ICGP QSIP Protocol Development and Evidence Synthesis

for Quick Reference Guides

Definition

The ICGP Quality and Safety in Practice Quick Reference Guides (QRG)s are a 'synthesis of the evidence' on a chosen topic. The QRGs aim to summarise the best available evidence in the context of Irish General Practice.

Is a review required?

This is the first step is to ensure that the QRG is relevant to Irish General Practice. It is essential to check if there are existing or ongoing reviews available that would meet the needs of Irish GPs sufficiently.

Review Protocol

A protocol to state the objectives of the review is essential. Decisions about the review question, inclusion criteria, search strategy, study selection, methodological quality assessment, data synthesis and plans for dissemination should be addressed.

Defining the Research Topic

A well-defined review question ensures clarity in the review process. If the review question is broad, it may be more appropriate to break this down into a series of specific questions.
"PICO" defines the research question and inclusion/ exclusion criteria:
Patient: what patient population does the review refer to, e.g. adults/ children/ primary or secondary care.
Intervention: test/treatment to be reviewed
Comparator: what is the reference standard, e.g. will the studies be comparing it to the current best treatment available.
Outcome: what outcomes is the review using to compare results.

For other research questions the PRO approach to defining the research question may be more appropriate

P: Population
R: Risk
O: Outcome

The Search Strategy; How to identify the Evidence

An extensive search is required. A wide number of databases should be used to perform the search (e.g PubMed, EMBASE, CINAHL, Cochrane, Scopus, Google Scholar). Cross-referencing with the reference list of relevant studies will improve the search. Several sources of evidence on the topic should be used (e.g. TRIP database, Bandolier, York Effective Healthcare, BMJ Clinical Evidence, NICE, SIGN).
We strongly recommend that authors use systematic review evidence where available.

Designing a Search Strategy

There are several important questions to ask when designing a search strategy:

- What search terms should be searched as descriptors or as "keywords"? The keywords are derived from the research question
- What Boolean operators should be used? (AND, OR, NOT)

- Where should truncation characters be used? (e.g. parent* will retrieve parent, parents, parental)
- What are limiting features available to narrow results? (e.g. use of Publication Type codes, period, language)?

MeSH (Medical Subject Headings) are the controlled vocabulary used to index citations in PubMed and are useful to design the search. The main concepts extracted from the research question are entered in a table. Each concept will require multiple synonyms and will connect to the next concept by the AND operator. The search terms can be entered one at a time in PubMed then combined in the PubMed advanced page using the search history. See the tutorial in PubMed : https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/020_700.html

Example of a search for a review of the benefit of Vitamin D in Chronic Fatigue Syndrome:

("Vitamin D*" OR "dietary supplement*" OR calciferol OR cholecalciferol OR ergocalciferol) AND ("Chronic fatigue" OR CF* OR "fatigue disease" OR "fatigue syndrome" OR "myalgic encephalomyelitis" OR ME).

Data extraction
Data extraction is the process of reading through a study and extracting the relevant information from each study. Designing a form to complete data extraction for each study is recommended. Having two reviewers for this process is advisable.

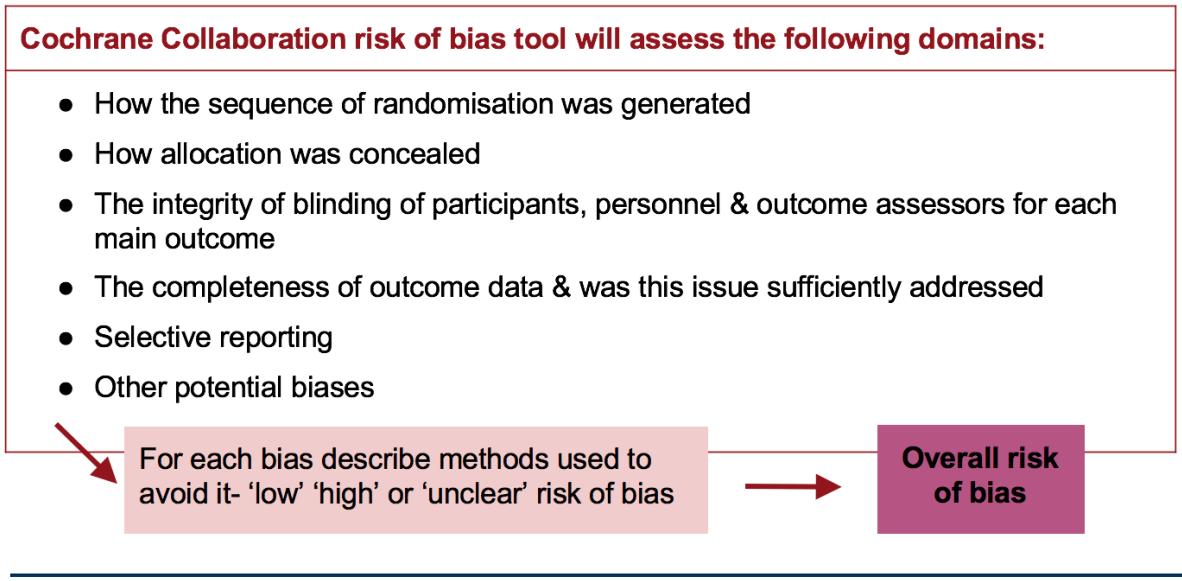
Grading the Evidence
The Oxford Centre for Evidence-based Medicine Grading system is the approach chosen by the QSIP committee. (1)

LEVELS OF EVIDENCE
Level 1: Evidence obtained from systematic review of randomized controlled trials
Level 2: Evidence obtained from at least one randomized trial
Level 3: Evidence obtained from at least one nonrandomized controlled cohort/follow-up study
Level 4: Evidence obtained from at least one case-series, case-control/historically controlled study
Level 5: Evidence obtained from mechanism-based reasoning

Limitations of the Grading system
Authors need to be aware of the limitations of this grading system:
•It lacks an inbuilt methodological quality assessment. Authors must use a checklist to assess the methodological quality of included studies to assess 'good quality evidence' and 'well conducted' studies.

Methodological Quality Assessment
Study quality may affect study results and conclusions. Many different quality assessment tools are available, e.g. Cochrane risk of Bias Tool for RCTs (described in Figure 1 & appendix B) , NIH Quality assessment Tool (Observational Studies), AMSTAR (systematic reviews). Quality assessment should be conducted by a minimum of two people independently.

Figure 1. Illustration of the Cochrane Collaboration risk of Bias Tool for Randomised Control Trials



•The Oxford Centre for Evidence-based Medicine Grading system does not provide a recommendation and additional questions must be asked by the clinician before applying it in practice as a result.

Additional Questions

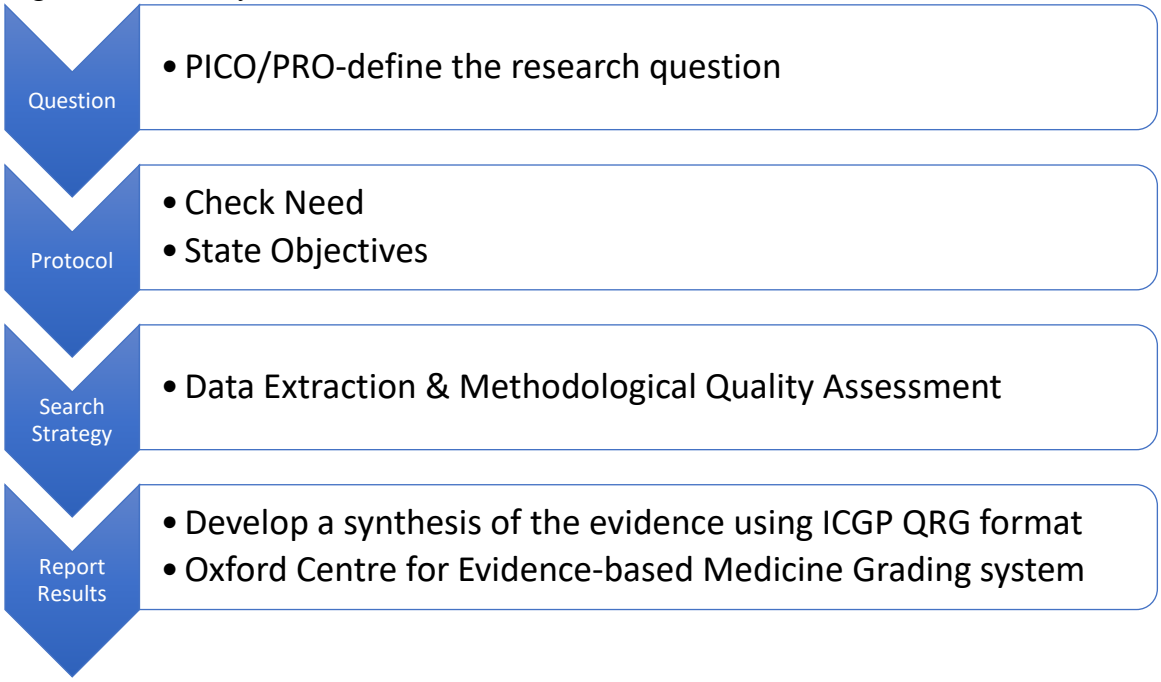
1. Does the study have **external validity**? Is it generalisable to the patients in the review protocol?

2. Is the study both statistically significant AND **clinically significant** (e.g. systolic blood pressure falling by 1mmHg may be clinically irrelevant)

3. **Is another treatment better**? Another therapy could be 'better' concerning both the desired beneficial and adverse events, or another therapy may simply have a different benefit/harm profile (but be perceived to be more favourable by some people).

4. Are the **patient's values and circumstances compatible with the treatment**?

Figure 2. Summary of ICGP Author Guidelines for the QRG



Process for Publication:
The final document will be sent to the ICGP library to check the references are correct.
The document will be reviewed by the QSIP project officer for formatting, check permission for images and for minor errors.
The author will need to review the final document.
The document is sent for conversion to PDF and upload to website. Once the document has been published it is not possible to make changes to the document.

If you require additional support you can contact the Quality in Practice project officer qip@icgp.ie

Updating the QRG
All updates are required to use the Oxford Centre for Evidence-based Medicine Grading system and the current version of the ICGP template.
The purpose of an update is to include any new relevant evidence since the update was published and to reflect changes in clinical guidelines or practice.
This will require performing a new search of the evidence.
Ideally it will be performed by the original author of the guide
New authors can be sourced if authors are unable to commit their time.
The updates are required every three years but amendments should be arranged if there is major new evidence or changes in legislation which significantly affect clinical practice.

Useful Resources
Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0.[updated March 2011]. Chichester: The Cochrane Collaboration 2011, JPT Higgins, S Green – 2018 , www.cochrane-handbook.org

Cochrane online learning modules:
https://training.cochrane.org/interactivelearning

Steps in Planning and implementing a literature Search, Barbara Folb, University of Pittsburgh.
http://hsls.libguides.com/ld.php?content_id=8696619

Systematic Review: The Process: Databases & Grey Literature
https://guides.mclibrary.duke.edu/sysreview/databases

PubMed Tutorials
https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/cover.html

NIH Quality Assessment Tools https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

AMSTAR Checklist to assess systematic Reviews
https://amstar.ca/Amstar_Checklist.php

Cochrane risk of Bias tool for Randomised Controlled Trials : http://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm

Oxford Centre for Evidence Based Medicine
OCEBM levels of evidence. Link to introductory and background document
https://www.cebm.net/2016/05/ocebm-levels-of-evidence/

Appendix A

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case- control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning

What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

Appendix B

Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomised Controlled Trials

Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Appendix C

NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Appendix D

AMSTAR 2: Assessing the Methodological Quality of Systematic Reviews

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

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☐ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☐ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☐ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☐ Yes
☐ No

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

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix E

An Example of Grading the Evidence

Example
Migraine Quick Reference Guide

Study
Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults; Cochrane systematic review 2017, Law S Derry S Moore AR;

Data Extracted
NSAID and triptans are recommended for the treatment of acute Migraine.

AMSTAR 2 checklist used to assess the quality of the evidence
=>High quality review

GRADE assigned
Level of evidence 1

Additional Questions
The results are largely based on treatment given in a secondary care outpatient department. The results were clinically and statistically significant with a NNT 3 for mild migraine and 5 for moderate to severe migraine and the treatment was compatible with patients values and circumstances (withdrawal due to side effects was low)
A better treatment has not been identified.

AMSTAR 2 Results

Printer Friendly Version

Article Name: Migraine

You are currently logged on as Guest. You need to be logged on as a member to submit your score.
Log On

Migraine is a High quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYesYesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes Yes Yes Yes Yes Yes Yes Yes Yes

5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes

10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	Yes
NRSI	Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

References

1. Jeremy Howick IC, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton. ". . Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document) [Available from: https://www.cebm.net/index.aspx?o=5653.