

The Royal College of Pathologists

Development of systematic reviews to provide evidence for alert thresholds for critical laboratory results

Macquarie University Workshop Day 14 June, 2019





Introduction and housekeeping items

The literature review protocol



- A systematic literature review will be performed on each pathology analyte
- One analyte per person
- Performed in teams of 3
- Guidance and supervision from research team at Australian Institute of Health Innovation
- 16 week program to completion









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Please ask if you have any other questions or concerns



Bathrooms: Behind the lifts in the corridor

Refreshments:

Provided, but extra for purchase at on-site café ground floor, 75 Talavera Road or Macquarie University Hospital next door

Nearby amenities: Macquarie Shopping Centre on Herring Road (taxi rank)

Emergency



Introduction to evidence-based laboratory medicine

Evidence-based practice in the diagnostic pathway





Evidence on its own is not enough



WHY IS THE IMPLEMENTATION OF EBP SO IMPORTANT?

- 4 out of 10 adult patients receive care that is not based on current evidence or guidelines²
 - Ineffective treatments
 - Unnecessary treatments (or tests)
 - Potentially harmful treatments
- There are gaps in implementing evidence into routine clinical practice³
 - This is despite evidence-based guidelines often being available
- Translating evidence into practice can¹
 - Improve outcomes and quality of life for patients
 - Improve productivity
 - Reduce healthcare costs



²Grimshaw JM, Eccles MP, Lavis JN, Hill SJ & Squires JE 2012, 'Knowledge translation of research findings', *Implement Sci*,7(50):50.9
³Runciman WB, Hunt TD, Hannaford NA, Hibbert PD, Westbrook JI, Coiera EW, Day RO, Hindmarsh DM, McGlynn EA & Braithwaite J 2012, 'CareTrack: assessing the appropriateness of health care delivery in Australia', *Med J Aust*, 197(2):100-5.

Evidence-based laboratory medicine (EBLM) in the diagnostic process





Evidence demonstrating **impact** of laboratory testing on clinical outcomes is limited

The diagnostic phase of laboratory testing





- Interface between laboratory and diagnostic phases is critical
 - Which test results flagged?
 - Which get called through?
 - Time critical
- Effective communication of these results from laboratory to physician is fundamental to patient safety
- Accreditation/Regulatory bodies mandate laboratories have a High Risk Result (HRR) protocol

What are "high risk" laboratory results?





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What's the problem with the current alerting system?



- Lack of standardised:
 - Alert lists
 - Communication protocols
 - Escalation policies
 - Alert thresholds
- Risk of interpretation errors by clinicians
- Significant threat to patient safety
- WHAT EVIDENCE was used to derive these thresholds?
- **HOW** can we harmonise thresholds?

Clinical Chemistry 62:11 000-000 (2016)

Reviews

What Alert Thresholds Should Be Used to Identify Critical Risk Results: A Systematic Review of the Evidence

Craig A. Campbell,^{1,2*} Andrew Georgiou,¹ Johanna I. Westbrook,¹ and Andrea R. Horvath²

BACKGROUND: Pathology laboratories are required to immediately report results which indicate a patient is at critical risk, but there is little consensus about what values are deemed critical. The aim of this review was to systematically review the literature on alert thresholds for common chemistry and hematology tests in adults and to provide an explicit and ranked source of this evidence.

priate alert thresholds that signify actionable, critical or significant risk to patient well-being. © 2016 American Association for Clinical Chemistry

When a pathology laboratory generates a test result that is indicative of a life threatening situation, it is standard

"There is a lack of evidence and explicit reasoning in the literature to support the selection of alert thresholds for communicating critical risk laboratory results."

Supporting best practice through evidence



HARMONISATION INITIATIVE



Royal College of Pathologists of Australasia & Australasian Association of Clinical Biochemists (RCPA-AACB) High Risk Results Working Party

Recruitment and scholarships facilitated by AACB-RCPA

> Laboratory professionals gather and synthesise evidence

List of nominated tests for which evidencebased thresholds are urgently needed





WP in consultation with laboratories & clinicians Creation of standardised best practice guidelines

Improve diagnostic reliability and accuracy across laboratories

What forms the evidence?

Aims:

•

OUTCOME-BASED RESEARCH

- Link established alert thresholds with clinical outcomes
- Inform patient outcome-based primary research studies
- Inform guideline creation and translation into practice







Before searching for evidence in databases to answer clinical questions, it is essential to understand the different **types and levels of evidence**, and which is best to answer your clinical question

Types of research evidence:

- Primary evidence consists of original individual (primary) studies
 - includes case studies, cohort studies and controlled trials etc
- Secondary evidence consists of evidence that has been synthesised from primary studies
 - includes <u>systematic reviews</u>, meta-analyses and various types of summaries of evidence

Levels of research evidence: Various systems are used...

NHMRC* Levels of Evidence



*NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL

In Australia, the NHMRC Levels of Evidence is often used, particularly for NHMRC Clinical Practice Guidelines.

	Design
Level	Design
I	A systematic review of level II studies
Ш	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	 A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group
III-3	 A comparative study without concurrent controls: Historical control study Two or more single-arm studies Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post- test outcomes

What constitutes evidence?



WHAT TO LOOK FOR IN A STUDY

- Prognosis
- Diagnosis
- Treatment effectiveness

• What are your outcomes?





Introduction to systematic reviews

What is a systematic review of the literature?



FROM COCHRANE

- An appraisal and synthesis of primary • research papers
 - a rigorous and clearly documented methodology in both the search strategy and the selection of studies
- This minimises bias in the results ٠
- The clear documentation of the process ٠ and the decisions made allow the review to be reproduced and updated
- Gold standard for determining evidence-• based practice
- Increasingly used to guide policy and • direction of future research



Identify the issue and determine the question

What are systematic reviews?



FROM COCHRANE



What are systematic reviews?

Prepared by the Cochrane Consumers and Communication Group and generously support by Cochrane Australia.



Characteristics of a systematic review



- A clearly stated set of objectives with predefined eligibility criteria for studies
- An explicit, reproducible methodology
- A systematic search that attempts to identify all studies that would meet the eligibility criteria
- An assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias
- A systematic presentation, and synthesis, of the characteristics and findings of the included studies.



What's the difference between a systematic review and a literature review?



Bettany-Saltikov, J. (2010). Learning how to undertake a systematic review: Part 1. *Nursing Standard*, 24(40): 47-55.

	Systematic review	Literature review
Question	Focus on single question	May describe an overview
Protocol	A peer review plan or protocol included	No protocol
Background	Both provide summaries of the available literature on	a topic
Objectives	Clear objectives stated	May or may not have objectives
Inclusion and exclusion criteria	Criteria stated before review conducted	Criteria not specified
Search strategy	Comprehensive search conducted in a systematic way	Strategy no explicitly stated
Process of selecting articles	Usually clear and explicit	Not described
Process of evaluating articles	Comprehensive evaluation of study quality	Evaluation may/may not be included
Process of extracting relevant information	Usually clear and specific	Not clear or explicit
Results and data synthesis	Clear summaries of studies based on high quality evidence	Summary based on studies where quality of articles may not be specified. May be influenced by reviewer's theories, needs, beliefs
Discussion	Written by an expert or group of experts with a detail issues	ed and well grounded knowledge of the

Systematic literature reviews – what are the steps?



- 1. Form a focused research question
- 2. Develop inclusion/exclusion criteria
- 3. Register the review protocol
- 4. Search the literature
- 5. Screen the literature and assess the quality of the studies
- 6. Extract and manage data
- 7. Synthesise the data
- 8. Write review and publish results* (future opportunity)



PRISMA



PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES

http://www.prisma-statement.org

PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.



PRISMA checklist



Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS		·	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	

PRISMA checklist continued



Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

PRISMA flow diagram



IMPORTANT TO KEEP TRACK AT EACH STEP



doi:10.1371/journal.pmed1000 097

Exclusion reasons must match your partner's



USING SERUM CALCIUM AS AN EXAMPLE



PROSPERO



INTERNATIONAL PROSPECTIVE REGISTER OF SYSTEMATIC REVIEWS

https://www.crd.york.ac.uk/prospero/

PROSPERO includes protocol details for systematic reviews relevant to health and social care, welfare, public health, education, crime, justice, and international development, where there is a **health related outcome**



Why is prospective registration of systematic reviews important?



- Provides **transparency** in the review process
- Helps **counter publication bias** by providing a permanent record of prospectively registered reviews, irrespective of whether they are eventually published or not
- Helps safeguard against reporting biases by revealing any differences between the methods or outcomes reported in the published review and those planned in the registered protocol
- Improves quality and increases confidence that policy or practice informed by the findings of a systematic review is drawing on best-quality evidence
- Registration allows those commissioning or planning reviews to identify whether there are any reviews **already underway** that address their topic of interest

PROSPERO registration



WHAT IS REGISTRATION?

- Submission and publication of key information about the design and conduct of a systematic review
- Applications are assessed to ensure that they fall within scope and that the required data have been provided
- □ No quality assessment or peer review is involved
- □ Records are published on an open access electronic database
- Registration information can be amended should plans change
- All such changes are published and an audit trail of previous versions made available in the public record
- Registration records are permanent and registrants are asked to provide links to subsequent reports and publications
- PROSPERO assigns each registered review with a unique registration number. This number can be cited in publications and reports to provide the link between the planned and completed review, as recommended by PRISMA 2009 and many publishers.



Developing a research question

Why is a research question essential to the research process?



- Research questions help you focus your study
- Research question is what you will ask to address a research problem
- This is actually part of your methodology, and one of the very first steps in it
- The specificity of a well-developed research question helps the researcher avoid the "all-about" paper and work toward supporting a specific, arguable thesis

The research question should be



FOR SYSTEMATIC REVIEWS

- **clear**: provides enough specifics that audience can easily understand its purpose without needing additional explanation
- focused: narrow enough that it can be answered thoroughly in the space the writing task allows
- **concise**: expressed in the fewest possible words
- complex: not answerable with a simple "yes" or "no," but rather requires synthesis and analysis of ideas and sources prior to composition of an answer
- arguable: its potential answers are open to debate rather than accepted facts
- FINER (Hully 2007): <u>feasible</u>, <u>interesting</u>, <u>novel</u>, <u>ethical</u>, and <u>relevant</u>

Some things to consider when developing your research question





Types of research questions



LITERATURE SEARCHING FOR CLINICAL CARE AND EVIDENCE-BASED PRACTICE

- Background questions- general knowledge, contain 2 parts:
 - A question root (who, what, where, when, why, how) and
 - A disorder, test, treatment, or other aspect of healthcare
 - These questions can often be answered from a textbook or clinical database, etc.
 - E.g. How do you treat heart failure?
- Foreground questions- specific knowledge
 - That affect clinical decisions
 - Include a broad range of biological, psychological, and sociological issues
 - These are the questions that generally require a search of the primary medical literature and that are best suited to the PICO format
 - E.g. In adults with heart failure, would adding warfarin to standard therapy reduce thromboembolism?

When should I use PICO?



LITERATURE SEARCHING FOR CLINICAL CARE AND EVIDENCE-BASED PRACTICE

Р	Patient, Population, or Problem	How would I describe a group of patients similar to mine?
I	<u>I</u> ntervention, Prognostic Factor, or Exposure	Which main intervention, prognostic factor, or exposure am I considering?
С	<u>C</u>omparison or Intervention (if appropriate)	What is the main alternative to compare with the intervention?
0	<u>O</u> utcome you would like to measure or achieve	What can I hope to accomplish, measure, improve, or affect?
	What <u>Type</u> of question are you asking?	Diagnosis, Etiology/Harm, Therapy, Prognosis, Prevention
	Type of <u>S</u> tudy you want to find	What would be the best study design/methodology?



PICO and research question interactive activity



Identify the PICO concepts in the research question



Is animal-assisted therapy more effective than music therapy in managing aggressive behavior in elderly people with dementia?

Population: *elderly patients with dementia* Intervention: *animal-assisted therapy* Comparison intervention: *music therapy* Outcome measures: *aggressive behaviour*



IS IT TOO NARROW VS BROAD, FOCUSED OR UNFOCUSED, TOO SIMPLE OR COMPLEX?

Too narrow: What is the childhood obesity rate in Sydney, NSW?

Less narrow: How does the education level of the parents impact childhood obesity rates in Sydney, NSW?

The second question demonstrates the correct amount of specificity and the results would provide the opportunity for an argument to be formed.



IS IT TOO NARROW VS BROAD, FOCUSED OR UNFOCUSED, TOO SIMPLE OR COMPLEX?

Unfocused and too broad: What are the effects of childhood obesity in the United States?

More focused: How does childhood obesity correlate with academic performance in elementary school children?

The more focused question has a very clear focus for which data can be collected, analysed, and discussed.



IS IT TOO NARROW VS BROAD, FOCUSED OR UNFOCUSED, TOO SIMPLE OR COMPLEX

Too simple: How are school systems addressing childhood obesity?

More Complex: What are the effects of intervention programs in the elementary schools on the rate of childhood obesity among 3rd - 6th grade students?

The second question is more complex and requires both investigation and evaluation which will lead the research to form an argument that may be discussed.



WHAT DO YOU THINK IS WRONG AND HOW WOULD YOU IMPROVE IT?

Does the US or Australia have a better healthcare system?

Explanation: The first question is too broad and overly subjective: there's no clear criteria for what counts as "better". This means it is not easily researchable. An improvement would use clearly defined terms and narrow its focus to a specific population.

A better alternative: How do the US and Australia compare in health outcomes and patient satisfaction among general practice patients with chronic illnesses?

Make your own research question using PICO



EACH TEAM CHOSES ONE QUESTION, THEN PRESENT TO EVERYONE

Use of antibiotics in children

Vitamin supplementation or alternative medicine in treating disease

Role of diet in health

- The immune system and vaccine research
- The increasing rate of peanut allergies
- Medication errors in hospitals
- Role of rehabilitation in brain injuries
- Aboriginal health in remote areas of Australia

Impact of medical imaging on sports injury diagnosis

The guiding research question for EBLM project



THIS IS A GUIDE ONLY AND WILL NEED TO BE TAILORED TO EACH ANALYTE

What is the evidence for critical risk alert thresholds for (<u>test name</u>) results that require immediate medical attention and action due to <u>the high-risk of</u> <u>imminent death or major patient harm</u> (outcome)?



Eligibility – what are your inclusion and exclusion criteria?

Inclusion and exclusion criteria



WHICH STUDIES FROM YOUR SEARCH ARE ELIGIBLE FOR INCLUSION?

- Inclusion and exclusion criteria set the boundaries for your review
- They are determined after setting the research question usually before the search is conducted
- From PRISMA: Specify study characteristics (e.g., PICOS, length of followup) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility
- When you search for evidence, it's important to attempt to find all eligible studies and consider them for inclusion in your review
- If you don't find the evidence, it can't be reviewed!

Common Inclusion/Exclusion Criteria



Geographic Exposure Date Language location of interest of study The participants in the It is usually not If there has been a It may be necessary to study may need to have limit the review to only necessary to arrange previous review undertaken that is being experienced a particular studies targeting the translation of scientific condition to be updated then it is not same population group works unless the review considered for inclusion of interest for a broader is attempting to come to necessary to go back (e.g. received prenatal a definite conclusion over ground covered in original study or to the earlier review. classes, given a countries which share about a very specific Instead refer to it and the particular drug, had a similar demographic or clinical outcome which disease at a particular findings from that study economic factors with requires every applicable paper to be in the introduction. graded level or higher). the target group. included. Study Peer Reported Setting design outcomes review

Sometimes reviews will exclude non-peer reviewed literature but grey literature such as technical reports and web based guidelines may be important for certain research questions.



The inclusion of a study

may depend on whether

particular outcomes of

appropriate, consistent

manner. The outcomes

may be excluded if they

are self reported rather

than using objective

measures.

interest have been

reported and in an

The study may be excluded or included based on where the participants were located (e.g. school, hospital, inpatient, community based care).



restricted to only adult or child studies or to certain age groups. The Medline, Embase and Cinahl databases have age groups as subject headings for included articles.

Type of publication

The inclusion of only Systematic reviews selected study designs usually search for is a way to make the original studies. review much more Commonly excluded manageable and publications are reviews applicable to the and editorials. Letters research question. may also be excluded Study designs can however this should be include those in which done with caution as participants were sometimes the letter format will be used to surveyed at one point in time (e.g. crossreport small scale sectional studies and studies. ecological studies) and study designs that are conducted over time.

Some of these can be worked into search filters and your search terms during database searching, others can be reasons for exclusion during the literature screening step

Your inclusion/exclusion criteria provide you with not only a refined search strategy, but also a strict way of deciding which studies to keep or exclude during your literature screening



Important information

The training program

KEY DATES

- More detail about each of the modules will be emailed to participants throughout the program
- Feedback will be provided on three key deliverables
- Zoom meetings and workshops will be facilitated for each team by Macquarie research team
- Macquarie research team will be available by email or video conference for specific questions

Date	Modules and deliverables		
14 June 2019	Macquarie University Workshop		
Weeks 1-2 (17-28 June)	Module 1: Developing the research question		
Weeks 3-4 (1-12 July)	Module 2: Synthesis of the search strategy		
Week 4 (8-12 July)	Deliverable 1: Submit (a) A search strategy containing keywords and subject headings for each database including inbuilt filters; (b) PROSPERO registration summary before submitting		
Weeks 5-10 (15 July-23 August)	Module 3: Screening the literature		
Week 6 (22-26 July)	Zoom meeting: Endnote skills workshop		
Week 8 (5-9 August)	Zoom meeting: Literature screening Q & A		
Week 10 (19-23 August)	Deliverable 2: Submit an Endnote library containing all final papers and PRISMA flow chart		
Weeks 11-14	Module 4: Data extraction		
(26 August-20 September)	Module 5: Quality assessment		
Week 11 (26-30 August)	Zoom meeting: Quality assessment workshop		
Week 13 (9-13 August)	Zoom meeting: Final data extraction and write up Q& A		
Week 15-16 (23 September-4 October)	Module 6: Report writing and presentation to AACB		
Week 16 (30 September-4 October)	Deliverable 3 (week 16): Submit report containing (a) 1-page referenced background of the test and its impact on outcomes; (b) Standardised results table; (c) Quality assessment of the level of the underlying evidence		







Thank you



