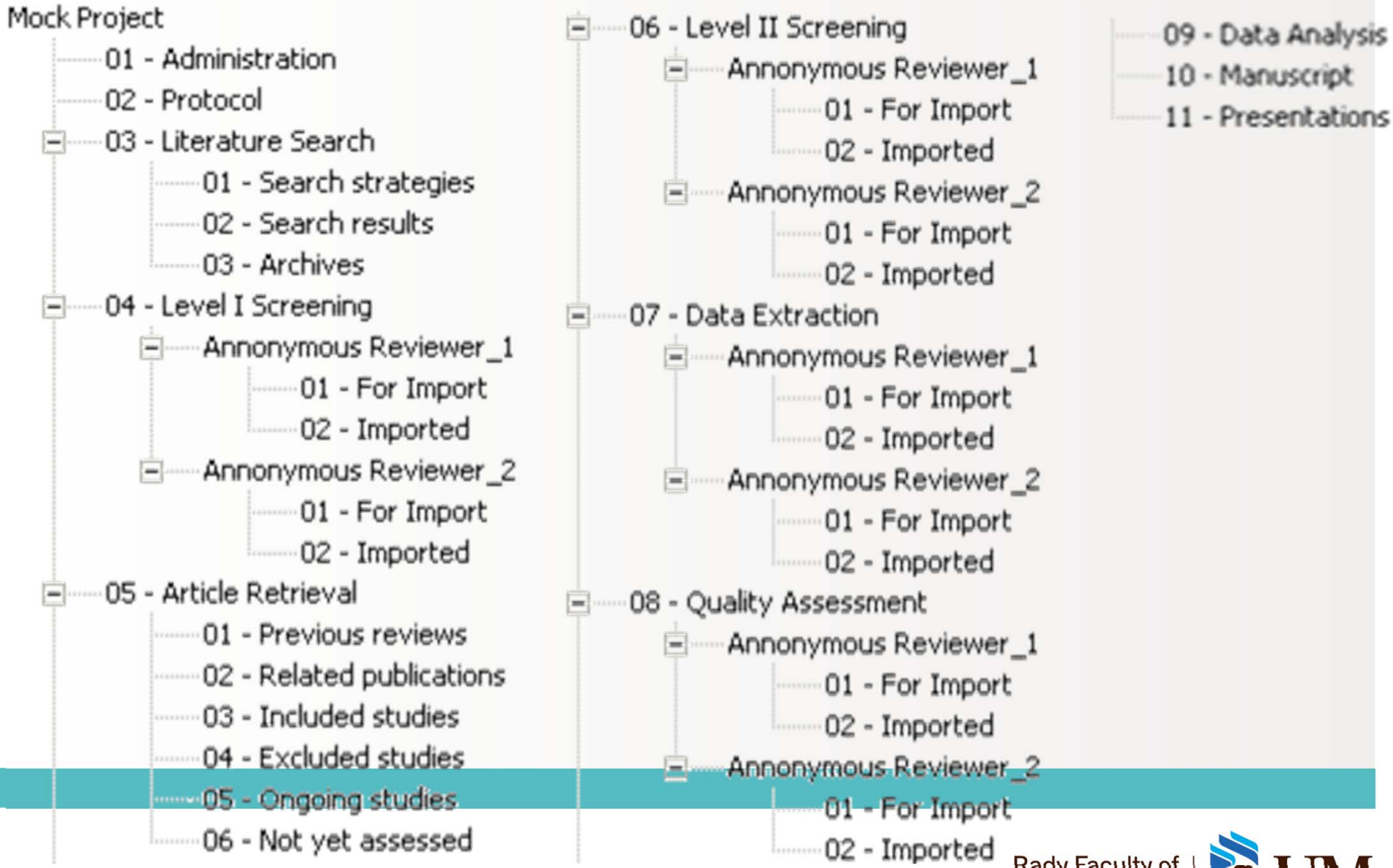
08 - Quality Assessment

09 - Data Analysis

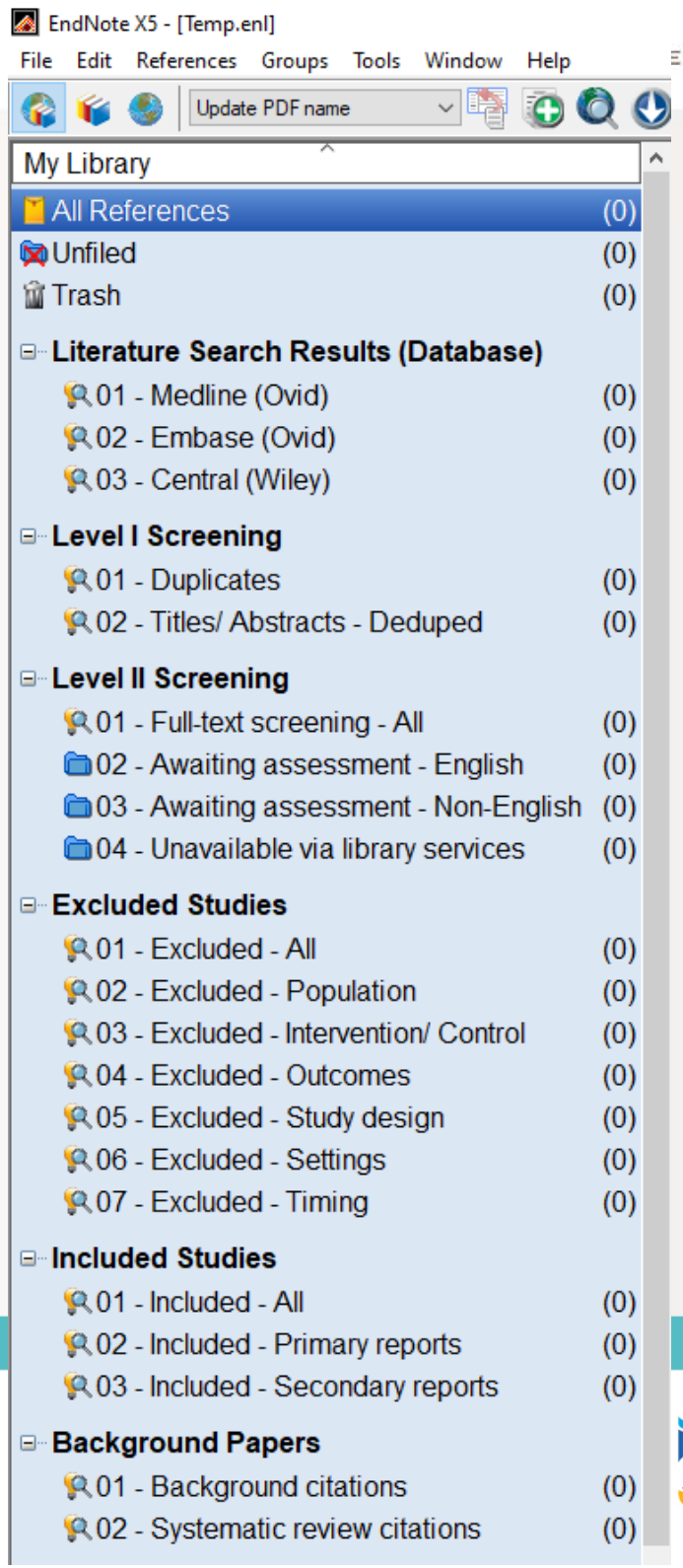
10 - Manuscript

11 - Presentations

Folder structure



EndNote structure



Here's what you need to do next

- Construct your clinical question
- 'PICOS style'
- Helpful bits (for this course only)
  - Should have ~2-15 RCTs
  - Make sure a SR wasn't done in the past 5 years. If one has been done… are you justified conducting another?
- Assemble your systematic review team
  - Identify a clinical content expert for your review, if you are not the 'expert'
  - Consider identifying another person to do screening, data extraction, quality assessments with you

For next class:

- **Searching like a pro:** How to conduct a comprehensive literature search
  - Present an overview of the considerations required for effective SR searching
  - Show how to plan, execute and document a structured search strategy
  - Run searches in PubMed, EMBASE, and CENTRAL (in the Cochrane Library)


EXPLORER INNOVATOR ADV
REBEL ADVENTURER TRAILBLAZER
INNOVATOR CHALLENGER REBEL VISIONARY
REBEL PIONEER CREATOR EXPLORER TRAILBLAZER INNOVATOR
ADVENTURER EXPLORER ADVENTURER TRAILBLAZER REBEL PIONEER CREATOR EXPLORER REBEL PIONE
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