150 YEARS OF CELEBRATING THE MAHATMA

आज़ादी का अमृत महोत्सव

BEGINNER'S GUIDE FOR SYSTEMATIC REVIEWS

A STEP BY STEP GUIDE TO CONDUCT SYSTEMATIC REVIEWS AND META-ANALYSIS

(AN ICMR PUBLICATION)

ANJU SINHA, GEETHA R. MENON, DENNY JOHN

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Indian Council of Medical Research
2022

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सत्यमेव जयते

प्रोफेसर (डा.) बलराम भार्गव, पदम श्री
एमडी, डीएम, एफआरसीपी (जी.), एफआरसीपी (ई.), एफएसीसी,
एफएएसए, एफएएमएस, एफएनएएस, एफएएससी, एफ.एन.ए., डी.एस.सी.
सचिव, भारत सरकार
स्वास्थ्य अनुसंधान विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
महानिदेशक, आई सी एम आर

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Department of Health Research
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भारतीय आयुर्विज्ञान अनुसंधान परिषद
स्वास्थ्य अनुसंधान विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
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Foreword

I am happy to write this foreword for Beginner's Guide for Systematic Reviews. This book is mainly aimed at public health and social science researchers for undertaking systematic reviews. The aim of this guide is to promote high standards in commissioning, conducting, and providing practical guidance for undertaking systematic reviews evaluating the effects of health interventions.

Over the last decade, the demand for use of the best available research evidence to inform health care decision making and public policy has increased considerably. Systematic reviews aim to identify, appraise, and summarize the findings from all relevant individual studies on a topic. Well conducted Systematic Reviews provide the best evidence to guide clinical practice, they are considered a cornerstone for the recommendations of Evidence-based practice guidelines and should be an integral part of planning future research activities. The Beginner's Guide has been written for those with an understanding of health research & seeking skills for conducting systematic reviews. The guide is also aimed at those who commission systematic reviews, such as the government and funding organisations. Though the book is mainly aimed at health practitioners, some researchers working on systematic reviews on social sciences might also find it useful.

I appreciate the efforts of the contributors in preparing the Beginner's Guide. As we release this guide, I envision that it would serve a variety of audiences such as policymakers, researchers, clinicians and other health professionals who need to be aware of evidence-informed decision-making in health care.

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Acknowledgements

This book has been produced through collaborative efforts of the contributing authors. The book draws on the collective learning from the systematic reviewing conducted by the authors, and also from the learning's that has arisen from interacting with systematic review workshop participants from India (ICMR, DHR, NICPR, NIREH, PGIMER) Nepal, Bangladesh, Ghana, Germany, and Scotland, and researchers embarking on a systematic review from developing countries.

We acknowledge Ms Supreet Kaur, who was a data programmer in the HIV project at ICMR-NIMS when this book was being written, for her inputs in chapter 5 and in preparing a list of textbooks as additional resources in this book.

In addition, the authors are grateful to the reviewers Prof Meenu Singh from PGIMER, Chandigarh and Prof. Sreekumaran Nair, JIPMER, Puducherry who have a rich experience in teaching, training and conducting systematic reviews. Their valuable inputs and review have helped in improving the contents of this book.

We hope this book becomes a useful guide for beginners and early career researchers who are planning to undertake systematic reviews.

Dr. Anju Sinha
Dr. Geetha R. Menon
Dr. Denny Hohn

Anju Sinha: Consultant Scientist Division of RBMCH, ICMR Hqrs, New Delhi. Dr. Anju is a clinician by training specializing in Epidemiology & Public Health, with overall 27 years of research experience in implementation of large community-based field trials funded by international agencies. At the Indian Council of Medical Research she worked as a Program Officer in the area of Neonatal and Child Health, HIV prevention, and Evidence Based Child Health. She has initiated a funding scheme on secondary data, supporting systematic reviews and building capacity of Indian scientists in systematic reviews. She is the recipient of the Aubrey Sheiham award in Primary Health Care and the Kenneth Warren award from the Cochrane. She is a Steering Committee member Public Health Evidence South Asia (PHESA), Scientific Advisory Group member International Life Sciences Institute (ILSI), India, member Technical Advisory Committee of Health Technology Assessment India (HTAIn), member Cochrane Neonatal and Cochrane Acute Respiratory Infections Groups, Cochrane Child Health and Public Health Fields & Rapid Review Methods Group and the Campbell Collaboration. She is Director of the Cochrane Affiliate Centre at ICMR Hqrs & Co Chairs the Cochrane India Network. She is involved with Evidence to policy translation, policy briefing, Health Technology Assessments and identifying new research priorities.

Geetha R. Menon is a Senior Scientist trained as a Biostatistician working for the ICMR-National Institute of Medical Statistics. She has an experience of more than 3 decades and has contributed to biomedical research both as a primary researcher and as a research manager. She has a doctorate degree in Biostatistics and has significant experience of analysing data from large scale surveys and epidemiological studies, doing statistical modelling, and undertaking Systematic Reviews and Meta-Analysis. She has been involved in planning and designing research studies, teaching biostatistics to researchers and medical faculties and conducting capacity building workshops in research methodology, systematic reviews and health economics. Geetha has co-authored over 100 scientific publications in national and international journals and has co-edited two books viz. *Road Traffic & Safety (Transportation Issues, Policies and R&D*) and *Understanding and Treating Head Injuries.* She is the recipient of the ISCB Young Scientist Award 2006, Dr. Kelly P O'Keefe Academician & Researcher of the Year Award 2013, Statistical Alliance for Vital Events (SAVE) – Queen Elizabeth Advanced Scholars (QES) 2018, and Indian Society of Medical Statistics BG Prasad Award 2020.

Denny John is Adjunct Professor, Faculty of Life and Allied Health Sciences, Ramaiah University of Applied Sciences, Bengaluru; and Adjunct Faculty, Amrita Institute of Medical Sciences & Research Centre, Kochi. Denny has experience of working across several review types, such as effectiveness, cost-effectiveness, barriers/facilitators, prevalence/incidence, risk/aetiology and diagnostic test accuracy. Denny's research focusses mainly on economic evidence in systematic reviews including equity components. With a background in epidemiology and health economics, he has considerable methodological and statistical expertise, including conducting cost-effectiveness alongside randomized controlled trials and observational studies, as well systematic reviews and meta-analyses. Denny is Chair, Cochrane & Campbell Economic Methods Group (CCEMG), and Advisory Member, Disability Coordinating Group, Campbell Collaboration, and Co-Chair, Early Career Network, Health Technology Assessment International (HTAi). He was on the Editorial Board for 'Evidence, policy, impact: WHO guide for evidence-informed decision-making', published by World Health Organization in 2021.

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1. Introduction

1.1 What Is a Systematic Review?

A systematic review is a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyze data from the studies that are included in the reviews[1].

Diverse range of information sources and an explosion of knowledge have made it impossible for clinical researchers to stay abreast with advances in a given field. Systematic reviews and meta-analyses were conducted in health in 1970s and 1980s. Both the terms meta-analyses and systematic reviews were used interchangeably and often created confusion among the readers. Chalmers and Altman[2] suggested that the term 'Meta-Analysis' may be used only for statistical synthesis or quantitative methods of combining the evidence from individual studies and it may or may not be part of a systematic review.

Systematic reviews are most often used to study the effectiveness of a particular drug treatment compared with a placebo or any other alternative treatment. However, these cover a wide range of other issues like:

- Surgical and nursing techniques e.g. the best ways of carrying out knee replacements or the best methods of dressing for chronic wounds
- Psychosocial interventions e.g. community-based interventions for people with schizophrenia
- Public-health interventions e.g. impact of mobile health (mHealth) interventions in health care delivery or lifestyle interventions in reducing the prevalence of type II diabetes
- Adverse effects of drugs or other treatments
- Economic evaluations e.g. evaluation of implementation intervention in public health or drug trials to identify which intervention is cost effective
- Although Systematic Reviews are predominantly used in intervention studies, researchers also use this technique in economic evaluation, diagnostics tests accuracy, prevalence/incidence etc.

1.2 Why do we need a systematic review?

Systematic reviews are needed for the following reasons

a. To keep abreast of all previous and new research

b. To introduce a new treatment that is expected to be better than an existing one

c. To discontinue an old treatment which might be out dated, harmful or less cost effective

d. To draft guidelines for health and social interventions or treatment management

e. To arrive at a consensus where conflicting evidence is reported

1.3 What is the difference between a narrative review and a systematic review?

In comparison with literature or traditional narrative reviews, systematic reviews are much time-intensive and need a research team with multiple skills and contributions. Table 1 provides a description of these differences.

There are some cases where systematic reviews are unable to meet the necessary objectives of the review question. In such a case, scoping reviews (which are sometimes called scoping exercises/scoping studies) may be more useful to consider. Table 2 provides the characteristics of narrative reviews, scoping reviews and systematic reviews.

Table 1 : Differences between a narrative review and a systematic review

	Narrative Review	*Systematic Review*
Goals	Provides summary or overview of topic	Answers a focussed review question
Question	Can have a broad topic or a specific question. Hypothesis might not be stated.	Clearly defined review question using PICO as a guide. Hypothesis is stated.
Authors	One or more	Three or more
Protocol	No protocol	A peer review protocol or plan is included
Objectives	May or may not be identified	Has clearly stated objectives
Inclusion/ exclusion criteria	Criteria not usually specified	Criteria stated before the review is conducted
Search strategy	No detailed search strategy, mostly conducted using keywords and snow-balling	Detailed and comprehensive search strategy

	Narrative Review	*Systematic Review*
Sources of literature	Non-exhaustive and not stated always. Prone to publication bias.	List of databases, grey literature and other sources are considered.
Selection criteria	Usually subjective or no selection criteria. Prone to selection bias.	Selection process usually clear and explicit
Appraisal of study quality	Variation in evaluation of study quality of studies	Use of standard checklists for rigorous appraisal of study quality
Extracting relevant information	Not explicit and clear	Clear and specific
Synthesis	Summary based on studies which have not been checked for quality and can be influenced by the reviewers needs and beliefs	Clear summaries of studies based on high quality evidence Narrative, quantitative or qualitative synthesis
Conclusions	Sometimes evidence based but could be prone to researcher bias (influence of author's personal belief)	Evidence-based
Timeline	Weeks to months	Months to years
Requirements	Understanding of topic, and searching of 2-3 databases	At least one of the authors with good knowledge of the topic, searches done for all relevant databases
Value	Provides summary of literature on the topic Conclusions may be subjective hence minimal reproducibility of findings Cannot be continuously updated	Provides high-quality evidence, and supports evidence-based practice Detailed and accurate documentation of methods using PRISMA means results can be reproduced Periodically updated to include new evidence

Table 2: Characteristics of narrative reviews, scoping reviews and systematic reviews

	Narrative Reviews	Scoping Reviews	Systematic Reviews
A priori review protocol	No	Yes (some)	Yes
PROSPERO registration of the review protocol	No	No[a]	Yes
Explicit, transparent, peer reviewed search strategy	No	Yes	Yes
Standardized data extraction forms	No	Yes	Yes
Mandatory Critical Appraisal (Risk of Bias Assessment)	No	No[b]	Yes
Synthesis of findings from individual studies and the generation of 'summary findings'	No	No	Yes[c]

[a] Current situation; this may change in time.

[b] Critical appraisal is not mandatory; however, reviewers may decide to assess and report the risk of bias in scoping reviews.

[c] by using statistical Meta-Analysis (for quantitative effectiveness, or prevalence or incidence, diagnostic accuracy, aetiology or risk, prognostic or psychometric data), or meta-synthesis (experiential or expert opinion data) or both in mixed method reviews[3].

1.4 Where to find systematic reviews?

Before undertaking a systematic review, it is necessary to look for ongoing reviews or completed reviews on the topic of interest. Below are some useful websites to start searching for systematic reviews.

- Database of Abstracts of Reviews of Effects (DARE) https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
- Cochrane Database of Systematic reviews

  https://www.cochranelibrary.com/cdsr/reviews
- National Institute for Health and Care Excellence UK Database of Uncertainties about the Effects of Treatments (DUETs) ; https://www.evidence.nhs.uk/

- National Institute for Health Research – Health technology Assessment NIHR-HTA

  https://www.nihr.ac.uk/explore-nihr/funding-programmes/health-technology-assessment.htm

- Campbell Library of Systematic Reviews

  https://campbellcollaboration.org/better-evidence.html

- Evidence for policy and Practice Information (EPPI) Centre - https://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9

- Database of promoting health effectiveness reviews : https://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9

- Agency for Healthcare Research and Quality

  https://www.ahrq.gov/research/findings/evidence-based-reports/search.html

- Scottish Intercollegiate Guidelines Network: https://www.sign.ac.uk/our-guidelines.html

- BMJ Evidence based medicine:https://ebm.bmj.com/pages/collections/ebm_verdict/

- PROSPERO International prospective register of systematic reviews

- Turning Research into practice (TRIP): https://www.tripdatabase.com/

- Search filters in major databases e.g. Medline, EMBASE, PSYCHLIT, CINAHL (for search filters see 'searching for specific study types' below)

Summary

- A systematic review is a study that identifies a specific review question, identifies relevant studies using a comprehensive search strategy, appraises the quality of these studies and summarizes their results in a scientific manner
- Systematic reviews can be conducted on many different types of primary studies
- Systematic reviews can be used for informing policies that impact quality, safety and values of health care
- Systematic reviews provide summary evidence from available literature but narrative reviews do not follow scientific review methodology

2. Getting Started

Before initiating a systematic review, it is important to consider four main aspects in managing the review:

a) **Formation of a review team**- A systematic review team should include experts with a range of skills including expertise in information retrieval, epidemiologist or clinical expert, systematic review methods, statistics, and other aspects e.g. health economist if required for cost-effectiveness/cost-benefit analysis reviews and qualitative expects for research methods where appropriate.

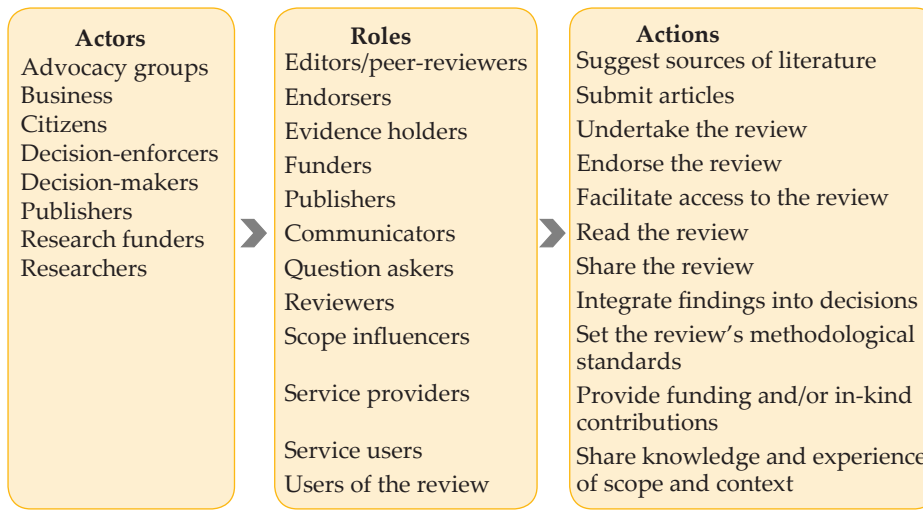
b) **Formation of an advisory group** – An advisory group including health care professionals, patient representatives, service users and experts in research methods who may be consulted at key stages may be necessary for the funding agencies.

c) **Timeline-** The timelines for completing various evidence synthesis activities may vary. However, organizations such as Cochrane and Campbell Collaboration suggest completing a review within a year.

d) **Stakeholder engagement**- Various studies have emphasized the importance of engaging stakeholders to ensure that systematic reviews are shaped by members from the policy and practice community who would be using them[4,5]. Figure 1 provides a conceptual model of stakeholders and the actors.

e) **Software**- The selection of software will need to be considered for various stages of the systematic review process. Table 3 provides a list of some of the software applications found useful at various stages of the review.

Figure 1: Conceptual model of stakeholders, identified by the actors, their roles and their actions



Example

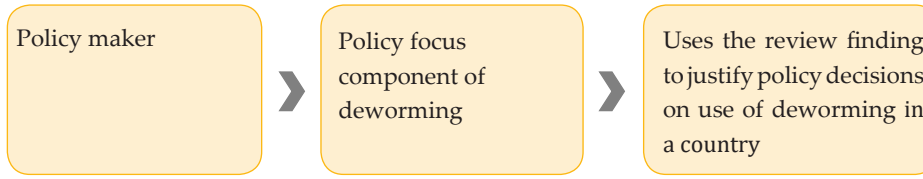


Table 3: Software for various processes in the systematic review

Activity	Software	Cost	Organisation
Reference management	Zotero	Free	RRCHNM
	Mendeley	Paid	Elsevier
	EndNote	Paid	Clarivate Analytics
	Reference Manager	Paid	Thomson Reuters
	EPPI Reviewer	Paid	EPPI Centre
Screening	Covidence	Free/Paid	Covidence
	EPPI Reviewer	Paid	EPPI Centre
	Rayyan	Free	Qatar Foundation
	MS-Excel[$]	Free	Microsoft
	SUMARI	Free	JBI
	DistillerSR	Free for students, 4 mnths	Evidence Partners
	EPPI Reviewer	Paid	EPPI Centre
Coding	EPPI Reviewer	Paid	EPPI Centre
	MS-Excel	Free	Microsoft
	SUMARI	Free	JBI
Data extraction	EPPI Reviewer	Paid	EPPI Centre
	MS-Excel[$]	Free	Microsoft
	SRDR	Free	CEBM
	SUMARI	Free	JBI
	DistillerSR	Free for students, 4 months	Evidence Partners
Critical Appraisal	EPPI Reviewer	Paid	EPPI Centre
	MS-Excel	Free	Microsoft
	QARI	Free	JBI
	MAStARI	Free	JBI
	ACTUARI	Free	JBI

Activity	Software	Cost	Organisation
Meta-Analysis	RevMan	Free	Cochrane
	STATA	Paid	STATA Corp
	SPSS	Paid	SPSS Inc
	R	Free	CRAN
	CMA	Paid	CMA Corp
	MedCalc	Paid	MedCalc Inc
	Mix 2.0	Paid	Biostat XL
	OpenMeta Analyst	Free	CEBM
	MAStARI	Free	JBI
Qualitative	nVivo	Paid	QSR International
	QARI	Free	JBI
Mixed Methods	MAXQDA	Paid	VERBI GmbH

[$]MS-Excel would need to be formatted to conduct the various components of the review process. JBI softwares are available only for reviews with the Joanna Briggs Institute (JBI), Australia.

The following sites have some learning resources for beginners:

- Campbell Collaboration: https://www.campbellcollaboration.org/
- Cochrane: https://www.cochrane.org/
- EPPI-Centre: https://eppi.ioe.ac.uk/cms/
- Systematic Review Toolbox: http://systematicreviewtools.com/
- International Initiative for Impact Evaluation (3ie): https://www.3ieimpact.org/
- Centre for Evidence Based Medicine https://www.cebm.net/
- Centre for Reviews and Dissemination Databases: https://www.crd.york.ac.uk/crdweb/
- Health Evidence Network (HEN), WHO: https://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/health-evidence-network-hen
- Africa Evidence Network: www. https://www.africaevidencenetwork.org/en/
- The EQUTOR Network: https://www.equator-network.org/
- The GRADE Working Group: www. https://gradeworkinggroup.org/
- NIHR HTA: https://www.journalslibrary.nihr.ac.uk/#/

2.1 Writing a Systematic Review Protocol

A review protocol is a guide for a well written systematic review. It explains the rationale for conducting the systematic review, states the hypothesis and outlines the methodology to be used. It is important to note that the protocol is a priori statement of aims and methods of the systematic review, and referred back to whenever is needed during the systematic review process. Research question(s), aims and methods are considered in advance to identify the relevant literature to ensure the conduct of the review with minimal bias, access to peer review, greater efficiency in review process[6]. Protocol development is often an iterative process that requires discussion within the review team, advisory group and sometimes with the funding agency. Peer review and publication makes the protocol publicly available.

A Cochrane review protocol is considered as an individual publication. Non-Cochrane protocols should be registered on PROSPERO - an international database of prospectively registered systematic reviews in health and social care[7]. Key features from the review protocol are recorded and maintained as a permanent record. Systematic reviews should be registered at inception (i.e. at the protocol stage) to help avoid unplanned duplication and to enable the comparison of reported review methods with what was planned in the protocol[8]. This prevents duplication (research waste) and makes the process easy when the full systematic review is sent for publication.

By writing a protocol and adhering to it during the review process, the researcher makes it clear that the decisions taken while conducting the review are not arbitrary, the decision to include or exclude studies in the review are not guided by individual choices or prejudices (bias) of the authors or prior knowledge about their results. There are several resources available for the beginners such as the Cochrane Handbook[9], PRISMA Extension for protocols (PRISMA-P)[10], Institute of Medicine-Standards for systematic reviews[11] etc.

Systematic Review should be undertaken by a team of individuals with different areas of expertise. The team should consist of a person with clinical expertise, a person with systematic review experience, a methods person with statistical expertise, and someone with multidisciplinary experience. Someone from the relevant location/population allows double-checking of inclusion of studies and data collection.

2.2 Components of a Systematic Review protocol

The protocol for a systematic review is written using the following format.

Background: This section for a Cochrane systematic review has a structured format. Under the sub-heading **Description of the condition,** the health condition/disease under consideration is described with definitions and epidemiological information as evidenced from latest research.

Description of the intervention (for intervention reviews) has a description of the intervention to be evaluated in the systematic review; recent publications on this intervention from the literature should be aligned to the review. The mechanism of action of the intervention is described in a paragraph: **How the intervention might work**, followed by justification for conducting the systematic review under: **why it is important to do this review**. In this section the authors are required to mention about other published systematic reviews on the topic, if there are any, the gaps therein that would be addressed in the present review.

Objectives: The primary and secondary objectives of the review are stated under objectives. Additionally, the pre-specified sub-group analyses within the major comparisons need to be listed here.

Methods: This section of the protocol elaborates on the **criteria for considering studies for the review** (inclusion/exclusion criteria): **types of studies** (randomized, quasi-randomized, cluster-randomized in intervention reviews), **types of participants (**the study population**,** age groups, sex, gestation etc. need to be described) **types of intervention** (the formulation, mode of administration, doses etc. need to be mentioned) and **types of outcome measures: Primary, secondary** under different comparison should be described, The procedure to be followed for screening of titles abstracts and full text articles requires that all the steps are completed by two persons. In case of disagreements, a third person (usually more experienced) involved as a team member is approached for resolution. Reviewers may choose to perform a blinded review of the articles retrieved through search.

Search Methods for identification of studies: A comprehensive and up to date and reproducible search is a hallmark of a systematic review. This includes electronic Searches as well as searching other resources (hand searching, non-indexed journals, conference proceedings and grey literature, cross-references/citation searching/manufacturers/personal contacts). It is a pre-requisite that at least 2-3 electronic databases are searched, in order to qualify as a systematic review. The reviewers need to decide what databases (MEDLINE via Pub med, EMBASE, Cochrane central register of controlled trials (CENTRAL) Cumulative Index to Nursing and Allied Health Literature (CINAHL) and sources will be searched, in the context of their topic. The time period for search needs to be specified, search terms and key words have to be written and a search strategy needs to be written down. Search is

a complex activity in the conduct of a systematic review, requiring skills as well as access to databases, and resources. It is recommended to seek help from an information specialist/librarian. Cochrane review groups assist the review authors with searching through their designated search coordinators. It is advisable to consider each of the components of the **P**articipants, **I**nterventions, **C**omparator/comparison and **O**utcomes (**PICO**) to derive the search terms. It is important to mention how the reviewers would search for unpublished data (grey literature), conference abstracts. The name of the person who will run the searches, if known, should also be mentioned.

Searching regional databases (e.g. IndMed), clinical trial registries (e.g. CTRI), hand-searching of non-indexed journals, conference proceedings and unpublished (grey) literature should be attempted by the reviewers and described in the methodology.

Data Collection and Analysis: This section comprises of the following sub-headings and their description.

Selection of studies: In a systematic review all steps are performed by two reviewers independently. This is crucial for avoiding personal biases at any step of the conduct of the review. Selection of studies is done as per the laid down inclusion exclusion criteria. Two review authors independently review the titles and abstracts of articles identified by searches for eligibility. Studies are classified as included, excluded or unclear. Full articles are retrieved after title and abstract screening to evaluate whether the study should be included or not based on the PICO of the review. Disagreements between the two reviewers are resolved by discussion or consultation with the third reviewer.

Data Extraction and management: Two review authors should independently extract data from the included studies on a predesigned and pretested data extraction sheet. Authors of the original studies may be contacted in case of incomplete information in the published article included in the review. The data to be extracted include general information (study ID, date of extraction, title, authors, and source of study if not published); study characteristics (study design, participants and inclusion/exclusion criteria used in the study); details of interventions (Including doses, treatment duration, comparison details, and duration of follow up).

Assessment of Risk of Bias in included studies: 'Risk of bias assessment tool and criteria are described in the *Cochrane Handbook for Systematic Reviews of Interventions* and are used to assess risk of bias for included studies. Two review authors should independently assess risk of bias in the included studies by assessing randomisation sequence generation; allocation

concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.

Measures of Treatment effect: Methods of statistical analyses are detailed under this sub-heading. The Cochrane Handbook provides a detailed description of the analytical methods to be used for dichotomous viz. risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals (CIs). For continuous outcomes, measures of effect as weighted mean differences (MDs) with 95% CIs and standardised mean difference (SMD) should be reported.

Unit of analysis issues: Analyses should consider the level at which randomisation was done -individual or cluster. In the event that cluster-randomised studies are going to be included appropriate adjustment for clustering would be required (multiply the standard error derived from the confidence interval of the effect estimate by the square root of the design effect). The generic inverse variance method in Review Manager 5.3 software can perform Meta-Analysis using inflated variances.

Dealing with missing data: Authors of original trials included in the review should be contacted in case of incomplete/missing data

Assessment of heterogeneity: Statistical heterogeneity can be assessed via visual inspection of forest plots of included trials, using the χ^2 test and the I^2 statistic. Trial characteristics (participants, design, interventions, outcomes, and risk of bias) are examined to identify the source of any observed heterogeneity. There are cut-offs recommended by Cochrane review groups for results of the I^2 test: < 25% none, 25% to 49% low, 50% to 74% moderate, and 75%+ high heterogeneity[12].

Assessment of reporting biases: Reporting biases are assessed by trying to identify whether the study was included in a trial registry, whether a protocol was published, and whether the methods section provides a list of outcomes. The reported outcomes can be compared with what has been mentioned in the trial protocol by the trial authors versus the outcomes reported in the published article.

Data Synthesis: In this section the systematic reviewers describe the statistical methods of combining data from included studies in a Meta-Analysis if possible. However, the studies should be similar, to be combined in the Meta-Analysis. Statistical guidelines are available in the *Cochrane Handbook for Systematic Reviews of Interventions*[9]. The Rev-Man software[13], free to download can be used for conducting the analyses. A fixed-effect

or a random-effects model may be chosen as appropriate. In case of high heterogeneity Meta-Analysis is not recommended, only a narrative summary of trial findings may be provided.

Risk of bias: Each individual study included in a systematic review should be assessed for key sources of bias. Selection bias could occur due to systematic differences in baseline characteristics between the groups compared in a study, or in randomized trials, from an inadequate generation of a random allocation sequence or inadequate concealment of allocations before group assignment. Other biases such as detection bias, performance bias, attrition bias and outcome reporting bias can also occur. It is important that review authors report the methods used to assess the risk of bias in individual studies, as well as the findings of the assessment. The Cochrane Collaboration's tool for assessing the risk of bias in a systematic review, each study is graded as low (-), high (+) or unclear (?) across different types of bias using a domain-based qualitative description of critical areas of potential bias in clinical trials. For meta-analyses, authors can conduct sensitivity analyses that exclude trials at high risk of bias to determine the effect on the results.

Quality of evidence: GRADE approach, as outlined in the *GRADE Handbook*, is used to assess the quality of evidence for the clinically relevant outcomes[14]. Two review authors independently assess the quality of evidence for each outcome. Evidence from RCTs is initially considered high but may be downgraded one level for serious (or two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. A software 'GRADE pro GDT' is used to create a 'Summary of findings' table to report the quality of the evidence. The GRADE approach yields an assessment of the quality of a body of evidence according to one of four grades. 1. **High**: We are very confident that the true effect lies close to that of the estimate of the effect. 2. **Moderate**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. 3. **Low**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. 4. **Very low**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity: Sub-group analyses are conducted to explore the reason for heterogeneity detected. Review authors should a priori determine and describe the possible sub-groups in their review under the comparisons envisaged.

Sensitivity analysis: Sensitivity analyses are conducted to assess the impact of high risk of bias on the outcome of meta-analyses by adding studies with high risk of bias to pooled studies with low risk of bias. Similarly, other assumptions can also be changed to see their changing effect on the overall estimate.

References: A list of references of studies included, excluded in the review and additional references used in the background section should be provided. The study ID usually comprises of the Surname of the author and the year of publication.

Acknowledgement: Authors may list the names of people who have helped them in the process of conducting the systematic review but who do not qualify as authors.

Appendices: The detailed search strategy is usually included in this section

Contribution of Authors: The contribution of each review author should be mentioned in this section.

Declaration of interest: Any conflicts of interests should be stated in this section

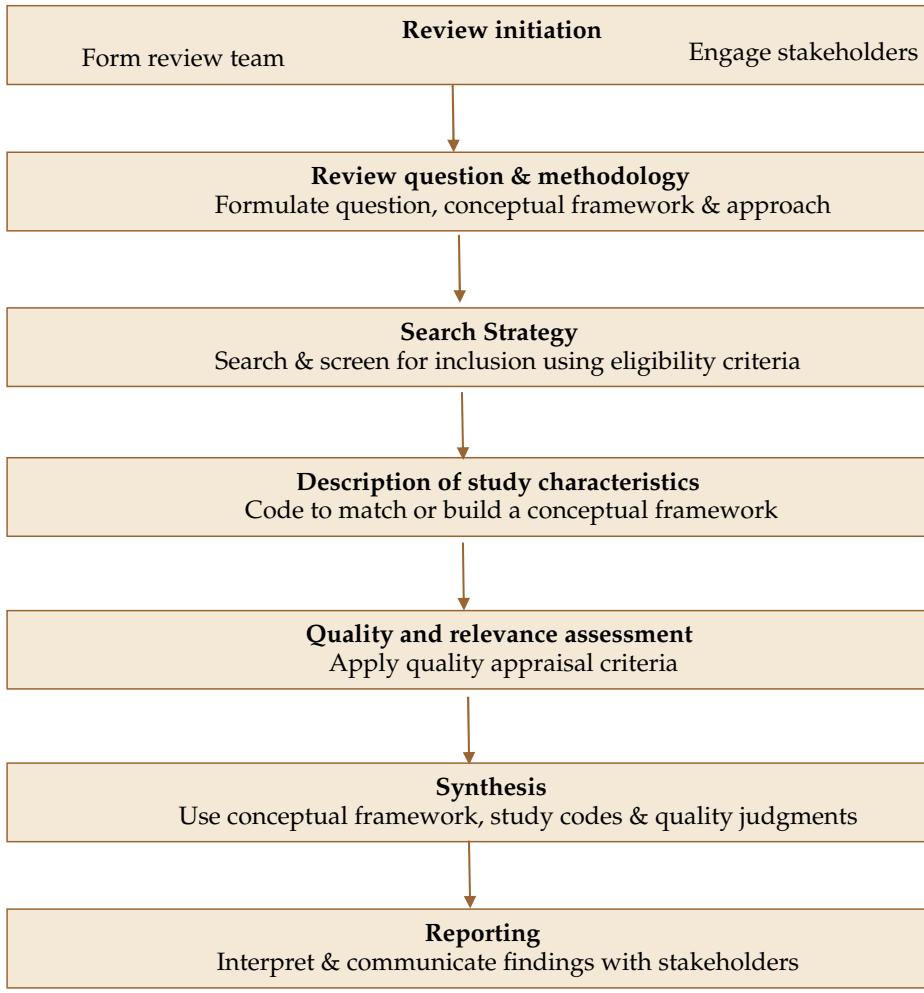
Sources of Support: If the authors have received funding to conduct the systematic review, they should mention it here. If not, they should acknowledge the internal support of their respective organizations.

Example of a Systematic Review Protocol: Sinha A, Pradhan A, Thumburu KK, Gupta N. Probiotics for the prevention or treatment of hyperbilirubinemia in late preterm and term neonates. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD012781. DOI: 10.1002/14651858.CD012781

3. Steps in a systematic review

A systematic review is based on a clearly formulated question, identifies relevant studies, appraises the quality and summarizes the evidence by an explicit methodology. Figure 2 shows the common stages in a systematic review.

Figure 2: Common stages of a systematic review



(Adapted from Gough, Oliver and Thomas, 2012[15])

3.1 Structure an answerable and focussed review question

Formulating a research question is the most critical and difficult part of any research design. The review question underpins all the aspects of the review methodology and every single step of the review is determined by the focussed review question. A review question defines the nature and scope of the review, identifies the keywords, determines the search strategy, provides guidance for selecting the primary research papers and guides the data extraction and synthesis of results. When formulating a review question, it is important to ensure that the question asked is an open question and not a statement. For example, rather than saying that "antiseptic washes prevent nosocomial infections in patients undergoing surgery "it would be better to ask "Are antiseptic washes more effective than non-antiseptic washes at preventing nosocomial infections in patients undergoing surgery?". Table 4 lists some review questions that guide in identifying primary research papers for a systematic review.

Table 4: Types of review questions

Type	Description	Example
Treatment or therapy	Which treatment is more effective? Does it do better than harm?	Is hydrocolloid occlusive dressing better than conventional gauze dressing in the healing of chronic wounds?
Prevention	How to reduce the risk of disease?	Does increasing physical activity reduce the risk of developing diabetes?
Diagnosis	How to select and interpret diagnostic tests?	Is MRI scan more effective than X ray in identifying hairline fractures?
Prognosis	How to anticipate the likely course of the disease?	Are babies who are bottle fed more likely to be obese in adulthood compared to babies who are breast fed?
Causation	What are the risk factors for developing a certain condition?	Does exposure to smoking in mothers who smoke during pregnancy increase risk of foetal death?

Once a tentative review question is formed it is essential to structure it into a well framed structured question that includes three or four elements. A structured question includes the population, the intervention, the comparative intervention and the outcomes that are measured. The acronym for this is PICO which stands for Population, Intervention, Comparator, and

Outcome. Depending on the type of study design there are variants of the acronym for eg. PEO for patient exposure and outcome, PICOC Population, Intervention, Comparator/s, Outcomes, Context etc. Depending on the study design, the components of the review question are accordingly identified. Table 5 provides a list of review questions and the corresponding components of the research question.

Table 5- The PICO process

Question type	**Patient problem**	**Intervention or exposure**	**Comparison**	**Outcome measures**
Treatment (Therapy)	The patient's disease or condition	A therapeutic measure for eg. surgical intervention or life style change	Standard of care, another intervention or placebo	Mortality rate, work days lost, pain, disability
Prevention	The patients risk factors and general health condition	A preventive measure, drug or life style change	May not be applicable	Disease incidence, mortality rate, work days lost
Diagnosis	Target disease or condition	A diagnostic test or procedure	Current reference standard or gold standard test for the problem	Measure of test utility, sensitivity, specificity, odds ratio
Prognosis (Natural History)	The main prognostic factor or clinical problem in terms of its severity and duration	Time or watchful waiting	Usually not applicable. Sometimes the standard treatment	Survival rates, mortality rates, rates of disease progression
Etiology or harm (Causation)	Risk factors, current health problems, general health condition	The intervention or the exposure of interest including some indication of strength(dose) of the risk factor and the duration of the exposure	May not be applicable	Disease incidence, rates of disease progression, mortality rates

The templates below and the figure 3 shows how to build research questions in different scenario and how the components are related

THERAPY

In_____, what is the effect of _____on _____ compared with _____?

PREVENTION

For _____ does the use of _____ reduce the future risk of _____ compared with _____?

DIAGNOSIS OR DIAGNOSTIC TEST

Are (Is) _____ more accurate in diagnosing _____ compared with _____?

PROGNOSIS

Does _____ influence _____ in patients who have _____?

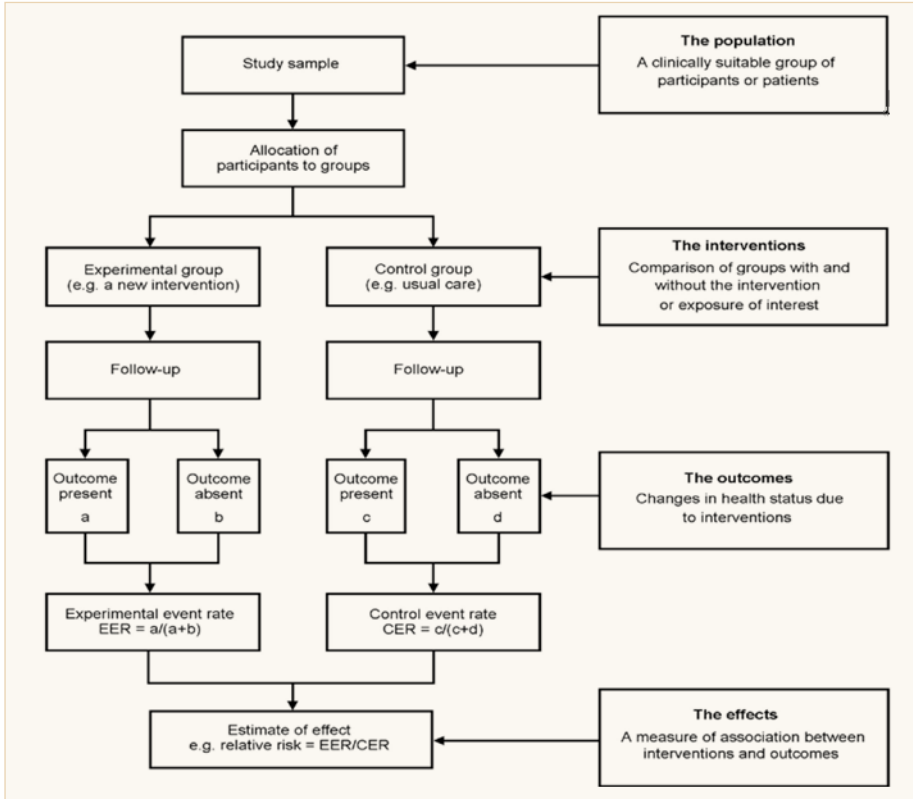
ETIOLOGY

Are _____ who have _____ at _____ risk for/of _____ compared with _____ with/ without_____?

EXPERIENTIAL

How do _____ diagnosed with _____ perceive _____?

Figure 3: Structured questions for systematic reviews and relation between question components in a comparative study



(Adapted from Khan, Kunz, Kleijnen, & Antes, 2003[16])

Ideally once the research question is stated with the four or five relevant elements, the objectives and the title of the systematic review become clear. The template in Box 1 provides examples on how to state the problem statement, create the review question, and set the objectives and finally form a title for the review.

Box 1-Quantitative review of domestic violence an example

Problem statement: Little is known on the effectiveness of advocacy programmes as compared to other treatments on women's quality of life among those who have experienced domestic violence

Review question: For women who have experienced domestic violence, how effective are advocacy programmes compared to other treatments on improving the quality of life

Aim: The aim of this study is to evaluate the effectiveness of advocacy programmes as compared to other treatments on improving the quality of life of those women who have experienced domestic violence

Objectives:

* Search papers on effectiveness of advocacy programmes and other treatments
* Collect data on the effectiveness of advocacy programmes and other treatments
* Compare the primary studies on the different treatments
* Compare the findings of this review with other reviews
* Provide guidelines for helping women who have experienced domestic violence

Title: A systematic review on the effectiveness of advocacy programmes as compared to other treatments on improving the quality of life of those women who have experienced domestic violence.

3.2 Types of systematic reviews

Although systematic reviews are predominantly conducted to assess the effectiveness of health interventions, researchers and health professionals are also concerned with other questions that need different approaches. Forcibly pushing the question into the PICO format (population, intervention, comparator and outcome), even though the question may be on diagnostic test accuracy or prognosis can confound the remainder of the review process. Based on the type of question addressed, about 13 types of reviews have been identified by Zachary et al[17]. Table 6 provides the list of different review types.

3.2.1 Effectiveness reviews

Effectiveness is the extent to which an intervention has an effect. The PICO approach is recommended here to define the population (e.g. demographic and socioeconomic, factors and setting), intervention (e.g. variations in dosage/intensity, delivery mode, and frequency/duration/ timing of delivery), comparator (active or passive) and outcomes (primary and secondary) including benefits and harms.

3.2.2 Experiential (qualitative) reviews

Experiential reviews are qualitative in nature that focusses on the perspective of the individuals' experience, analysing human experiences and cultural, social phenomena. They can be important in exploring and explaining why

interventions are or are not effective from a person-centred perspective. With qualitative evidence, there is no outcome or comparator to be considered. PICO is recommended for question development with P and I defined as patient and experience eg. response to pain. Context may be geographic location, specific racial or gender or setting such as acute care or primary healthcare or community.

3.2.3 Costs/economic evaluation reviews

Costs/Economics reviews assess the costs of a certain intervention, process, or procedure. Health economic evaluations are useful to inform health policy. The PICO approach best fits here with the population, intervention and comparator that include the nature of services/care delivered, time period of delivery, dosage/intensity, co-interventions. Context can also be considered in these types of questions e.g. health setting(s).

3.2.4 Prevalence and/or incidence reviews

Prevalence or incidence reviews measure disease burden. These types of reviews inform health care planning and allocation of resources, delivery of health services and evaluate changes and trends in diseases over time. The CoCoPop framework can be used for such reviews. The health condition, disease, symptom, and its measurement, diagnosis needs to be identified. Environmental factors define the context or specific setting relevant to the review question

3.2.5 Diagnostic test accuracy reviews

Systematic reviews assessing diagnostic test accuracy are important for clinicians and other healthcare practitioners to determine the accuracy of the diagnostic tests to identify the presence or absence of a condition for treatment plan in a patient. For these review questions, PIRD is recommended where the population consists of all participants who will undergo the diagnostic test. It could be a comparison of this test with the gold standard, for the diagnosis of the intended condition viz disease, disability or injury.

3.2.6 Aetiology and/or risk reviews

Systematic reviews of aetiology and risk are important for making health policy decisions and prevention of adverse health outcomes. These reviews determine whether and to what degree a relationship exists between an exposure and a health outcome. PEO is recommended for these types of review questions. The risk factor associated with the condition, the dose and nature of the exposure, the duration of exposure, disease, symptom or

health condition, the population at risk, the context/location, are relevant in such reviews. The outcomes of interest include the health policy issues.

3.2.7 Expert opinion/policy reviews

Expert opinion and policy analysis systematic reviews focus on the synthesis of narrative text and/or policy to either complement empirical evidence or, in the absence of research studies, stand alone as the best available evidence. In the absence of research studies, the best available evidence can be drawn from text and opinion to guide researchers and policy makers. PICo can be used where reviewers need to describe the characteristics of the population, such as age, gender, level of education or professional qualification, interventions may be areas of practice management. The use of a comparator and outcome is not required.

3.2.8 Psychometric reviews

Psychometric systematic reviews are conducted to assess the quality in terms of its validity, reliability, responsiveness etc of health measurement instruments for a specific construct. The construct, name of the outcome measurement, the target population, the type of measurement instrument of interest (e.g. questionnaires, imaging tests) and the measurement properties on which the review investigates, needs to be clearly specified.

3.2.9 Prognostic reviews

Prognostic research provides information on the course of a disease and potential outcomes. These reviews should identify the relationship between specific prognostic factors and an outcome and/or prognostic/prediction models and prognostic tests.

3.2.10 Methodology systematic reviews

Methodology Systematic reviews are performed to examine any methodological issues relating to the design, conduct and review of research studies and also evidence syntheses. The types of studies (RCTs and quasi-RCTs), the comparisons of interest and the primary and secondary outcome measures should be identified.

3.2.11 Implementation reviews

Systematic reviews of implementation research studies are performed to study the strategies used to integrate evidence based practices to real world settings.

3.2.12 Predictors reviews

Reviews of studies to identify predictors of poor clinical outcomes, improvement in health and social outcomes, quality of life, behavioural changes etc. are conducted by synthesising evidence from observational studies

3.2.13 Barriers and facilitators reviews

Reviews that synthesize research on barriers to and facilitators of the various health outcomes. It provides an overview of factors related to uptake and implementation of a health intervention and health promoting behaviours. These reviews help the policy makers in making efforts to overcome the barriers and promote facilitating factors.

Table 6: Types of reviews

Aim	Question Format	Type of review	Example
To evaluate the effectiveness of a certain treatment/ practice in terms of its impact on outcomes	Population, Intervention, Comparators, Outcomes (PICO)	Effectiveness	What is the effectiveness of exercise for treating diabetes compared to no treatment or comparison treatment?
To investigate the experience or meaningfulness of a particular phenomenon	Population, Phenomena of Interest, Context (PICo)	Experiential (Qualitative)	What is experience of children with epilepsy?
To determine the costs associated with a particular approach/ treatment strategy, particularly in terms of cost-effectiveness or benefit	Population, Intervention, Comparator/s, Outcomes, Context (PICOC)	Costs/ Economic Evaluation	What is the cost-effectiveness of HIV vaccines in low- and middle-income countries?
To determine the prevalence and/or incidence of a certain condition	Condition, Context, Population (Co CoPop)	Prevalence and/or Incidence	What is the prevalence of diabetes in India?

Aim	Question Format	Type of review	Example
To determine how well a diagnostic test works in terms of its sensitivity and specificity for a particular diagnosis	Population, Index Test, Reference Test, Diagnosis of Interest (PIRD)	Diagnostic Test Accuracy	What is the diagnostic test accuracy of nutritional tools (such as the Malnutrition Screening Tool) compared to the Patient Generated Subjective Global Assessment amongst patients with colorectal cancer to identify undernutrition?
To determine the association between particular exposures/risk factors and outcomes	Population, Exposure, Outcome (PEO)	Etiology and/ or Risk	Are adults exposed to arsenic at risk of lung cancer?
To review and synthesize current expert opinion, text or policy on a certain phenomenon	Population, intervention or Phenomena of Interest, Context (PICO)	Expert opinion/ policy	What are the national policies to reduce maternal mortality?
To evaluate the psychometric properties of a certain test, normally to determine how the reliability and validity of a particular test or assessment	Construct of interest or the name of the measurement (s), Population, Type of measurement, instrument, Measurement properties (CoPoTIM)	Psychometric	What is the reliability, validity, responsiveness and interpretability of methods (manual muscle testing, isokinetic dynamometry, hand held dynamometry) to assess muscle strength in adults?

Aim	Question Format	Type of review	Example
To determine the overall prognosis for a condition, the link between specific prognostic factors and an outcome and/or prognostic/prediction models and prognostic tests	Population, Prognostic Factors (or models of interest), Outcome (PFO)	Prognostic	In adults with low back pain, what is the association between individual recovery expectations and disability outcomes?
To examine and investigate current research methods and potentially their impact on research quality	Types of studies, Types of Data, Types of Methods, Outcomes (SDMO)	Methodology	Organizational ethics research: A systematic review of methods and analytical techniques
To evaluate the factors that are associated with successful/failure of implementation programs /projects/ interventions	SCOOPS (setting, condition/ circumstance, output, outcome, process, strategy)	Implementa-tion	Systematic review on implementation of mobile health (mHealth) projects in Africa: What works? What doesn't work and why?
To identify the factors associated with a certain condition	Condition, Predictor, Population (CoPrePop)	Predictors	What are the childhood predictors of adult obesity?
To identify the factors that are barriers and/or facilitators for access/ uptake of a program	Population, Factors (Barriers/ Facilitators), Intervention (PFaI)	Barriers and facilitators	Barriers and facilitators to health screening in men: A systematic review

3.3 Identify relevant studies through a comprehensive search strategy

The search strategy used in the review ideally should follow established guidelines such as MECIR (Methodological Expectations of Cochrane Intervention Reviews)[18] or MECCIR (Methodological Expectations of

Campbell Collaboration Reviews)[19]. As per the Cochrane Handbook; 'Systematic reviews of interventions require a thorough, objective and reproducible search of a range of sources to identify as many relevant studies as possible. This is a major factor in distinguishing systematic reviews from narrative reviews and helps to minimize bias and therefore assist in achieving reliable estimates of effects.

When a systematic review is conducted, it is important to retrieve all the relevant studies both published and unpublished that may answer the proposed research question. A comprehensive search strategy underlies the quality of search and the quality of findings of the review. A search has to be both sensitive and specific. Sensitive means the search that picks up all the research studies that are potentially relevant and specific means, it selects only those that are directly relevant.

Step 1 Identify the component parts in the review question ie the P, I, C, O.

The previous section discussed in detail on the structure of a review question using these components.

Step 2 Identify any keywords and synonyms

The second step is to identify keywords and synonyms for all component parts of the review question. Keywords describe subject areas, and having a good set of keywords, would minimize the number of irrelevant returns. Keywords can be identified using dictionaries, textbooks, lecture notes and published articles. Synonyms are words which have the same or similar meaning. Authors use different words and phrases to describe subject areas. It is necessary to ensure that all synonyms and keywords are included in the search strategy to avoid missing potentially relevant documents. Box 2 provides an example of key words and the synonyms.

Box 2: List of keywords and synonyms related to a question

Terms that have the same/close meaning	Hypertension vs High blood pressure
Terms that have different spellings or acronyms	Leukemia vs Leukaemia
Complex concepts described inconsistently	Long-term patient-reported satisfaction after contralateral prophylactic mastectomy … vs Surviving breast cancer: women's experiences with their changed bodies
Umbrella terms and specific names	Sexually-transmitted infections Herpes, genital warts, syphilis, gonorrhoea, chlamydia
Keywords and database-specific "subject headings"	Cancer, tumour, tumour, carcinoma Neoplasms (MESH)

Step 3. Construct search strategy string

To retrieve the most relevant search results, a search string needs to be constructed. A search string is a combination of keywords, truncation symbols, and Boolean operators that is entered into the search box of a library database or search engine.

For eg: A systematic review to analyse long-term continence disturbance after lateral internal sphincterotomy for chronic anal fissure was carried out. The PIO component of the research question was

P= Patients with Chronic Anal Fissure

I= Lateral internal sphincterotomy

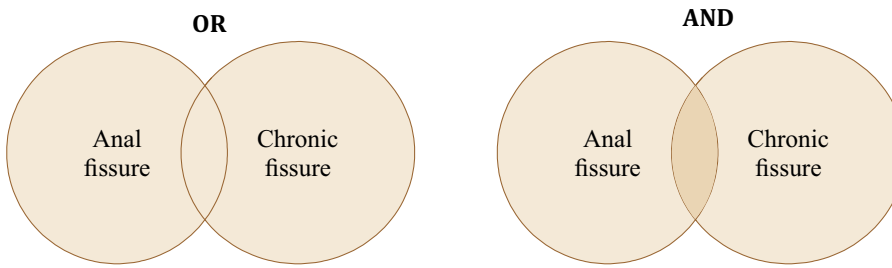
O=Long term continence disturbance

The keywords and the synonyms for the components are as given in Box 3

Box 3: Keywords and synonyms for the systematic review example

PICO element	Alternative terms
Chronic anal fissure(P)	'anal fissure', 'fissure-in-ano', 'chronic fissure',
Lateral internal sphincterotomy(I)	'lateral internal sphincterotomy', 'sphincterotomy', 'fissurectomy', 'advancement flap', 'diltiazem', 'nitro-glycerine' and 'botulinum toxin'
Long term continence disturbance(O)	'incontinence', 'continence disturbance', 'accidental bowel motion', 'urge incontinence', 'liquid incontinence', 'faecal incontinence', 'soilage', 'seepage'

Boolean Operators



For each PICO element we combine all alternative terms with an OR

For e.g. for P the combination would be: #1 anal fissure OR fissure-in-ano OR chronic fissure.

Likewise, we combine the terms for the other two elements, #2 for I and #3 for O.

In the end we use an AND to incorporate results of all PICO elements i.e. #1 AND#2 AND #3.

The truncation wildcard * and? can be used with the terms for a wider search.

3.4 Undertake a comprehensive search

After completing the search strategy string, a comprehensive search should be done using data bases and all other sources of information that are most relevant to the review question. Sources of information could be online data bases, specialist data bases, journal articles, grey literature, subject gateways, conference papers and proceedings, dissertation abstracts, contacting the experts and books.

3.5 Select databases

3.5.1 Published literature- Where to search?

The data bases for searching published literature are varied and depend on the type of review and the context or subject of the systematic review. Box 4 provides a list of sources.

Box 4: Sources of published literature

Name	Note
Core	
Cochrane Library Cochrane Reviews Cochrane Protocol Other reviews Trials	Intervention and diagnostic reviews Critically appraised and re-structured abstracts Register of clinical trials
Medline	Three different versions: PubMed, OVID Medline and EBSCO Medline (Books@ovid, Full text, Medline from 1946, and Epub Ahead of print, In-Process, In-Data review & other Non-Indexed Citations)
Embase	Pharmacological literature, conference abstracts Medical devices(from 1947)
Web of Science	Conference abstracts, citation searching, social sciences Education, Conference Proceedings Citation Index - Science (CPCI-S; 1990 onwards). Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SS&H; 1990 onwards)
Campbell Systematic Reviews	Social sciences

Name	Note
SCOPUS	Conference abstracts, citation searching (from 1996), patents, scientific webpages, Trade Publications, Book series
Clinicaltrials.gov Clinical Trials Registry of India (CTRI) South Asian Database of Controlled Clinical Trials (SADCCT)	Trials registered in US and global Trials registered in India Controlled clinical trials and their sources in India and other South Asian countries
Indexing of Indian Medical Journals (IndMED)	Indexed selected peer reviewed medical journals published from India. It supplements international indexing services like PubMed. It covers about 100 journals indexed from 1985 onwards.
Subject/Study Dependent	
CINAHL	Nursing and allied health
Psychinfo	Psychology & psychiatry
ERIC	Education
TOXLINE	Effects of drugs and chemicals
PedRO	Physiotherapy (randomized controlled trials and systematic reviews only)
PEDE (Pediatric Economic Database Evaluation)	Paediatric economic evaluations inventory of health state utility weights reported in cost-utility analyses
CEA Registry	Cost-utility analyses on a wide variety of diseases and treatments

3.5.2 Grey literature- Where to search?

Grey literature are materials and research produced by organizations outside of the traditional commercial or academic publishing and distribution channels. These publication types include reports, working papers, government documents, white papers and evaluations. Grey literature covers published material not indexed in databases such as Medline, Embase etc, which index principally journal literature. These include technical reports, official publications, conference papers, dissertations, patents, research in progress, usually produced by academic, government and professional organisations. It is important to search grey literature sources in order to

minimise bias in your search results. Box 5 provides a list of sources of grey literature.

Box 5: Sources of grey literature

Name	Note
Google Scholar	Initial background searches Include along with PubMed
Open Grey (www.opengrey.eu)	System for information on grey literature in Europe
Social Science Research Network (http://ssrn.com/)	Specialised research networks (economics, business & management) in each of the social sciences. Includes abstracts database of forthcoming papers and working papers as well as Electronic Paper Collection of full text documents.
ProQuest	Masters, MPhil and PhD theses database of international universities
Shodhganga	Reservoir of theses from Indian universities

3.6 Tailor search strategy to database(s)

Different databases will need different search fields for conducting a search:

e.g. **PubMed**:
Search the Text Word field for free-text terms and MeSH Terms for controlled vocabulary terms.
e.g. sunshine[tw], sunlight[tw], Sunbathing[mh], Suntan[mh]

e.g. **Embase**:
Search the Title and Abstract field *:ti, ab* for free-text terms and
Emtree terms 'term'/exp for controlled vocabulary terms.
e.g. sunshine:ti,ab, sunlight:ti,ab, 'sun exposure'/exp, 'sunlight'/exp

Syntax for PubMed (From Cochrane Handbook, 6.4.11.1)

#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 randomized [tiab]
#4 placebo [tiab]
#5 drug therapy [sh]
#6 randomly [tiab]
#7 trial [tiab]
#8 groups [tiab]

#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 animals [mh] NOT humans [mh]
#11 #9 NOT #10

3.7 Save search and export results

It is vital that the search strategy is transparent and repeatable, and hence for each source searched, a record should be made (Table 7). The full list of results from each search and source must be recorded for transparency and can be efficiently managed using reference management software such as Endnote, Zotero etc. Many systematic review software such as Covidence, EPPI Reviewer etc, allow importing the search results from RIS file directly from such reference management software.

3.8 Select studies for inclusion based on pre-defined criteria

The relevant articles are screened using the inclusion criteria at different levels of reading to impose a number of filters of increasing rigor, i.e. first reading of article titles and abstracts to remove spurious hits; and for those passing through this stage an assessment of the full text. In order to manage errors during the screening process, it is a good practice that two reviewers undertake both title/abstract and full-text screening. A kappa analysis can be performed to check for consistency in the interpretation of the selection criteria between the two reviewers. A kappa rating of 'substantial' (0.5 or above) is recommended to pass the assessment. It is important that the selection of each article captured during the search should be recorded as per PRISMA flowchart (see Figure 8).

Table 7: Saving a search strategy and the number of records

	Keywords from Pubmed[20]	**Publication data January 1 1990 to March 1 2015 Number of records**
#1	("calcium hydroxide" OR (medicament OR "intracanal medicament") OR dressing	24834
#2	(irrigation OR irrigating OR irrigated OR irrigant OR irrigate OR(rinse OR rinsing OR rinsed)	55869
#3	((remov*) OR (eliminat*)	565298
#4	(endodontics OR "root canal" OR "dental pulp activity" OR teeth OR tooth)	129733
#5	#1 AND #2 AND #3 AND #4	156

3.9 Description of study characteristics

Once the full text of each article is identified for inclusion in the systematic review, the next step is to extract appropriate and relevant data using a standardized data extraction/coding form. Coding instruments, such as coding sheets and codebook, are designed for specific research[21] synthesis and are based on the types of interventions, outcome variables, and other data. Brown et al[22] categorizes that coded data fall into the following four basic categories: (1) methodological and substantive features, (2) study quality, (3) intervention descriptors, and (4) outcome measures. In order to design an accurate and comprehensive coding scheme, there is a need for a thorough knowledge of the included studies that are to be included in the synthesis. The important variables identified to be coded in every research synthesis, include: (i) Source of the study; (ii) Year of publication; (iii) Type of research design. Once the coding sheet is completed, a codebook has to be developed to guide the coding process, containing each variable that is important, and should be pilot tested.

Many reviewers extract information on study characteristics, methodology, population, interventions and outcomes, with the outcomes varying based on the types of study designs included. For example, if RCTs are included, the outcomes are usually expressed as risk ratios (RR), odds ratio (OR) or difference between means for continuous outcomes; for diagnostic studies, the outcomes extracted are the measures of test performance (e.g. sensitivity and specificity). Box 6 provides good practice guidelines for data extraction from primary studies

Box 6: Good practice for data extraction

Good practice could involve the following steps, which improve transparency, repeatability and objectivity:

- Data extractions should always present the primary data as reported in the primary study; if any corrections or transformations are needed these should be presented additionally so that all data are traceable to the primary study
- Notation of the location of data within each article and means of extraction if data are located within figures.
- Description of any pre-analysis calculations or data transformations (e.g. standard deviation calculation from standard error and sample size and calculation of effect sizes.

- Details of a pre-tested data extraction form.
- Data extraction in a subset of articles by multiple reviewers and checking, for example with a kappa test (for human error/ consistency)
- Inclusion of appendixes of extracted information
- Contact made with authors requesting data where it is missing from relevant articles

Adapted from Collaboration for Environment Evidence, 2013[23]

It is difficult to design a single form that meets a reviewer's requirement. A data extraction form should be comprehensive including all the relevant information needed for reporting and analysing the data. Below is a data extraction form provided by the Cochrane collaboration[22]. This can be used for both RCT and non RCT reviews.

Data collection form

Intervention review – RCTs and non-RCTs

This form can be used as a guide for developing your own data extraction form. Sections can be expanded and added, and irrelevant sections can be removed. It is difficult to design a single form that meets the needs of all reviews, so it is important to consider carefully the information you need to collect, and design your form accordingly. The information included on this form should be comprehensive, and may be used in the text of your review, 'Characteristics of included studies' table, risk of bias assessment, and statistical analysis.

Notes on using a data extraction form:

- Be consistent in the order and style you use to describe the information for each included study.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.
- You will need to protect the document in order to use the form fields (Tools / Protect document)

Review title or ID

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*

Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

Notes:

1. General Information

1. Date form completed *(dd/mm/yyyy)*	
2. Name/ID of person extracting data	
3. Report title (title of paper/ abstract/ report that data are extracted from)	

4. **Report ID** (if there are multiple reports of this study)	
5. **Reference details**	
6. **Report author contact details**	
7. **Publication type** (e.g. full report, abstract, letter)	
8. **Study funding source** (including role of funders)	
Possible conflicts of interest *(for study authors)*	
9. **Notes:**	

2. Eligibility

Study Characteristics	**Review Inclusion Criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	**Yes/ No / Unclear**	**Location in text** *(pg & ¶/ fig/table)*
10. **Type of study**	Randomised trial	...	
	Non-randomised trial	...	
	Controlled before-after study • Contemporaneous data collection • At least 2 intervention and 2 control clusters	...	
	Interrupted time series OR Repeated measures study • At least 3 timepoints before and 3 after the intervention • Clearly defined intervention point	... ...	
	Other design (specify):	...	
11. **Participants**		...	
12. **Types of intervention**		...	

Study Characteristics	**Review Inclusion Criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	**Yes/ No / Unclear**	**Location in text** *(pg & ¶/ fig/table)*
13. **Types of outcome measures**		...	
14. **Decision:**			
15. **Reason for exclusion**			
16. **Notes:**			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & ¶/fig/ table)*
17. **Population description** *(from which study participants are drawn)*		
18. **Setting** *(including location and social context)*		
19. **Inclusion criteria**		
20. **Exclusion criteria**		
21. **Method/s of recruitment of participants**		
22. **Notes:**		

4. Methods

	Descriptions as stated in report/ paper	**Location in text** *(pg & ¶/fig/ table)*
23. **Aim of study**		
24. **Design** *(e.g. parallel, crossover, non-RCT)*		
25. **Unit of allocation** *(by individuals, cluster/ groups or body parts)*		
26. **Start date**		
27. **End date**		
28. **Duration of participation** *(from recruitment to last follow-up)*		
29. **Notes:**		

5. Risk of Bias assessment

See Chapter 8 of the Cochrane Handbook. Additional domains may be required for non-randomised studies.

Domain	**Risk of bias** *Low/ High/ Unclear*	**Support for judgement**	**Location in text** *(pg & ¶/fig/table)*
30. **Random sequence generation** *(selection bias)*	...		
31. **Allocation concealment** *(selection bias)*	...		
32. **Blinding of participants and personnel** *(performance bias)*	...	**Outcome group: All/**	

Domain	**Risk of bias** *Low/ High/ Unclear*	**Support for judgement**	**Location in text** *(pg & ¶/fig/table)*
(if required)	...	**Outcome group:**	
33. **Blinding of outcome assessment** *(detection bias)*	...	**Outcome group: All/**	
(if required)	...	**Outcome group:**	
34. **Incomplete outcome data** *(attrition bias)*	...		
35. **Selective outcome reporting?** *(reporting bias)*	...		
36. **Other bias**	...		
37. **Notes:**			

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	**Location in text** (pg & ¶/fig/ table)
38. **Total no. randomised** *(or total pop. at start of study for NRCTs)*		
39. **Clusters** *(if applicable, no., type, no. people per cluster)*		
40. **Baseline imbalances**		
41. **Withdrawals and exclusions** *(if not provided below by outcome)*		
42. **Age**		

	Description as stated in report/paper	Location in text (pg & ¶/fig/ table)
43. **Sex**		
44. **Race/Ethnicity**		
45. **Severity of illness**		
46. **Co-morbidities**		
47. **Other treatment received** *(additional to study intervention)*		
48. **Other relevant sociodemographics**		
49. **Subgroups measured**		
50. **Subgroups reported**		
51. **Notes:**		

7. Intervention groups

Copy and paste table for each intervention and comparison group

7.1 Intervention Group 1

	Description as stated in report/paper	Location in text *(pg & ¶/fig/ table)*
52. **Group name**		
53. **No. randomised to group** *(specify whether no. people or clusters)*		
54. **Description** *(include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention)*		
55. **Duration of treatment period**		
56. **Timing** *(e.g. frequency, duration of each episode)*		

	Description as stated in report/paper	Location in text *(pg & ¶/fig/ table)*
57. **Delivery** *(e.g. mechanism, medium, intensity, fidelity)*		
58. **Providers** *(e.g. no., profession, training, ethnicity etc. if relevant)*		
59. **Co-interventions**		
60. **Economic variables** *(i.e. intervention cost, changes in other costs as result of intervention)*		
61. **Resource requirements to replicate intervention** *(e.g. staff numbers, cold chain, equipment)*		
62. **Notes:**		

8. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/ paper	Location in text *(pg & ¶/fig/ table)*
63. **Outcome name**		
64. **Time points measured** *(specify whether from start or end of intervention)*		
65. **Time points reported**		
66. **Outcome definition** *(with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious)*		

	Description as stated in report/ paper		Location in text *(pg & ¶/fig/ table)*
67. **Person measuring/ reporting**			
68. **Unit of measurement** *(if relevant)*			
69. **Scales: upper and lower limits** *(indicate whether high or low score is good)*			
70. **Is outcome/tool validated?**	... *Yes/No/Unclear*		
71. **Imputation of missing data** *(e.g. assumptions made for ITT analysis)*			
72. **Assumed risk estimate** *(e.g. baseline or population risk noted in Background)*			
73. **Notes:**			

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

For randomised or non-randomised trial - Dichotomous outcome

	Description as stated in report/paper	Location in text *(pg & ¶/ fig/table)*
74. **Comparison**		
75. **Outcome**		
76. **Subgroup**		

<table>
<tr><th></th><th colspan="4">Description as stated in report/paper</th><th>Location in text
(pg & ¶/ fig/table)</th></tr>
<tr><td>77. Time point
(specify whether from start or end of intervention)</td><td colspan="4"></td><td></td></tr>
<tr><td rowspan="3">78. Results
Note whether:
... post-intervention OR
... change from baseline
And whether
... Adjusted OR
... Unadjusted</td><td colspan="2">Intervention</td><td colspan="2">Comparison</td><td rowspan="3"></td></tr>
<tr><td>No. events</td><td>No. participants</td><td>No. events</td><td>No. participants</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">79. Baseline data</td><td colspan="2">Intervention</td><td colspan="2">Comparison</td><td rowspan="3"></td></tr>
<tr><td>No. events</td><td>No. participants</td><td>No. events</td><td>No. participants</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>80. No. missing participants and reasons</td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>81. No. participants moved from other group and reasons</td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>82. Any other results reported</td><td colspan="3"></td><td></td><td></td></tr>
<tr><td>83. Unit of analysis
(e.g. by individuals, health professional, practice, hospital, community)</td><td colspan="3"></td><td></td><td></td></tr>
</table>

	Description as stated in report/paper		Location in text *(pg & ¶/ fig/table)*
84. **Statistical methods used and appropriateness of these methods** *(e.g. adjustment for correlation)*			
85. **Reanalysis required?** *(if yes, specify why, e.g. correlation adjustment)*	... *Yes/No/Unclear*		
86. **Reanalysis possible?**	... *Yes/No/Unclear*		
87. **Reanalysed results**			
88. **Notes:**			

For randomised or non-randomised trial - Continuous outcome

	Description as stated in report/paper	Location in text *(pg & ¶/ fig/table)*
89. **Comparison**		
90. **Outcome**		
91. **Subgroup**		
92. **Time point** *(specify whether from start or end of intervention)*		
93. **Post-intervention or change from baseline?**		

<table>
<tr><th colspan="2"></th><th colspan="6">Description as stated in report/paper</th><th>Location in text
(pg & ¶/ fig/table)</th></tr>
<tr><td rowspan="3">94. Results
Note whether:
... post-intervention OR
... change from baseline
And whether
... Adjusted OR
... Unadjusted</td><td colspan="3">Intervention</td><td colspan="3">Comparison</td><td rowspan="3"></td></tr>
<tr><td>Mean</td><td>SD (or other variance)</td><td>No. participants</td><td>Mean</td><td>SD (or other variance)</td><td>No. participants</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">95. Baseline data</td><td colspan="3">Intervention</td><td colspan="3">Comparison</td><td rowspan="3"></td></tr>
<tr><td>Mean</td><td>SD (or another variance)</td><td>No. participants</td><td>Mean</td><td>SD (or other variance)</td><td>No. participants</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="2">96. No. missing participants and reasons</td><td colspan="4"></td><td></td></tr>
<tr><td colspan="2">97. No. participants moved from other group and reasons</td><td colspan="4"></td><td></td></tr>
<tr><td colspan="2">98. Any other results reported</td><td colspan="4"></td><td></td></tr>
<tr><td colspan="2">99. Unit of analysis
(e.g. by individuals, health professional, practice, hospital, community)</td><td colspan="4"></td><td></td></tr>
<tr><td colspan="2">100. Statistical methods used and appropriateness of these methods
(e.g. adjustment for correlation)</td><td colspan="4"></td><td></td></tr>
<tr><td colspan="2">101. Reanalysis required?
(if yes, specify why)</td><td>...
Yes/No/ Unclear</td><td colspan="3"></td><td></td></tr>
</table>

	Description as stated in report/paper		Location in text *(pg & ¶/ fig/table)*
102. **Reanalysis possible?**	... *Yes/No/ Unclear*		
103. **Reanalysed results**			
104. **Notes:**			

For randomised or non-randomised trial - Another outcome

	Description as stated in report/paper				Location in text *(pg & ¶/fig/ table)*
105. **Comparison**					
106. **Outcome**					
107. **Subgroup**					
108. **Time point** *(specify whether from start or end of intervention)*					
109. **Type of outcome**					
110. **Results**	Inter-vention result	SD (or other variance)	Control result	SD (or other vari-ance)	
	Overall results		SE (or other variance)		
111. **No. participant**	Intervention		Control		

	Description as stated in report/paper		Location in text *(pg & ¶/fig/ table)*
112. **No. missing participants and reasons**			
113. **No. participants moved from other group and reasons**			
114. **Any other results reported**			
115. **Unit of analysis** *(e.g. by individuals, health professional, practice, hospital, community)*			
116. **Statistical methods used and appropriateness of these methods**			
117. **Reanalysis required?** *(if yes, specify why)*	...		
118. **Reanalysis possible?**	...		
119. **Unit of analysis** *(e.g. by individuals, health professional, practice, hospital, community)*			
120. **Notes**			

For controlled before-after study

<table>
<tr><th></th><th colspan="4">Description as stated in report/paper</th><th>Location in text
(pg & ¶/fig/table)</th></tr>
<tr><td>121. Comparison</td><td colspan="4"></td><td></td></tr>
<tr><td>122. Outcome</td><td colspan="4"></td><td></td></tr>
<tr><td>123. Subgroup</td><td colspan="4"></td><td></td></tr>
<tr><td>124. Timepoint
(specify whether from start or end of intervention)</td><td colspan="4"></td><td></td></tr>
<tr><td>5. Post-intervention or change from baseline?</td><td colspan="4"></td><td></td></tr>
<tr><td rowspan="4">126. Results</td><td>Intervention result</td><td>SD (or other variance)</td><td>Control result</td><td>SD (or other variance)</td><td rowspan="4"></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="2">Overall results</td><td colspan="2">SE (or other variance)</td></tr>
<tr><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td rowspan="2">127. No. participants</td><td colspan="2">Intervention</td><td colspan="2">Control</td><td rowspan="2"></td></tr>
<tr><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>128. No. missing participants and reasons</td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>129. No. participants moved from other group and reasons</td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>130. Any other results reported</td><td colspan="4"></td><td></td></tr>
</table>

	Description as stated in report/paper		Location in text *(pg & ¶/fig/ table)*
131. **Unit of analysis** *(individuals, cluster/ groups or body parts)*			
132. **Statistical methods used and appropriateness of these methods**			
133. **Reanalysis required?** *(specify)*	... *Yes/No/ Unclear*		
134. **Reanalysis possible?**	... *Yes/No/ Unclear*		
135. **Reanalysed results**			
136. **Notes:**			

For interrupted time series or repeated measures study

	Description as stated in report/ paper	Location in text *(pg & ¶/fig/ table)*
137. **Comparison**		
138. **Outcome**		
139. **Subgroup**		
140. **Length of timepoints measured** *(e.g. days, months)*		
Total period measured		

	Description as stated in report/ paper		Location in text *(pg & ¶/fig/ table)*
141. **No. participants measured**			
142. **No. missing participants and reasons**			
143. **No. timepoints measured**	8. **Pre-intervention**	9. **Post-intervention**	
144. **Mean value** *(with variance measure)*			
145. **Difference in means (post – pre)**			
146. **Percent relative change**			
147. **Result reported by authors** *(with variance measure)*			
148. **Unit of analysis** *(individuals or cluster/ groups)*			
149. **Statistical methods used and appropriateness of these methods**			
150. **Reanalysis required?** *(specify)*	... *Yes/No/ Unclear*		
151. **Reanalysis possible?**	... *Yes/No/ Unclear*		
152. **Individual timepoint results**			

	Description as stated in report/ paper				Location in text *(pg & ¶/fig/ table)*
153. **Read from figure?**	... *Yes/No/ Unclear*				
154. **Reanalysed results**	**Change in level**	**SE**	**Change in slope**	**SE**	
155. **Notes:**					

10. Applicability

156. **Have important populations been excluded from the study?** *(consider disadvantaged populations, and possible differences in the intervention effect)*	... *Yes/No/Unclear*	
157. **Is the intervention likely to be aimed at disadvantaged groups?** *(e.g. lower socioeconomic groups)*	... *Yes/No/Unclear*	
158. **Does the study directly address the review question?** *(any issues of partial or indirect applicability)*	... *Yes/No/Unclear*	
159. **Notes:**		

11. Other information

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
160. **Key conclusions of study authors**		
161. **References to other relevant studies**		
162. **Correspondence required for further study information** *(what and from whom)*		
163. **Further study information requested** *(from whom, what and when)*		
164. **Correspondence received** *(from whom, what and when)*		
165. **Notes:**		

3.10 Quality assessment using critical appraisal tools

The indicators for quality assessment of the included studies should be considered and can be integrated into the study coding form. Critical appraisal assesses quality and relevance of the research and is defined as 'the process of carefully and systematically examining research to judge its trustworthiness and relevance in a particular context[25]. Critical appraisal is a complex process and is guided by the research question, and associated review method. It is vital that the assessment process be standardized and transparent as possible (see Box 7).

Box7-Description of critical appraisal process

A critical appraisal was conducted for the observational studies included in the Meta-Analysis, using the Critical Appraisal Skills Programme (UK) checklist, assessing the validity of the results from each study on a scale of high, medium, and satisfactory: high quality, the study was prospective and scored well on main quality parameters such as study method, result validity, precision of outcomes, and generalizability; medium quality, study method was sound and results were presented with precision; satisfactory quality, the study did not score well or did not contain any information on the main quality parameters such as study method, result validity, precision of outcomes, or generalizability.

Adapted from Zhou, Shukla, John, & Chen (2015)[26]

A generic assessment looks at the quality of the execution of the study, however may not necessarily consider whether the study is a good fit for answering the review question[15]. Review-specific judgements assess the appropriateness of the study design and analysis for answering the research question or how well matched the study is to the focus of the review in terms of its topic. Depending on the type of review undertaken, reviews may consider both of these assessments or only one.

The precise order in which critical appraisal and data extraction are undertaken varies from one systematic review to another depending on the type of systematic review. Mostly, there is an iterative relationship between the two, and there is no set guideline as to which should come first, however in interventional systematic reviews, risk of bias is assessed before data extraction for quantitative synthesis in Meta-Analysis

There are various checklists of critical appraisal tools that one can use. However, the selection of the checklist should be explained (such as use for RCT or non-RCT study designs) or adapt them to their own review with the decisions stated and justified. Similar to the screening process, it is advisable that two reviewers independently conduct the critical appraisal of the selected studies and group the studies into high, medium and low quality.

Table 8 - Critical appraisal of cohort studies example

		Quantitative		Qualitative	Mixed Method		
		Liu (2013)	Ranson (2001)	Basaza (2010)	Alatinga (2011)	Ozawa (2009)	Sinha (2006)
1.	Is the research aim clearly stated? (Yes/ No)	1	1	1	1	1	1

		Quantitative		Qualitative	Mixed Method		
		Liu (2013)	Ranson (2001)	Basaza (2010)	Alatinga (2011)	Ozawa (2009)	Sinha (2006)
2.	Description of the context? (Yes/No)	1	1	1	1	1	1
3.	Description of the sampling procedures? (Yes/No)	1	1	1	1	1	1
4.	Are sample characteristics sufficiently reported? (sample size, location, and at least one additional characteristic?) (Yes/No)	1	1	1	1	1	1
5.	Is it clear how the data were collected (e.g. for interviews), is there an indication of how interviews were conducted? (Yes/No)	1	1	1	1	1	1
6.	Methods of recording of data reported? (Yes/No)	1	1	1	1	1	0
7.	Methods of analysis explicitly stated? (Yes/No)	1	1	1	1	1	1
8.	Did the study address a clearly focussed issue? (Yes/No)	0	1	1	1	1	1
9.	Was the cohort recruited in an acceptable way? (Yes/No)	0	1	1	1	1	1

		Quantitative		Qualitative	Mixed Method		
		Liu (2013)	Ranson (2001)	Basaza (2010)	Alatinga (2011)	Ozawa (2009)	Sinha (2006)
10.	Was the exposure accurately measured to minimise bias? (Yes/No)	1	1	1	1	1	0
11.	Was the outcome accurately measured to minimise bias? (Yes/No)	1	1	1	1	1	0
12.	Have the authors identified all important confounding factors? (Yes/No)	1	1	1	1	1	1
13.	Have they taken account of the confounding factors in the design and/or analysis? (Yes/No)	1	1	1	1	1	1
14.	Was the follow up of subjects complete enough? (Yes/No)	1	1	1	1	1	1
15.	Was the follow up of subjects long enough? (Yes/No)	1	1	1	1	1	1

(Adapted from Panda, Dror, Koehlmoos, et al., 2013)[27]

3.11 Quality of evidence

GRADE (Grading of Recommendations, Assessment, Development and Evaluations) is a transparent framework for developing and presenting summaries of evidence. It is the most widely adopted tool for grading the quality of evidence and for making clinical/public health recommendations.

With regards to the systematic review question, the quality of evidence for each study outcome is rated using GRADE quality rating. GRADE has four levels of evidence- also known as certainty in evidence or quality of evidence: very low, low, moderate, and high (Table 9). Evidence from randomised controlled trials starts at a high quality and evidence from observational data starts at low quality due to the residual confounding.

The certainty in evidence is increased or decreased for reasons as described below.

Table 9: GRADE certainty ratings

Certainty	*What it means*
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated Effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is Similar to the estimated effect

For each risk of bias, imprecision, inconsistency, indirectness, and publication bias, authors have the option of decreasing their level of certainty by one or two levels (e.g. from high to moderate), using a 'Summary of findings' table.

Standard Cochrane 'Summary of findings' tables includes the following elements using one of the accepted formats. Further guidance on each of these are available on Cochrane Training website.

1. A brief description of the comparison addressed in the 'Summary of findings' table, including both the experimental and comparison interventions.
2. A list of the most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes.
3. A measure of the typical burden of each outcomes (e.g. illustrative risk, or illustrative mean, on comparator intervention).
4. The absolute and relative magnitude of effect are measured for each (if both are appropriate).

5. The numbers of participants and studies contributing to the analysis of each outcomes.
6. A GRADE assessment of the overall certainty of the body of evidence for each outcome (which may vary by outcome).
7. Space for comments.
8. Explanations (formerly known as footnotes).

'Summary of findings' tables are supported by detailed tables, known as 'evidence profiles', that provide greater detail than the tables of both of the individual considerations feeding into the grading of certainty and of the results of the studies. An example of a 'Summary of findings' table is provided in table 10.

Table 10: Summary of findings

Ciclopirox 8% lacquer compared to Vehicle for fungal infections of the toenails[28]

Patient or population: people with fungal infections of the toenails
Intervention: Ciclopirox 8% lacquer
Comparison: Vehicle
Setting: Outpatient clinics

Outcomes	Anticipated absolute effects* (95%CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Vehicle	Risk with Ciclopirox 8% lacquer				
Complete cure: 48 weeks	Study population 4 per 1000 41 per 1000 (8 to 219)		RR 9.29 (1.72 to 50.14)	460 (2 RCTs)	⨁⨁⨁⊖ Low	NNTB=3
Adverse events (directly related to treatment, collected over the course of the studies, they are not measured/ reported for specific timepoints)	Study population 70 per 1000 112 per 1000 (62 to 204)		RR 1.61 (0.89 to 2.92)	460 (2 RCTs)	⨁⨁⨁⊖ Low	The most commonly reported adverse events were application site reactions (transient tingling, burning, or pain with treatment use), rashes (mild

Outcomes	Anticipated absolute effects* (95%CI)		Relative effect (95% CI)	No of partici-pants (stud-ies)	Quality of the evidence (GRADE)	Comments
	Risk with Vehicle	Risk with Ciclopirox 8% lac-quer				
						erythema in the skin surrounding the nail), and alterations in nail colour or shape. These adverse reactions did not require additional treatment.
Mycologi-cal cure: 48 weeks	Study population 96 per 1000 303 per 1000 (185 to 492)		RR 3.15 (1.93 to 5.12)	460 (2 RCTs)	⊕⊕⊕⊖ Moderate[b]	NNTB = 2
Clinical cure- not measured	-	-	-	-	-	-

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; NNTB: Number needed to treat for an additional beneficial outcome

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantiallydifferent

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded by two levels to low-quality evidence: one level due to imprecision as there are very large and variable confidence intervals across both studies, with low event rates (fewer than 100). Also downgraded by one level due to risk of bias, as most information is from studies at unclear risk of bias.

[b] Downgraded by two levels to low-quality evidence: one level due to imprecision since the 95% CI includes both a meaningful increase in risk, and no increase in risk, and one level due to risk of bias, as most information is from studies at unclear risk of bias.

Adapted from: Topical and device-based treatments for fungal infections of the toenails[28].

4. Meta-Analysis

Meta-Analysis is a process of using quantitative methods to summarize the results from multiple studies, obtained and critically reviewed using a rigorous process (to minimize bias) for identifying, appraising, and synthesizing studies to answer a specific question and draw conclusions about the data gathered. The purpose of this process is to gain a summary statistic (i.e., a measure of a single effect) that represents the effect of the intervention across multiple studies. Gene V Glass coined the term "Meta-Analysis "in 1976. Since then the popularity of Meta-Analysis has increased significantly. The purpose is to increase the power of the evidence generated by combining small studies and improve the precision of the estimates by reducing uncertainty. It is similar to a simple cross-sectional study, in which the subjects are individual studies rather than individual persons.

A systematic review is a meta-analytic review only if it includes a quantitative estimation of the magnitude of the effect and its uncertainty (confidence limits). Collection of studies that examine the same phenomenon or relationships can be combined by using meta-analytical procedures and empirical observations. Thus, Meta-Analysis can be used to combine outcomes of treatment and comparison groups in randomized controlled trials; prevalence rates in cross sectional studies; correlation coefficients in studies of association or pre-post /before-after event rates in before after studies. Meta-Analysis combines effect sizes from different studies to provide an overall estimate while examining and quantifying the variability among study findings and the effect of sampling on primary studies.

The process of conducting a Meta-Analysis is similar to any other empirical study. It includes five steps:

1. Formulating a research question (part of a systematic review)
    - Defining a research question
    - Define Inclusion/Exclusion criteria
    - Locating and selecting studies
2. Data collection and evaluation
    - Data extraction
    - Define effect estimates
    - Tabulation of relevant parameters
3. Data analysis and interpretation
    - Testing homogeneity of studies
    - Investigate sources of heterogeneity
    - Choose appropriate statistical techniques

4. Presentation

Based on the outcome of interest the data from primary studies are extracted from the results section.

4.1 Effect measures

Continuous outcome

For each individual study, we assume two underlying populations representing the experimental versus control groups on a continuous outcome. Let μ_E and μ_C be the experimental and control population means, and σ_E^2 and σ_C^2 be the population variances, respectively. Such a design is applicable in studies that evaluate treatment outcome in behavioural sciences, education, medicine, etc. Under the assumptions of normal distribution and homoscedasticity, the usual parametric effect-size is the standardized mean difference (SMD), which is the difference between the experimental and control population means, μ_E and μ_C, divided by the pooled population standard deviation.

There are two approaches for estimating the SMD, one is the Cohens d method and the other is the Hedges'g method (with a small correction for small sample bias).

Cohen's d:

$$Cohen's\ d = \frac{x_1 - x_2}{s_{pooled}}$$

$$s_{pooled} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}$$

$$SE(d) = \sqrt{\frac{1}{n_1} + \frac{1}{n_2} + \frac{d^2}{2(n_1 + n_2 - 2)}}$$

Hedges' g

c(m)=1-3/(4m-1) with

m=$n_1 + n_2 - 2$

SE (g)= c(m)x SE(d)

d=$c(m)XCohen's\ d$)

Here

n_1=sample size of group 1; n2 =sample size of group 2

$\overline{x_1}$ = mean of group 1

$\overline{x_2}$ = mean of group 2

s1= s.d of group 1

$s2$ = s.d of group 2

Meta-analysts have provided arbitrary cut off points of 0.20, 0.50, and 0.80 to represent a small moderate and large effect. Sometimes SMD can be converted to odds ratios especially if there are studies which report results as continuous measurements and there are others which report the results as a binary outcome. In such cases the SMD can be converted to odds ratio by the formula $OR=\frac{\pi}{\sqrt{3}}SMD$

Correlation

For studies that report correlation between continuous variables, the correlation coefficient *r* itself can serve as the effect size. The standard error of r is approximately

$SE(r) = \frac{(1-r^2)}{\sqrt{n-1}}$ where n is the sample size.

To obtain the 95% confidence interval for the correlation coefficient r, it is first transformed into Z_r where

$$z_r = \frac{ln\frac{(1+r)}{(1-r)}}{2}$$

The log upper and lower bounds of z_r are

$L = z_r - (z_{1-\alpha/2}/\sqrt{n-3})$ $\quad U=z_r + (z_{1-\alpha/2}/\sqrt{n-3})$

The 95% confidence interval is= $[(e^{2L}-1)/(e^{2L}+1), (e^{2U}-1)/(e^{2U}+1)]$

If tests of association are combined, then the correlation coefficient(r) is the effect measure.

Odds ratio, Risk Ratio or Risk Difference

For data from a prospective study, such as a randomized trial, data is originally reported as the number of events and non-events in two groups in a 2X2 table:

	Events	Non events	Total
Experimental intervention	a	b	a+b
Control intervention	c	d	c+d
Total	a+c	b+d	a+b+c+d

Typically, the effect measures are the risk ratio, odds ratio, and/or risk difference. These are defined as follows:

Risk Ratio=RR $= \frac{\text{Risk of event in the experimental group}}{\text{Risk of event in the control group}} = \frac{a/(a+b)}{c/(c+d)}$

with the standard error of the log relative risk being

$$SE(\ln(RR)) = \frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d}$$

And 95% confidence interval

95% CI = exp(ln(RR)-1.96x SE(ln(RR)) to exp(ln(RR)+1.96xSE(ln(RR))

Odds Ratio= OR=$\frac{\text{Odds of event in the experimental group}}{\text{Odds of event in the control group}} = \frac{a/b}{c/d} = \frac{a \times d}{b \times c}$

With the standard error of the log odds ratio being

$$SE(\ln(OR)) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$$

And 95% confidence interval

95% CI = exp(ln (OR)-1.96x SE (ln (OR)) to exp (ln (OR)+1.96xSE(ln (OR))

Risk difference=RD= *risk of event in experimental group-risk of event in the control group* = $\frac{a}{a+b} - \frac{c}{c+d}$

with the standard error being $SE(RD) = \frac{a \times b}{(a+b)^3} + \frac{c \times d}{(c+d)^3}$

and 95% confidence interval

95% CI = RD-1.96x SE (RD) to RD+1.96xSE (RD)

Effect measures and their standard errors are extracted from primary studies by the reviewers in a tabular form for all the studies.

4.2 Heterogeneity

In Meta-Analysis, effect sizes from different studies are combined to obtain a summary effect. Heterogeneity in Meta-Analysis refers to the variation in the outcomes from different studies. Although results from multiple studies differ to some degree, heterogeneity occurs when their underlying target parameters differ. The heterogeneity in effect measures between studies could arise due to several factors:

- Study design (inclusion criteria, treatment, duration)
- Study quality (randomisation, blinding etc)
- Individual level (prognostic factors)
- Outcomes (chance results)
- inadequate sample size
- differences in participants
- differences in doses of intervention

- differences in study design
- differences in measuring instruments
- different patient follow-up
- different statistical analysis
- different reporting
- different patient response

It is important to understand the factors responsible for heterogeneity since these could influence the overall outcome of the Meta-Analysis.

The classical measure of statistical heterogeneity is Cochrane's Q test which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. Thus if $\bar{y}_1$, $\bar{y}_2$, $\bar{y}_3$, $\bar{y}_4$,..... $\bar{y}_k$ are the effect estimates from k different studies and $\bar{y}$ is the summary effect then $Q = \sum w_i \, (y_i - \overline{y})^2$ where w_i is the study weight i.e. inverse of the study's variance and the summation runs over all the k studies. Q is distributed as a chi-square statistic with k-1 degrees of freedom. The value of Q depends on the number of studies, how much each of the effect estimates deviate from the summary effect and the precision of the studies. If the standard error of an effect size is very low (and thus the precision is very high) even small deviations from the summary effect will be given a higher weight, leading to higher values of Q.

Q has low power as a comprehensive test of heterogeneity[29] when the number of studies is small, i.e. in most meta-analyses. Conversely, Q has too much power as a test of heterogeneity if the number of studies is large[30]. Q forms part of the DerSimonian-Laird random effects pooling method[31]. An additional test, due to Breslow and Day[32], is provided with the odds ratio Meta-Analysis.

It is arguably not possible to examine the null hypothesis that all studies are evaluating the same effect, by considering only the summary data from the studies: The heterogeneity test results should be considered alongside a qualitative assessment of the combinability of studies in a systematic review.

To solve the problems of the Q statistic and the non-comparability of the between-studies variance, among meta-analyses with different effect-size metrics, Higgins and Thompson[30] have proposed the I^2 index. The I^2 index quantifies the extent of heterogeneity from a collection of effect sizes by comparing the Q value to its expected value assuming homogeneity, that is, to its degrees of freedom (df = k – 1): $I^2 = 100\% \times (Q-df)/Q$. It is an intuitive

and simple expression of the inconsistency of studies' results. Unlike Q it does not inherently depend upon the number of studies considered.

The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance[30].

A rough guide to interpretation of I^2 is as follows[9]:

0-40%: might not be important

30-60%: may be moderate heterogeneity

50-90%: may represent substantial heterogeneity

75-100% considerable heterogeneity

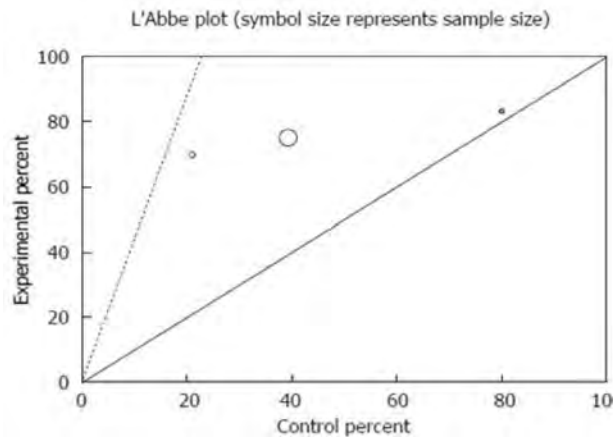
4.3 Graphical methods for identification of heterogeneity

A significant Q test indicates heterogeneity which is then tested further to identify the sources of heterogeneity. If heterogeneity is found then various methods could be adopted for investigating the possible reasons for it say for e.g. sensitivity or subgroup analysis, graphical methods, or Meta-regression. Subgroup analyses are done for subsets of participants either by gender or age group or by location or treatment regimen. One method of identifying heterogeneity is using graphs. There are many types of graphs that identify heterogeneity between the studies. Some of these are:

4.3.1 L' Abbé plot

A plot showing the observed event rate in the experimental group plotted against the observed event rate in the control group for each study. L' Abbé plots may be used to view the range of event rates among the trials, to highlight excessive heterogeneity.

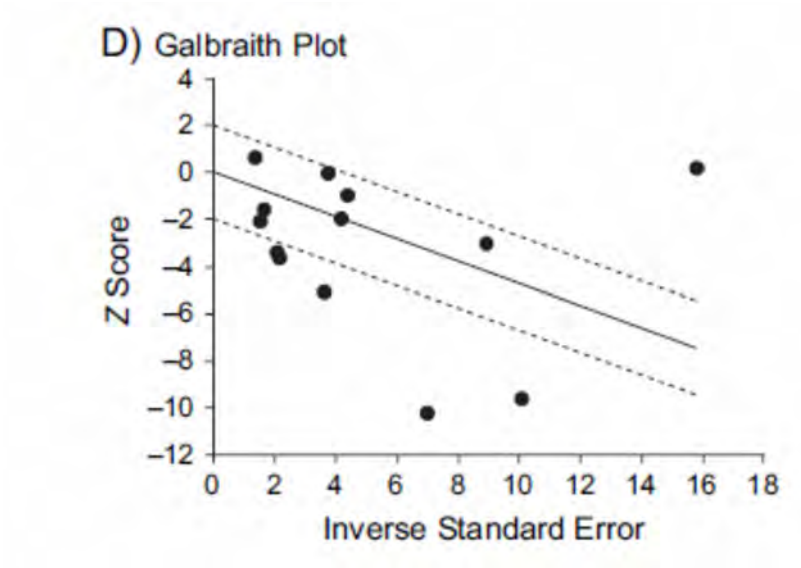
Figure 4: LÁbbe Plot



4.3.2 Galbraith plot

A plot of a standardized intervention effect (intervention effect divided by its standard error) against the reciprocal of the standard error (precision) (ES *vs* 1/SE). Imprecise estimates of effect lie near the origin, and precise estimates further away, giving the correct impression of being more informative. Vertical variation in points describes the extent of heterogeneity. Galbraith plots facilitate examination of heterogeneity, including detection of outliers.

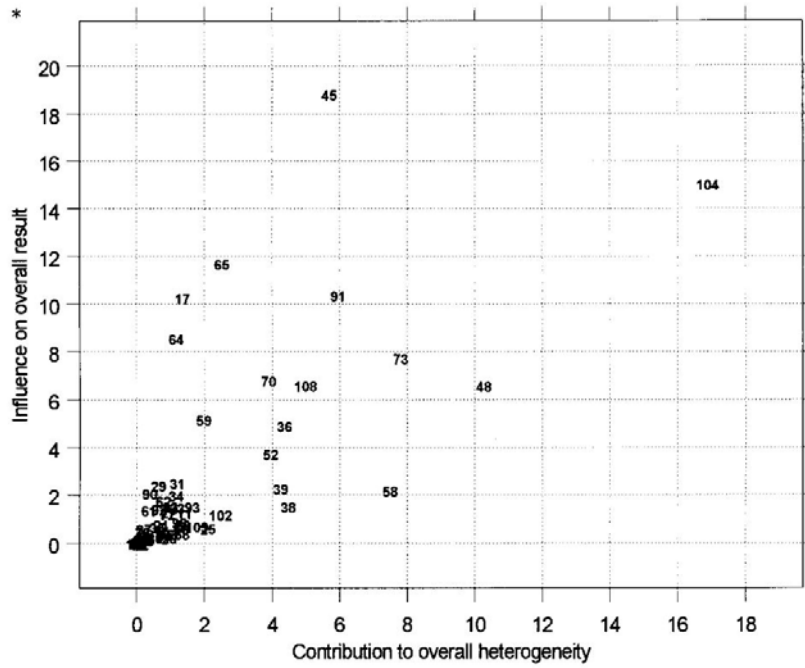
Figure 5: Galbraith Plot



4.3.3 Baujat plot

This plot allows for identifying trials, groups of trials or groups of patients that are sources of heterogeneity and for quantifying the contribution of these trials to the overall result. Each trial is represented by a dot on a 2-D graph. The X axis represents the contribution of the trial to the overall Cochran Q-test for heterogeneity. The Y axis represents the influence of the trial, defined as the standardized squared difference between the treatment effects estimated with and without the trial. This method identifies trials that contribute considerably to the overall heterogeneity and have a strong influence on the overall result.

Figure 6: Baujat Plot

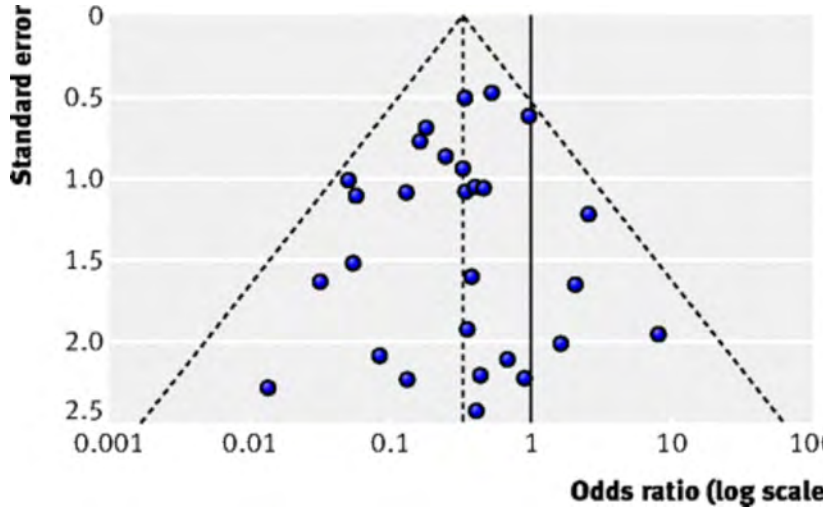


(Adapted from: Graphical displays for Meta-Analysis: An overview with suggestions for practice[33])

4.3.4 Funnel plot

The funnel plot is a scatter plot of effect estimate against a measure of precision (or study size). Mathematically, it plots the effect estimates of the studies against their standard errors. Funnel plots are used primarily as a visual aid for detecting bias or heterogeneity based on the level of asymmetry. A symmetric funnel shape plot indicates increasing scatter with decreasing precision (Figure 7). An asymmetric funnel may be the result of reporting bias (non-availability of results from small studies with non-significant results) to a systematic difference between smaller and larger studies, or to the presence of subsets of studies with different mean effect sizes Asymmetry can also arise with an inappropriate choice of effect measure, with an inappropriate choice of precision measure, with multiple inclusion of smaller (or larger) studies, or by chance. Whatever the cause, an asymmetric funnel plot leads to doubts over the appropriateness of a simple Meta-Analysis and suggests the need to investigate possible causes.

Figure 7: Funnel Plot



4.4 Meta-regression

When heterogeneity is identified between studies, the sources of heterogeneity need to be obtained. Metaregression like linear regression allows to study the effect of continuous, as well as categorical, characteristics of the studies on the effect size. In Meta-regression, the outcome variable is the effect estimate (for example, a standardised mean difference, a risk difference, a log odds ratio or a log risk ratio). The explanatory variables are characteristics of the studies that might influence the size of the intervention effect. The regression coefficient obtained from a Meta-regression analysis will describe how the outcome variable (the intervention effect) changes with a unit increase in the explanatory variable (the potential effect modifier). The statistical significance of the regression coefficient is a test of whether there is a linear relationship between the intervention effect and the explanatory variable. Meta-regression should generally not be considered when there are fewer than ten studies in a Meta-Analysis. Meta-regression may be performed using the 'metareg' macro available for the Stata statistical package.

The next step is to analyze the data using either of the two approaches the **Fixed effect method** and the **Random effect method**.

The Fixed effects model is based on the assumption that a single common (or 'fixed') effect underlies every study in the Meta-Analysis. This approach is usually applied when I^2 is small. It tries to answer the question that "Did the treatment produce any benefit on an average in the studies at hand?"

The basic assumptions are:

- Studies use identical methods, patients, and measurements;
- Produce identical results;
- Differences are only due to within-study variation.

In this model, all of the observed differences between studies is due to chance.

The Random effects model is based on the assumption that individual studies estimate different true effects. These true effects have a distribution with some central value and some degree of variability. Thus, the random effect model allows for random error plus between the studies variability, results in wider confidence intervals and tends to give larger weights to smaller studies than fixed effects model.

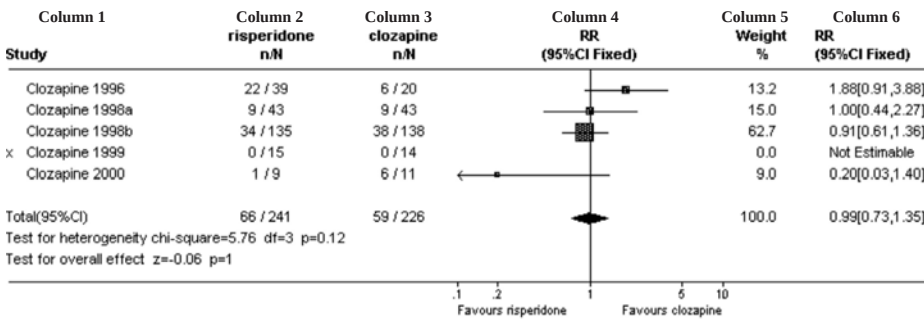
The basic assumptions are:

- Studies are a random sample from the universe of all possible studies
- Differences occur both due to between-study and due to within-study variability

4.5 Presentation

In Meta-Analysis the results are presented in a graphical form. A forest plot is a graphical representation that summarises all the essential information of a Meta-Analysis. Often there are 6 columns in a forest plot (Figure 8).

Figure 8: Forest plot comparing two interventions



Column 1: Studies IDs

The first column shows the list of included studies. These are depicted as name of the first author and the year of publication

Column 2 and column 3: Experimental group n/N and Control group n/N

These columns indicate the number of patients having the outcome of interest(n) out of the total number of patients (N) in the experimental or control group.

Column 4: Relative risk (fixed) 95% CI

This displays the study results. The boxes show the effect estimates from the single studies, while the diamond shows the pooled result. The horizontal lines through the boxes(whiskers) illustrate the length of the confidence interval. Longer whiskers mean, a wider confidence interval. For the summary measure, the confidence interval is the width of the diamond. The vertical line is the line of no effect which could be at 1 for depicting ORs or RRs and 0 when depicting continuous measurements.

If the boxes with whiskers and diamond lie away from the vertical line then the outcome is statistically significant. If the outcome of interest is adverse (e.g. mortality), the results to the left of the vertical line favour the intervention over the control. That is, if result estimates are located to the left, it means that the outcome of interest (e.g. mortality) occurred less frequently in the intervention group than in the control group (ratio < 1).

If the outcome of interest is desirable (e.g. remission), the results to the right of the vertical line favour the intervention over the control. That is, if the result estimates are located to the right, it means that the outcome of interest (e.g. remission) occurred more frequently in the intervention group than in the control group (ratio > 1).

The last possibility: if the diamond touches the vertical line, the overall (combined) result is not statistically significant. It means that the overall outcome rate in the intervention group is much the same as in the control group. This is the case in the figure above.

Column 5: Weight (%)

For the next column over, the weight (in %) indicates the influence an individual study has on the pooled result. In general, the bigger the sample size and the narrower the confidence interval (CI), the higher the percentage weight, the larger the box, and more the influence the study has on the pooled result. In general, the weights of effect sizes for individual studies is the inverse of variance.

Column 6: Relative risk (fixed) 95% CI

The rightmost column contains exactly the same information as is contained in the diagram in column 4, just in numerical format. So, we can observe the data both in picture and in numbers. This can be either the 95% CI of odds ratio (OR) or the 95% CI of relative risk (RR). The diagram above shows relative risk. When the 95% CI does not include 1, we can say the result is statistically significant.

More information is found in the lower left corner of the plot.

The p-value indicates the level of statistical significance. If the diamond shape does not touch the line of no effect, the difference found between the two groups was statistically significant. In that case, the p-value is usually < 0.05.

4.6 Reporting a systematic review and Meta-Analysis

The last step is the interpretation of the results, discussion of issues such as clinical applicability and writing of the manuscript for publication. To ensure that a systematic review is useful to the users, a transparent, complete and accurate account of why, what and how the review was done must be reported. Reviewers need to discuss the limitations of the primary studies included in their review, and limitations in how the review itself was conducted. Limitations of the primary studies, for example, may include issues relating to design flaws. Limitations of the review itself may include issues such as inclusion of only English language studies or inability to accurately interpret the summary estimates due to heterogeneity. A discussion of these limitations will enable readers to judge the strength of the evidence presented in the review. The review usually concludes with a discussion on the implications for clinical practice, and need for further research. If the evidence is strong and unequivocal, reviewers might recommend no further trials on that clinical question. Some reviews (e.g. reviews on screening tests such as mammography) may have important public health or policy implications that merit discussion.

For writing the manuscript for publication, reviewers have two useful guides: the PRISMA 2020[34] (Figure 9) guidelines for systematic reviews of studies that evaluate social, educational or health interventions and the MOOSE guidelines[35] for systematic reviews of observational studies. Many items of PRISMA 2020 are applicable to systematic reviews of studies on aetiology, prevalence or prognosis. Many journals now encourage authors to submit manuscripts formatted according to these guidelines. Moreover, these guidelines can serve as practical tools for the critical reader in assessing the quality of an individual Meta-Analysis. In addition to these guidelines, reviewers can find a variety of outstanding resources for conducting reviews on the list of websites mentioned in the previous chapter.

The following is a list of expected information for a systematic review:

1. A report of literature scoping containing combinations of search strings and the outcome of searches of different databases (this is usually as an appendix with the protocol).

2. A list of articles excluded after reading the full text, including reasons for exclusion

   (Note: a list of articles included is expected in the main text).

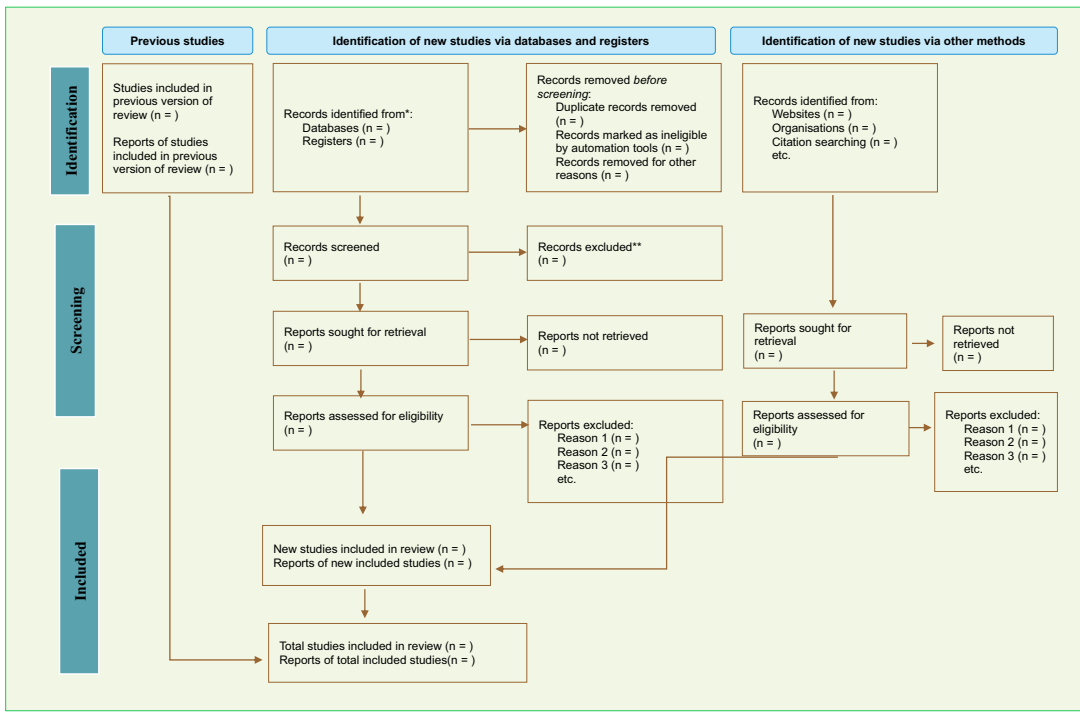
3. A list of articles that could not be obtained at full text despite efforts such as contacting the corresponding author, help from librarians, managing editor of relevant Cochrane review groups etc.: such articles are therefore potentially relevant but not fully screened.

4. Data extraction and quality assessment tables; for example, Excel files with data extracted from each included study (this may be included in the main text if a small number of studies is included).

Example of Systematic Review Report:

Panda, P, Dror, IH, Koehlmoos, TP, Hossain, SAS, John, D, Khan, JAM and Dror, DM (2016). *What factors affect uptake of voluntary and community-based health insurance schemes in low-and middle-income countries? A systematic review, 3ie Systematic Review 27*. London: International Initiative for Impact Evaluation (3ie)

Figure 9: PRISMA 2020 Flow diagram



5. Systematic review and Meta-Analysis software

5.1 Systematic review software

A systematic review as we have discussed in the previous chapters follows some basic steps. There are some statistical software that help the researcher to conduct different steps of a systematic review. These software provide solutions for screening, searching and data analysis. some of the software that are useful during the systematic review are:

Rayyan QCRI

Rayyan is a freely available web and mobile application that helps expedite the initial screening of abstracts and titles. It is easy-to-handle, user-friendly and reduces the load of reviewers by performing quick tasks. The Rayyan software helps accelerate the initial screening of abstracts and titles using a process of semi-automation and data extraction with cloud-based architecture that allows it to scale accordingly during the peak times and as the number of users grows and they can create more reviews and upload more citations. Rayyan mobile app works in a way that one can download the review while online and then screen even in the absence of a network, and then, after getting the network, it will automatically sync back to server. The advantage of using Rayyan is that it learns from reviewers' decision, that is, which study the reviewer wants to include and which to exclude. By removing stop words and stemming, Rayyan extracts all the possible combination of words and these are then used as features by a Support Vector Machine (SVM) classifier. SVM plays an important role as it learns from the included and excluded citations builds a model and a classifier accordingly. One can get access to Rayyan web by using the following link: https://rayyan-prod.qcri.org/welcome. Rayyan is integrated with *Review Manager (RevMan*), a Cochrane software used for preparing and maintaining Cochrane reviews.

COVIDENCE

One of the software used for systematic review management is **COVIDENCE** which is paid but free to use for those authoring Cochrane reviews. It is one of the most popular systematic review tools that can facilitate screening of abstracts and full text, data extraction, import citations from reference managers like EndNote. It is a core component of Cochrane's review production toolkit. https://utas.libguides.com/SystematicReviews/Tools .

EPPI Reviewer

EPPI (Evidence for Policy and Practice Information) Reviewer is free for all the Cochrane contributors. EPPI Reviewer has many features including reference management, data extraction, storage, annotation and coding of files, easy export of review data so that it can be used with other software applications. It can customize tools according to the demands of a specific review. You can create your account on EPPI Reviewer by clicking on the following link:

https://eppi.ioe.ac.uk/EPPIReviewer-Web/home

https://community.cochrane.org/help/tools-and-software/eppi-reviewer

Abstrackr, SRDR Plus and OpenMeta

Brown School of Public Health introduced softwares like **Abstrackr, SRDR Plus** and **OpenMeta** for systematic review and Meta-Analysis related work. **Abstrackr** software is used for screening of systematic reviews, citation and to upload your abstracts. **SRDR (The Systematic Review Data Repository) Plus** is a tool for extracting, managing and archiving data whereas **OpenMeta** is an open source platform to implement Meta-Analysis. One can create account on these three through this link:

https://www.brown.edu/public-health/cesh/resources/software

(https://utas.libguides.com/SystematicReviews/Tools)

DistillerSR

DistillerSR is a priced software that automates the management of literature review using AI and intelligent workflows. It is integrated with EBSCO, Ovid and PubMed and other existing libraries and automatically updates the review when new published references on the topic of interest is added with its additional Module *DistillerSR LitConnect*. It reduces the review screening time by automatically categorizing the references. It helps detect and remove duplicates faster through AI powered screening and automatically identifies conflicts and disagreements between reviewers. The software has open access integrations thereby uploading full text copyright compliant documents from PMC. The *DistillerSR CuratorCR* module reduces data extraction time by preventing duplication of efforts. It is able to capture complex data and reduce the time of the reviewers in data cleaning and effect measure computations. It helps in building reports, PRISMA diagrams and other standard reports. Further details can be obtained at https://www.evidencepartners.com/.

CADIMA

CADIMA is a free web-based tool that facilitates conduct of systematic review. The software allows unlimited multiple reviewers at any stage of the review process. Review questions in any discipline can be addressed in CADIMA. It allows automated duplicate removal, assures automated screening and allows bulk pdf upload. There are tutorials on the website for reviewers and the users can register for online workshops for understanding the functionality of the software. One can get more details from https://www.cadima.info/.

SYSREV

Sysrev is a web-based platform for data curation and systematic reviews. It provides an easy to access free platform in the public domain for collaborative systematic reviews. It allows users to upload documents, recruit reviewers, perform reviews and automate review tasks. Sysrev uses the FAIR-Findability, Accessibility, Interoperability, and Reuse of digital assets design that encourages better data stewardship and management to maximise data transparency and reproducibility. These principles incorporate assignment of unique identifiers for retrieval of metadata that supports reuse of data. It is a software that extracts data from various sources with a variety of import structures like XML, RIS citation format, PDF, JSON and HTML formats using a programming interface. It integrates data from pubmed.gov and clinicaltrials.gov. It generalizes the review process using a digital document. The user can get more details from https://sysrev.com/.

There are several organizations that work on syntheses of evidence in the form of systematic reviews such as **Equator Network, JBI Collaboration**, **Cochrane Collaboration** and **Campbell Collaboration.** The Cochrane Collaboration helps people make informed decisions in healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of healthcare interventions. The Campbell Collaboration is an international social science research network and both these use standards and guidelines for conducting and reporting high quality evidence.

One can sign-up for Campbell network from the link given below:

https://www.campbellcollaboration.org/

(https://campbellcollaboration.org/news-and-events/events/campbell-events/leveraging-global-regional-and-local-evidence-for-evidence-based-policy-making-in-india.html)

The CDSR (Cochrane Database Systematic Review) consists of all systematic reviews prepared by Cochrane Review Group. Cochrane reviews are updated regularly as new studies occur because studies can change the conclusion of review. To sign-in for Cochrane library, one can get the access from the given link: https://www.cochranelibrary.com/

(https://www.cochranelibrary.com/cdsr/about-cdsr)

The **JBI (Joanna Briggs) Collaboration** is one of the biggest collaborations that integrates evidence-based outcomes of healthcare globally which helps in decision-making. You can search for systematic review title by clicking on the following link: https://joannabriggs.org/ebp/systematic_review_register

Also, the systematic review title registration form is available on the above link.

JBI SUMARI is a software developed by JBI to implement the Meta-Analysis. If one wants to learn how JBI works in synthesis and Meta-Analysis, you can visit the following link: https://www.jbisumari.org/#tutorials

(https://wiki.joannabriggs.org/display/JBCI/JBI+EBP+Directory)

The **EQUATOR wizard** is very simple to use and easily understandable. The equator wizard includes common guidelines for generic study types. It has drop down boxes for selecting the area of interest. The **EQUATOR** also provides a book entitled **Guidelines for Reporting Health Research** that provides standardized reporting methods of important details in health research publications.

https://www.equator-network.org/reporting-guidelines-study-design/systematic-reviews-and-meta-analyses/?post_type=eq_guidelines&rgo=post_date

5.2 Meta-Analysis software

Meta-Analysis can be done using various software and every software has its own pros and cons. Before performing Meta-Analysis on any software, it is essential to know the methodology adopted. RevMan, Metawin, Comprehensive Meta-Analysis (CMA), Microsoft Excel, R, Stata, SAS, NetMetaXL, Python etc. are some of the software for performing Meta-Analysis. Some of them are freely available such as R, Python and some software requires external libraries (add-ins).

MS Excel

One way to perform Meta-Analysis in MS Excel is by entering the formulae for the computation This requires complete knowledge of methods in Meta-

Analysis. One can make forest plot in Excel after doing step-by-step analysis such as calculating effect size, standard error, study weights, weighted effect size, Q and I^2 etc. It helps in performing fixed-effect and random-effect Meta-Analysis. One can draw a forest plot in MS Excel by using scatter plot with the error bars.

The forest plot in MS Excel can not be customised to the need of the user. MS Excel is not freely available as it is a part of MS Office[36]. The **Confidence interval calculator** in MS Excel can be used to calculate confidence intervals for means or difference between means, proportions or odds, odds ratio, relative risk, sensitivity and specificity.

Meta-Essentials is a tool designed for MS Excel that contains several spreadsheets to conduct Meta-Analysis by computing required statistics, tables and graphs automatically based upon the input given by the user. It consists of moderator analysis, sensitivity analysis, Egger's regression, Galbraith plot, funnel plot, forest plot, Begg and Mazumdar rank correlation test etc. The spreadsheets are compatible with the MS Excel 2010, 2013 and 2016. Some worksheets of the workbook may work well with current versions but the earlier versions may not support the formatting and the formulae. One can download the user-manual for Meta-Essential tool from the link given below:

https://www.erim.eur.nl/research-facilities/meta-essentials/user-manual/

MetaEasy. **MetaEasy** is an add-in in MS-Excel that facilitates in performing Meta-Analysis. It is useful to produce reports, calculate the effect size, standard error etc. The add-in also supports advance Meta-Analysis such as maximum likelihood, profile likelihood and permutation methods. Overall, there are seven frequentist Meta-Analysis methods included in this add-in. In general, the forest plot contains a square for each study but MetaEasy also provides several squares in the forest plot for each study according to the multiple outcomes used in each study. It also calculates various heterogeneity measures such as Q-statistic, I^2 statistic and H_M^2, where H_M^2 is independent of the number of studies and ranges from 0 to ∞. 0 indicates perfect homogeneity. This add-in is freely available on the website: http://www.statanalysis.co.uk/. MetaEasy consists of five worksheets in which the first the sheet is used for entering the data and it will automatically calculate the effect size and standard error[37].

Another add-in for Meta-Analysis in MS Excel is **MetaXL** that supports Quality Effects (QE) model and also inverse variance heterogeneity. MetaXL has some different features for detecting publication bias, which are, LFK index (quantitative measure for publication bias) and Doi plot instead of Funnel plot. With the release of advance version of MetaXL, it introduces Network Meta-

Analysis as well as cumulative Meta-Analysis. http://www.epigear.com/index_files/metaxl.html

Another MS Excel add-in is **MIX 2.0** which is specially developed for educational purpose and can be freely downloaded from the link http://www.mix-for-Meta-Analysis.info. This platform also supports causal meta-analyses and the results obtained from **MIX** has been validated with Stata and Comprehensive Meta-Analysis version 2.

NodeXL and **NetMetaXL** are other MS excel add-ins that supports network Meta-Analysis.

R software

R is an open-source software and has many packages to perform different types of meta-analyses such as standard inverse variance Meta-Analysis, three-level Meta-Analysis, network Meta-Analysis etc. One needs knowledge of R programming to use these packages.

Metafor is the most commonly used package for Meta-Analysis in R. This package helps in calculating all types of effect sizes and also does data synthesis using fixed, random and mixed effect models. Metafor supports moderator analysis, Meta-regression and graphical plots like forest, Baujaut and funnel plot. This package also provides a variety of generalized linear models and meta-analytic multivariate/multilevel models.

The package **Meta** provides trim-and-fill method to evaluate bias, fixed and random effect Meta-Analysis, cumulative Meta-Analysis, meta regression, leave-one-out Meta-Analysis, subgroup Meta-Analysis and various graphical plots such as funnel, forest, Galbraith, baujaut, L'Abbe and bubble plot.

The package **robumeta** is used to conduct robust variance estimation (RVE) Meta-regression using both large and small sample RVE estimators using various weighting schemes. These methods are distribution free and provide valid point estimates, standard errors and hypothesis tests even when the degree and structure of dependence between effect sizes are unknown. It also includes functions to perform sensitivity analyses under correlated effects weighting and producing RVE-based forest plots.

The other packages such as **DTA MA (Diagnostic Test Accuracy Meta-Analysis), dmeta** and **Meta-CART** are also available to implement Meta-Analysis in R. A package **metaDigitise** helps in extracting descriptive statistics and raw data hidden in the figures (bar plot with standard error, box plot, scatter plot and also histogram) in primary research papers.

Python

The package in python to execute Meta-Analysis is **PythonMeta** which has many features to combine effect sizes such as RR, RD, OR, MD or SMD. This package also helps the users to draw funnel plot and forest plots and to check heterogeneity viz. Q-statistic/chi-square test. The latest version of this package is Version1.11 (July 2019). https://pypi.org/project/PythonMeta/.

The tool **Pymeta** is an online tool created and supported by **PythonMeta** package of Python Programming language. With the help of this tool, one can combine various effect measures and perform subgroup analysis, cumulative Meta-Analysis, sensitivity analysis and also has the power to draw plots like forest plot, funnel plot, cross-block plot etc.

Stata

Stata also has the feature to perform meta-analyses. There is a main community-contributed package **metan** that has all the commands required to perform standard Meta-Analysis. This package consists of several commands such as **labbe, metareg, metafunnel, metap, metabias, metatrim, metaan etc.** These commands are useful in the creation of graphical plots like Labbe plot, forest plot, funnel plot and effect size, Meta-regression etc. https://www.stata.com/support/faqs/statistics/Meta-Analysis/

The command **meta** supports effect size as well as summary statistics, forest plot, publication bias etc. The guide to perform Meta-Analysis on Stata can be downloaded from the following link: https://www.stata.com/manuals/meta.pdf

6. Disseminating Systematic Review Findings

Over the last decade, there have been substantial investments in the commissioning and funding of systematic reviews assessing effects of a range of different healthcare interventions. In order to improve the quality of healthcare, and health outcomes, the findings from systematic reviews need to be effectively communicated to practitioners and policy-makers. The following are some of the dissemination products for communicating findings from systematic reviews:

6.1 Evidence Summary

An Evidence Summary is a short one- or two-page document that describes in a lay and friendly language the findings from the best and most relevant evidence from systematic reviews on a particular health intervention with implications for further research. An Evidence Summary extracts information from systematic review(s), evaluates the information and presents the findings in a user-friendly manner such that decision-makers can quickly review the evidence and decide whether a particular innovation is likely to be effective in their own context.

Structure and Content of an Evidence Summary

1. ***Title***

The title usually consists of the topic reviewed and presented in the summary. It usually states the primary research question or issue of interest addressed in the summary.

2. ***Key messages***

This section summarizes the research findings and outlines the key messages that one is trying to communicate.

3. ***Background to the review question***

Under this section, one provides a brief background information on the topic being addressed by the evidence summary

4. ***Methods (a summary of reviewed studies and sources of information)***

This section presents a summary of the reviewed studies and the respective sources of evidence that were used to draw the key messages and conclusions. It is important to highlight how the reviewed studies were searched and selected as a reliable source of evidence.

5. *Evidence*

This section provides answers to the review question. It provides the level and quantity of evidence found for the review question. For clarity and impact, the evidence should be summarized in bullet points.

6. *Case studies*

It is usually helpful for practitioners and policy makers to also present studies that provide additional evidences relating to the review question if available. Case studies make an Evidence summary lively.

References to resources containing information about these case studies should be given.

7. References

All references cited in the text should be included under this section. The use of a standard referencing style is highly recommended.

8. Acknowledgements

It is important to acknowledge all those that contribute to the process of putting together the evidence summary.

1. Conflicts of interests must also be declared

2. Additional Information

Provide contact details including e-mail and phone numbers for readers to ascertain more information.

For more details on Evidence Summary, please look at The Supporting Policy-Relevant Reviews and Trials (SUPPORT) project at *www.supportsummaries.org*

6.2 Plain Language Summary (PLS)

A Plain Language Summary (PLS) is a short, easy-to-read summary of a published systematic review. The main aim of the PLS is to provide information to a patient, carer, or practitioner on the key points of scientific evidence from a systematic review without getting into the clinical and synthesis details. A PLS is supposed to be clear, understandable, and accessible (i.e. open-source), especially for lay persons in the particular field of healthcare. Cochrane has published Standards for the reporting of Plain Language Summaries in new Cochrane Intervention Reviews (PLEACS). An example of PLS is given in box 8.

Box 8: Plain language summary example

Nutritional labeling for healthier food or non-alcoholic drink purchasing and consumption

Nutritional labelling to promote healthier consumption and purchasing of food or drinks

A poor diet including excessive energy intake is an important cause of ill health. Nutritional labelling may help people to make healthier food choices.

What is the aim of this review?

This review investigated whether nutritional labels (i.e. labels providing information about nutritional content) persuade people to buy or consume different (healthy) kinds of food. We searched for all available evidence to answer this question and found 28 studies.

Key messages

There is evidence to suggest that nutritional labelling, with energy information (e.g. calorie counts) on menus, may reduce energy purchased in restaurants, but more high-quality studies are needed to make this finding more certain.

What was studied in the review?

Some studies assessed buying food or drinks from vending machines, grocery stores, restaurants, cafeterias, or coffee shops. Others assessed the amount of food or drink consumed during a snack or meal in an artificial setting or scenario (referred to as laboratory studies or settings).

What are the main results of the review?

Nutritional labelling on restaurant menus reduced the amount of energy (i.e. calories) purchased, but the quality of the three studies that contributed to this finding was low, so our confidence in the effect estimate is limited and may change with further studies. Eight studies assessed this same type of intervention in laboratory settings, but instead of evaluating how much energy participants purchased, these studies evaluated how much energy participants consumed. These studies did not conclusively demonstrate a reduction in energy consumed when menus or foods were labelled, and they were also of low quality.

In addition, six laboratory studies assessed how much energy participants consumed when they were given one food or drink option with or without labels, and five laboratory studies assessed how much energy participants consumed when foods were experimentally labelled as low energy or low fat when they were actually high-energy foods (i.e. mislabelling). Results from these two groups of studies were inconclusive and of low, or in the case of mislabelling studies, very low quality. We found some studies that assessed labelling on vending machines and grocery stores, but their results were not easy to interpret, so we could not use them to inform this review.

How up-to-date is this review?

The evidence is current to 26 April 2017.

6.3 Policy briefs

Reports that address the interests and needs of policy makers are referred to as policy briefs[38]. Policy briefs are based on systematic reviews to advance policymaking based on the best available evidence. The purpose of a policy brief is to create a short document providing findings and recommendations to an audience who may not necessarily be experts in that area. The audience for a policy brief can be the general public or particular entities of interest that seek solutions to problems or needs or who may require to be convinced of a different way of looking at an area of interest[39].

Examples of policy brief:

1. Community-based health insurance: how to promote effective and equitable coverage?

This brief is based on Factors affecting uptake of voluntary and community-based health insurance schemes in low- and middle income countries, 3ie Systematic Review 27, by Pradeep Panda, Iddo H Dror, Tracey Perez Koehlmoos, SA Shahed Hossain, Denny John, Jahangir AM Khan and David M Dror. It synthesises evidence from 54 studies (36 quantitative, 12 qualitative, and 6 mixed-method studies), covering 20 countries, mainly in Africa, South Asia and South East Asia, to understand the factors affecting uptake of CBHI schemes. Most studies reported on schemes in rural settings and in low-income countries, with only few lower-middle income countries and only very few upper-middle income countries(Adapted from the published policy brief).[27]

2. Oral Cholera Vaccines—worth a shot?

This policy brief is based on a synthesis that highlights that contrary to popular belief, cholera has its foothold firmly rooted in India. Frequently encountered symptoms of the disease are vomiting and at times, mild fever along with diarrhoea and faecal loss of salt and water leading to dehydration. Every year several outbreaks of the disease are reported from across the country. A few districts, based on the data from 'Integrated Disease Surveillance Program' (IDSP) (2011-2015), can even be labelled as endemic for cholera. However, we underline that the burden of cholera estimated for India is hamstrung by lack of robust surveillance and scarcity of incidence studies. Analysis of outbreak reports indicates that some settlements and populations are more vulnerable to diarrhoea and cholera compared to others. This heterogeneity provides an opportunity to prioritize areas for intervention but also cautions against applying incidence data obtained from one study from Kolkata to all of India. The short lasting nature of most of the recent cholera out-breaks

in India (2-3 weeks), requirement of two doses of the licensed OCV to be administered with a gap of 2 weeks in between and emerging evidence that considerable efficacy could be attained by single dose administration of the same vaccine call for pragmatic approaches. We recommend that a) existing surveillance system for cholera be strengthened, b) mapping of vulnerability to cholera as pertinent to population groups and geographical locations be continued and existing information be used for decision making, c) single dose bivalent killed OCV (licensed in India) be deployed in operational exploration mode in selected settings and in pre-cholera season and d) investment for safe water and sanitation as well as hygienic practices be boosted. The cost of inaction today could mean lives claimed by cholera in underserved areas, deepening of poverty and inequity, and perpetuation of expenses needed to tackle recurrent outbreaks of cholera and other diarrheal diseases tomorrow(Adapted from the published policy brief)[40].

3. Task shifting to optimise the roles of health workers to improve the delivery of maternal and child healthcare

This policy brief was prepared by the Uganda country node of the Regional East African Community Health (REACH) policy initiative. The purpose was to inform deliberations among policy makers and stakeholders. It summarises the best available evidence regarding the design and implementation of policies for extending the use of non-medically trained primary health care workers to deliver cost effective maternal and child health interventions[41].

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Other Resources

Sl. No	Title	Author(s)	Publisher	Year
1	The Handbook of Research Synthesis and Meta-Analysis, 2nd Edition	Larry V Hedges & Ingram Olkin	Academic Press	1985
2	Systematic Reviews	Ian Chalmers	BMJ	1995
3	Systematic Reviews: Synthesis of Best Evidence for Health Care Decisions	Cynthia Diane Mulrow	ACP Press	1998
4	Practical Meta-Analysis	Mark Lipsey & David Wilson	Sage	2000
5	Methods for Meta-Analysis in Medical Research	Alex J Sutton, Keith R. Abrams, David R Jones, Trevor A Sheldon, Fujian Song	Wiley	2000
6	Systematic Reviews in Health Care	Matthias Egger, George Davey-Smith & Douglas G. Altman	BMJ	2001
7	Systematic Reviews in Health Care: Meta-Analysis in Context	Matthias Egger, George Davey-Smith, Douglas Altman (Eds)	BMJ Books	2001
8	Systematic reviews in health care a practical guide	Glasziou Paul	Cambridge University Press	2001
9	Making Sense of Critical Appraisal	Olajide Ajetunmobi	CRC Press	2001
10	Meta-Study of Qualitative Health Research: A Practical Guide to Meta-Analysis and Meta-Synthesis	Barbara L. Paterson	Sage	2001
11	Meta-Analysis of Controlled Trials	Anne Whitehead	Wiley	2002

Sl. No	Title	Author(s)	Publisher	Year
12	Evidence-based Health Economics: From effectiveness to efficiency in systematic review	Cam Donaldson, Miranda Mugford, Luke Vale	BMJ	2002
13	Systematic Reviews and Meta-Analysis (Continuum Research Methods Series)	Carole Torgerson	International Publishing Group	2003
14	Publication Bias in Meta-Analysis	Hannah Rothstein, Alex Sutton, Michael Borenstein	Wiley	2005
15	Systematic Reviews in the Social Sciences: A Practical Guide	Mark Petticrew & Helen Roberts	Blackwell Publishing	2006
16	Cochrane Handbook for Systematic Reviews of Interventions	Julian PT Higgins & Sally Green (eds.)	Wiley	2008
17	Systematic Reviews and Meta-Analysis	Julia H Littell, Jacqueline Corcoran, & Vijayan Pillai	OUP	2008
18	Introduction to Meta-Analysis	Michael Borenstein, Larry V. Hedges, Julian P.T. Higgins, Hannah Rothstein	Wiley	2009
19	Research Synthesis and Meta-Analysis: A Step-by-Step Approach 4th edition	Harris Cooper	Sage	2009
20	Conducting research literature reviews: from the Internet to paper	Arlene Fink	Sage	2010
21	The Essential Guide to Effect Sizes: Statistical Power, Meta-Analysis, and the Interpretation of Research Results	Paul D. Ellis	Cambridge University Press	2010

Sl. No	Title	Author(s)	Publisher	Year
22	Doing Your Literature Review: Traditional and Systematic Techniques	Jill Jesson, with Lydia Matheson and Fiona M. Lacey	Sage	2011
23	Systematic reviews to support evidence-based medicine	Khalid Khan, Regina Kunz, Jos Kleijnen, Gerd Antes	Taylor & Francis	2011
24	Finding What Works in Health Care: Standards for Systematic Reviews	Institute of Medicine	The National Acadmies Press	2011
25	Applied Meta-Analysis for Social Science Research	Noel Y Card	The Guilford Press	2012
26	Advances in Meta-Analysis	Terri D. Pigott	Springer	2012
27	Evidence Synthesis for Decision Making in Healthcare	Nicky J. Welton, Alexander J. Sutton, Nicola J. Cooper, Keith R. Abrams and A. E. Ades	Wiley	2012
28	How to do a Systematic Literature Review in Nursing: A step-by-step guide	Josette Bettany-Saltikov	OUP	2012
29	Systematic synthesis of qualitative research	Michael Saini, Aron Shlonsky	New York University Press	2012
30	Finding and evaluating evidence: systematic reviews and evidence-based practice	Denise E. Bronson, Tamara S. Davis	OUP	2012
31	Applied Meta-Analysis with R	Ding-Geng (Din) Chen, Karl E. Peace	Chapman & Hall/CRC Biostatistics Series	2013

Sl. No	Title	Author(s)	Publisher	Year
32	Doing a Systematic Review: A Student's Guide	Angela Boland, Gemma Cherry, Rumona Dickson (Eds)	Sage	2014
33	Evidence-Based Health Care and Public Health: How to Make Decisions About Health Services and Public Health	Muir Gray	Elseiver Health Sciences	2014
34	Meta-Analysis with R	Guido Schwarzer, James R Carpenter, Gerta Rücker	Springer	2015
35	Using Mixed Methods research synthesis for literature reviews	Mike Heyvaert, Karin Hannes, Patrick Oughena	Sage	2016
36	An Introduction to Systematic Reviews	David Gough, Sandy Oliver, James Thomas (Eds)	Sage	2017
37	Doing a Systematic Review: A Student's Guide	Angela Boland & Gemma Cherry & Rumona Dickson [Boland, Angela]	SAGE	2017
38	How to Perform a Systematic Literature Review: A Guide for Healthcare Researchers, Practitioners and Students	Edward Purssell, Niall McCrae	Springer	2020
39	Systematic reviews in educational research	Olaf Zawacki - Richter, Michael Kerres Svenja Bedenlier Melissa Bond Katje Buntins Eds	Springer	2020
40	Principles and Practice of Systematic Reviews and Meta-Analysis	Sanjay Patole	Sppringer	2021

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"The book written by Dr. Anju Sinha, Dr. Geetha R. Menon and Dr. Denny John is well-written and concise. From a beginner's perspective, it is a quick guide that covers almost all topics ranging from formulation of a research question to the software used in meta-analysis with suitable examples at places."

- Meenu Singh

"The book came out very well. It will really be a guide for beginners. The book gives sources of all required materials for conducting a systematic review."

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