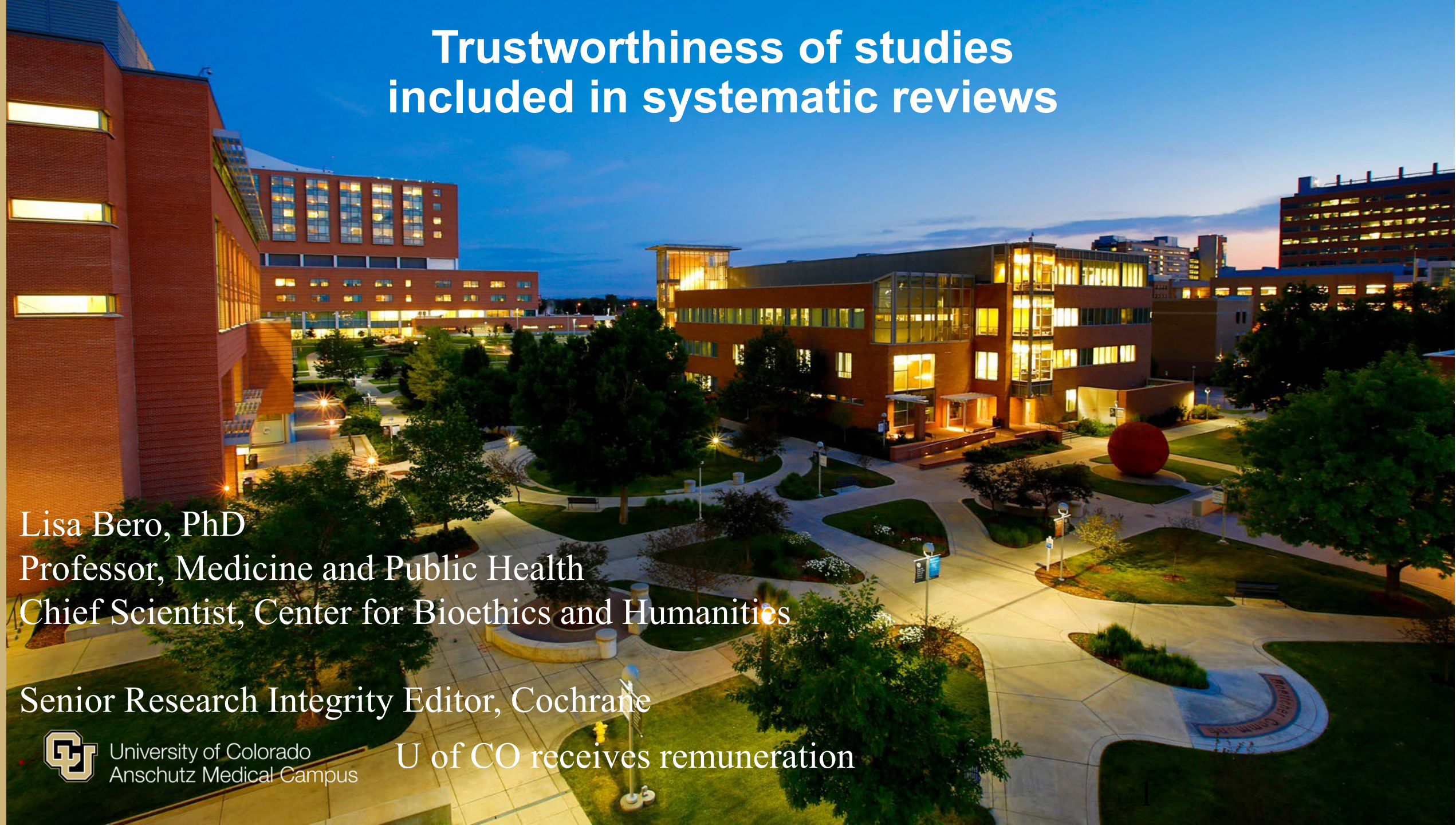
Trustworthiness of studies included in systematic reviews



Lisa Bero, PhD
Professor, Medicine and Public Health
Chief Scientist, Center for Bioethics and Humanities

Senior Research Integrity Editor, Cochrane

University of Colorado
Anschutz Medical Campus

U of CO receives remuneration

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Our Work > Consensus/Advisory Activity > Corrections and Retractions: Upgrading the Scientific Record

CONSENSUS/ADVISORY ACTIVITY

Corrections and Retractions: Upgrading the Scientific Record

12:10-1:30 PM	**Systematic Reviews and Corrections and Retractions** *Moderator:* Francis Kombe, Chief Executive Officer, EthiXPERT NPC, and Co-founder, African Research integrity Network; Member, Corrections and Retractions Study *Speakers*: • Lisa Bero, Professor, Professor of Medicine and Public Health, Chief Scientist for the Center for Bioethics and Humanities, University of Colorado Anschutz Medical Campus; Senior Research Integrity Editor, Cochrane • Florian Naudet, Professor of Therapeutics, Rennes University • Jack Wilkinson, Senior Lecturer in Clinical Trial Statistics, Division of Population Health, University of Manchester

A recording of the meeting is available here:
https://www.nationalacademies.org/projects/PGA-POLICY-24-13/event/45436

What is the other problem? Defining a problematic study

- "**Any published or unpublished study where there are serious questions about the trustworthiness of the data or findings, regardless of whether the study has been formally retracted**" (Cochrane)

- Does not consider intent
- Focus is on problematic studies, not researchers
- Includes different manifestations of problematic studies, including fabrication, falsification, image manipulation, research misconduct, ethics misconduct, detrimental or questionable research practices, plagiarism, duplicate publication and author misconduct
- Is different from risk of bias


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EDITORIAL

When beauty is but skin deep: dealing with problematic studies in systematic reviews

Stephanie L Boughton, Jack Wilkinson, Lisa Bero

https://bit.ly/3SsJO9F

Conducting the review

Policy

- DO NOT include retracted studies in the review
- DO NOT include problematic studies in the review (unless problems are resolved)

Implementation challenges

- Identifying retractions
  - Guidance in Cochrane Handbook, Problematic studies implementation guide, Retracted studies implementation guide
- Identifying problematic studies

What happens when a paper is retracted AFTER a review is published?

- Editorial note
- Update review (Cochrane)
- Retract review

COPE Guidance: editors should *retract a systematic review* publication if they *no longer have confidence in the results and conclusions* due to retracted or corrected included studies.

Decision Flowchart for retracting a review

Is the study/studies with an associated retraction an included study?

Do any other included studies have an associated retraction (or Expression of Concern)?

What is the scale of contribution of the study/studies with an associated retraction?

Is the study/studies with an associated retraction included in quantitative analysis? When the studies are removed, does the effect estimate and / or variability change?

Redo certainty of the evidence assessment without the study/studies with an associated retraction – Effect on certainty?

Flowchart implementation challenges

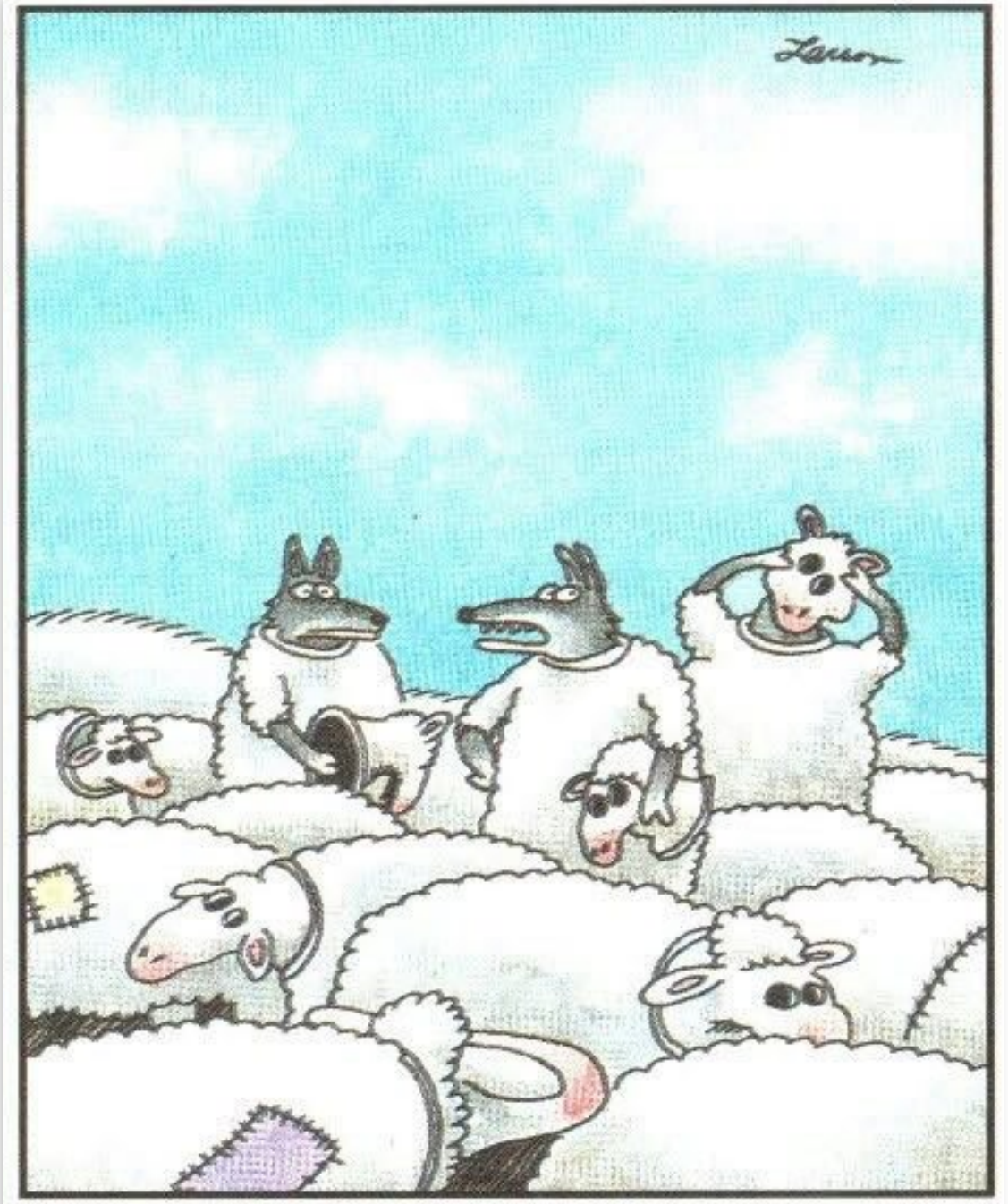
Author resources and willingness to apply framework

Does not distinguish between reasons for retractions

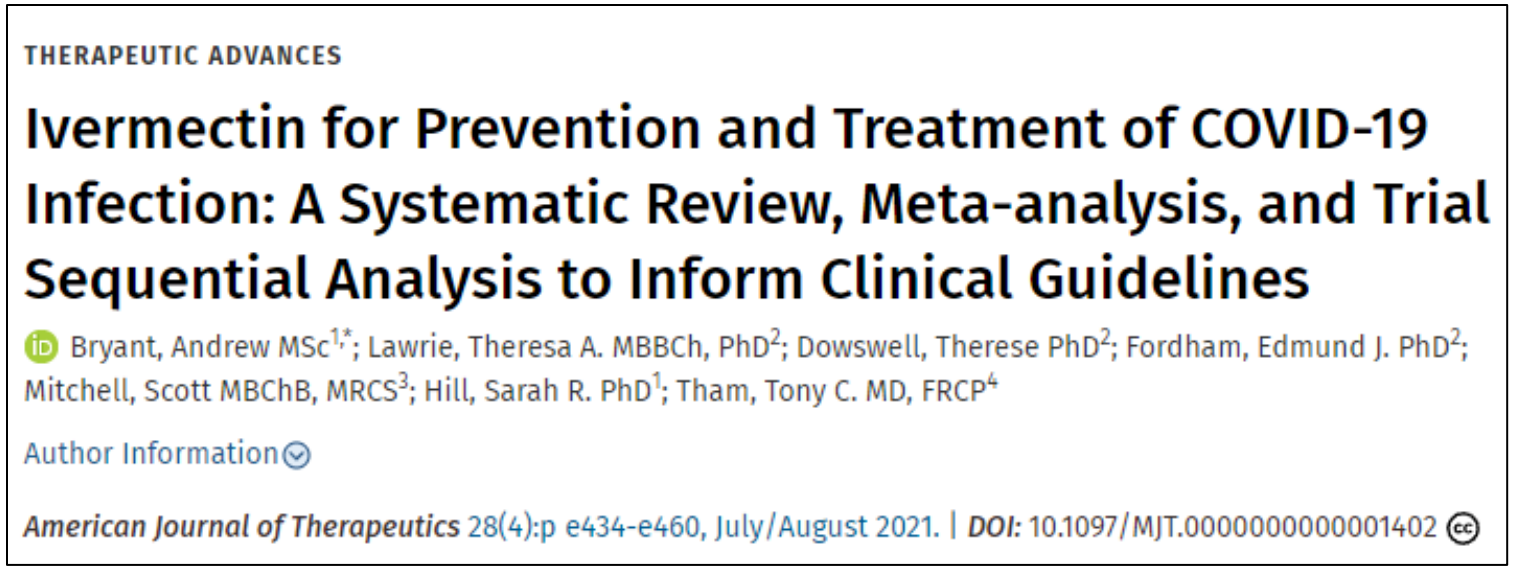
Specific thresholds will be contested (proportion of retracted data contributing to analysis, “confidence changing” effect estimates (*direction, magnitude, certainty*?), qualitative synthesis, or GRADE)

How big is the other problem? Prevalence of problematic studies

- 2-80% - depends on population studied, method used to detect problematic studies
- May affect the effect estimates and certainty of systematic reviews



"Wait a minute! Isn't anyone here a real sheep?"



THERAPEUTIC ADVANCES

Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines

Bryant, Andrew MSc[1,*]; Lawrie, Theresa A. MBBCh, PhD[2]; Dowswell, Therese PhD[2]; Fordham, Edmund J. PhD[2]; Mitchell, Scott MBChB, MRCS[3]; Hill, Sarah R. PhD[1]; Tham, Tony C. MD, FRCP[4]

Author Information

American Journal of Therapeutics 28(4):p e434-e460, July/August 2021. | *DOI:* 10.1097/MJT.0000000000001402

"large reductions in death are possible" suggested impressive benefit on mortality

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Review language : English

Title Abstract

Cochrane Reviews | Trials | Clinical Answers | About | Help

Cochrane Database of Systematic Reviews | Review - Intervention

Ivermectin for preventing and treating COVID-19

Maria Popp, Stefanie Reis, Selina Schießer, Renate Ilona Hausinger, Miriam Stegemann, Maria-Inti Metzendorf, Peter Kranke, Patrick Meybohm, Nicole Skoetz, Stephanie Weibel Authors' declarations of interest

Version published: 21 June 2022 Version history

https://doi.org/10.1002/14651858.CD015017.pub3

Research integrity assessment applied and 7 out of 18 eligible trials excluded. Remaining 11 trials showed no beneficial effect

How do we identify problematic studies?

"We became aware that they will start using the questions we give them as information about what we are looking for and then they will start clearing that up in any new submissions that are coming in." [P14, publishing industry]

Parker L, Boughton S, Lawrence R, Bero L.
J Clin Epidemiol. 151:1-17; 2022

INSPECT SR

INveStigating ProblEmatic Clinical Trials in Systematic Reviews

The University of Manchester

Cochrane

University of Colorado Anschutz Medical Campus

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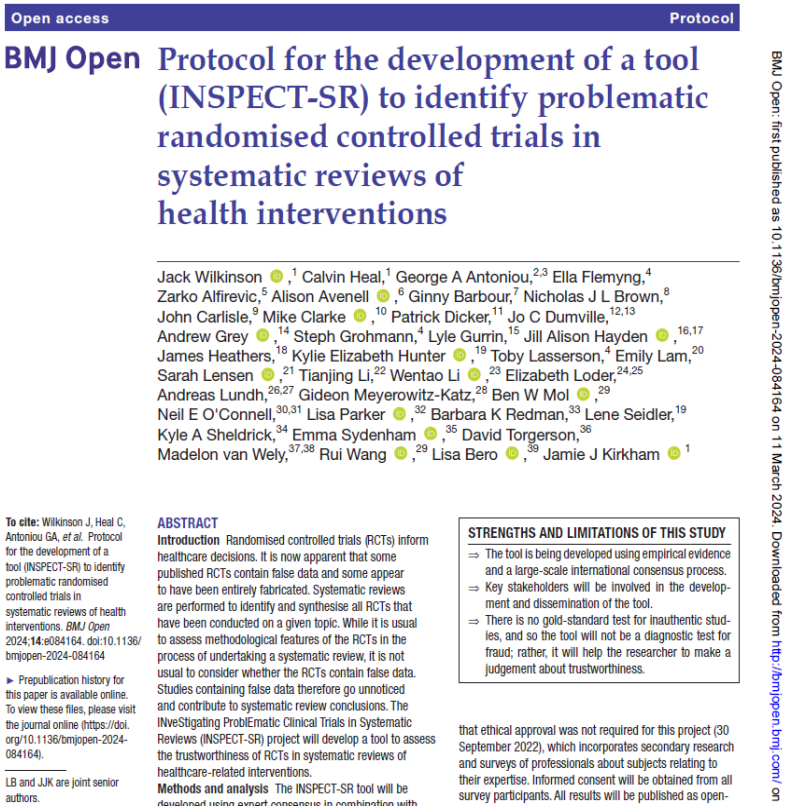


Open access Protocol

BMJ Open

Protocol for the development of a tool (INSPECT-SR) to identify problematic randomised controlled trials in systematic reviews of health interventions

Jack Wilkinson ,[1] Calvin Heal,[1] George A Antoniou,[2,3] Ella Flemyng,[4] Zarko Alfirevic,[5] Alison Avenell ,[6] Ginny Barbour,[7] Nicholas J L Brown,[8] John Carlisle,[9] Mike Clarke ,[10] Patrick Dicker,[11] Jo C Dumville,[12,13] Andrew Grey ,[14] Steph Grohmann,[4] Lyle Gurrin,[15] Jill Alison Hayden ,[16,17] James Heathers,[18] Kylie Elizabeth Hunter ,[19] Toby Lasserson,[4] Emily Lam,[20] Sarah Lensen ,[21] Tianjing Li,[22] Wentao Li ,[23] Elizabeth Loder,[24,25] Andreas Lundh,[26,27] Gideon Meyerowitz-Katz,[28] Ben W Mol ,[29] Neil E O'Connell,[30,31] Lisa Parker ,[32] Barbara K Redman,[33] Lene Seidler,[19] Kyle A Sheldrick,[34] Emma Sydenham ,[35] David Torgerson,[36] Madelon van Wely,[37,38] Rui Wang ,[29] Lisa Bero ,[39] Jamie J Kirkham [1]

To cite: Wilkinson J, Heal C, Antoniou GA, *et al*. Protocol for the development of a tool (INSPECT-SR) to identify problematic randomised controlled trials in systematic reviews of health interventions. *BMJ Open* 2024;**14**:e084164. doi:10.1136/bmjopen-2024-084164

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-084164).

LB and JJK are joint senior authors.

ABSTRACT

Introduction Randomised controlled trials (RCTs) inform healthcare decisions. It is now apparent that some published RCTs contain false data and some appear to have been entirely fabricated. Systematic reviews are performed to identify and synthesise all RCTs that have been conducted on a given topic. While it is usual to assess methodological features of the RCTs in the process of undertaking a systematic review, it is not usual to consider whether the RCTs contain false data. Studies containing false data therefore go unnoticed and contribute to systematic review conclusions. The INveStigating ProblEmatic Clinical Trials in Systematic Reviews (INSPECT-SR) project will develop a tool to assess the trustworthiness of RCTs in systematic reviews of healthcare-related interventions.

Methods and analysis The INSPECT-SR tool will be developed using expert consensus in combination with

STRENGTHS AND LIMITATIONS OF THIS STUDY

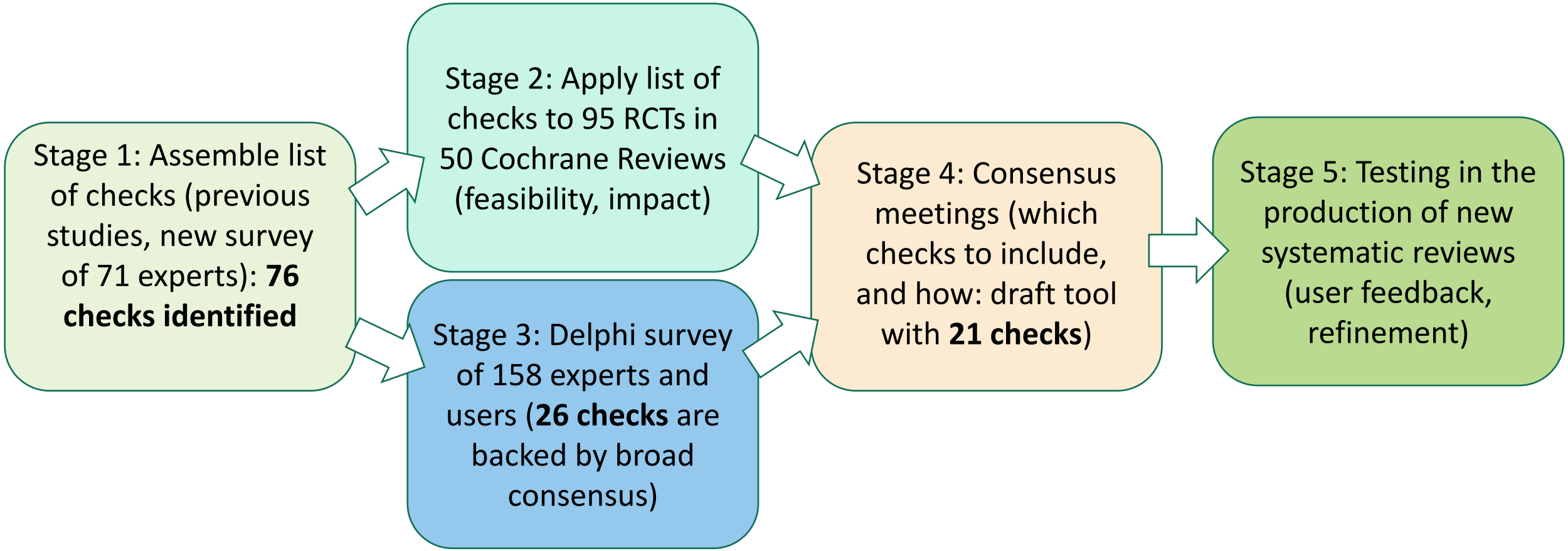
⇒ The tool is being developed using empirical evidence and a large-scale international consensus process.
⇒ Key stakeholders will be involved in the development and dissemination of the tool.
⇒ There is no gold-standard test for inauthentic studies, and so the tool will not be a diagnostic test for fraud; rather, it will help the researcher to make a judgement about trustworthiness.

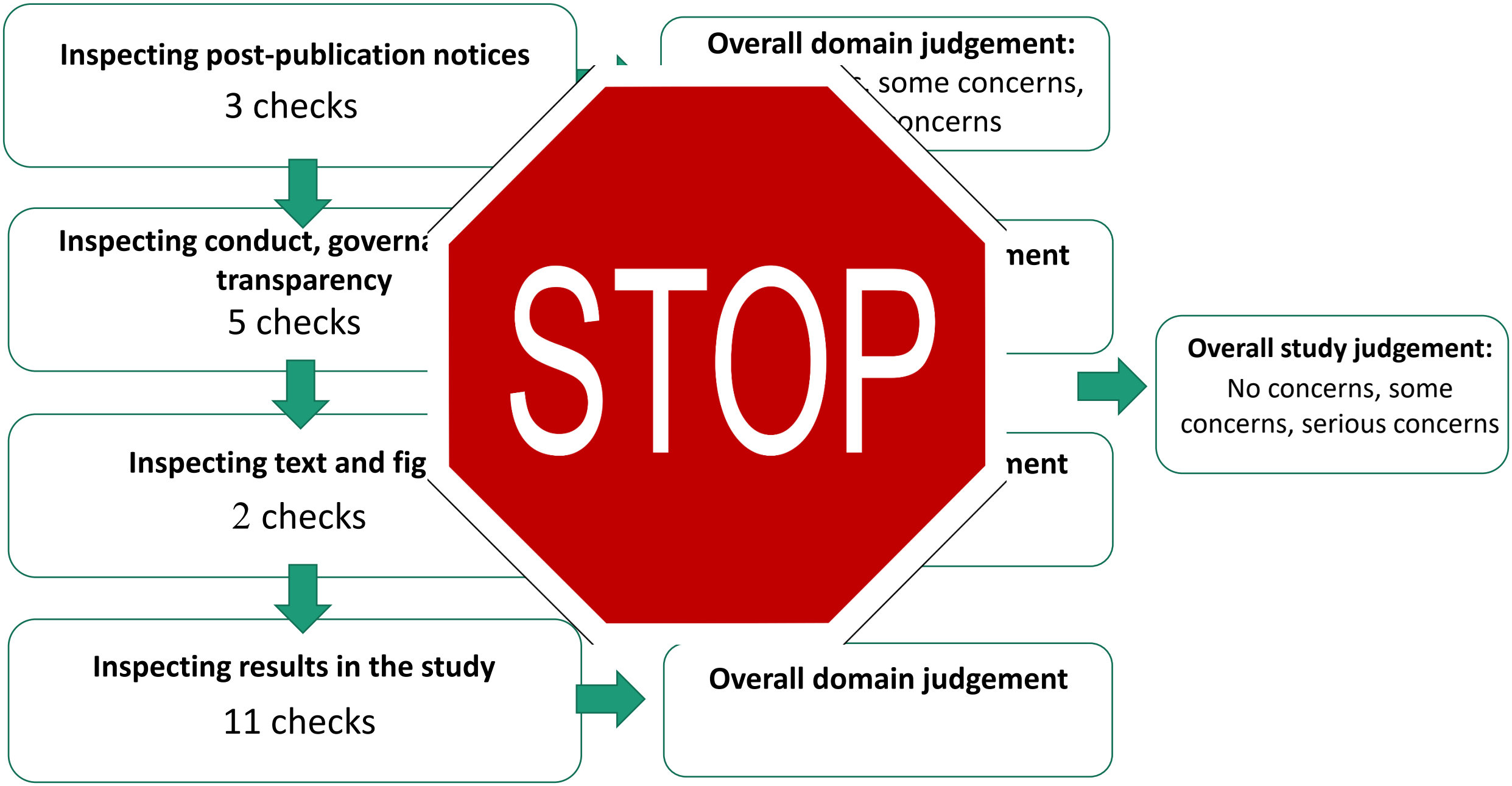
that ethical approval was not required for this project (30 September 2022), which incorporates secondary research and surveys of professionals about subjects relating to their expertise. Informed consent will be obtained from all survey participants. All results will be published as open-

An editable template and detailed guidance: https://osf.io/b74wj/files

INSPECT SR

Aim: To develop a tool for identifying problematic randomised controlled trials in the context of health systematic reviews




Inspecting post-publication notices
3 checks
Inspecting conduct, governa
transparency
5 checks
Inspecting text and fig
2 checks
Inspecting results in the study
11 checks
Overall domain judgement:
some concerns,
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STOP
Overall domain judgement
Overall study judgement:
No concerns, some concerns, serious concerns

More to do

- Searchable, open archive of research integrity investigations using INSPECT-SR
- Training
- INSPECT-AI: AI/LLM implementation of parts of INSPECT-SR
- INSPECT-SR IPD: for Individual Patient Data
- INSPECT-SR OBS: for studies with observational designs
- INSPECT-SR JR: for journal editors

Systematic reviewers ….

1. Can control the content of their review and are therefore **obligated** as authors of the review to produce an unbiased, trustworthy evidence synthesis.

2. Should use **standardized, tested methods to identify problematic studies and exclude them** from reviews.

3. Should proactively **share their investigations with other actors in the publication pipeline** to trigger further action by other parties who have a stake in funding, creating, and publishing research.

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doi:10.1017/jme.2025.34

Thank you!

For more information:

Lisa Bero, PhD

lisa.bero@cuanschutz.edu