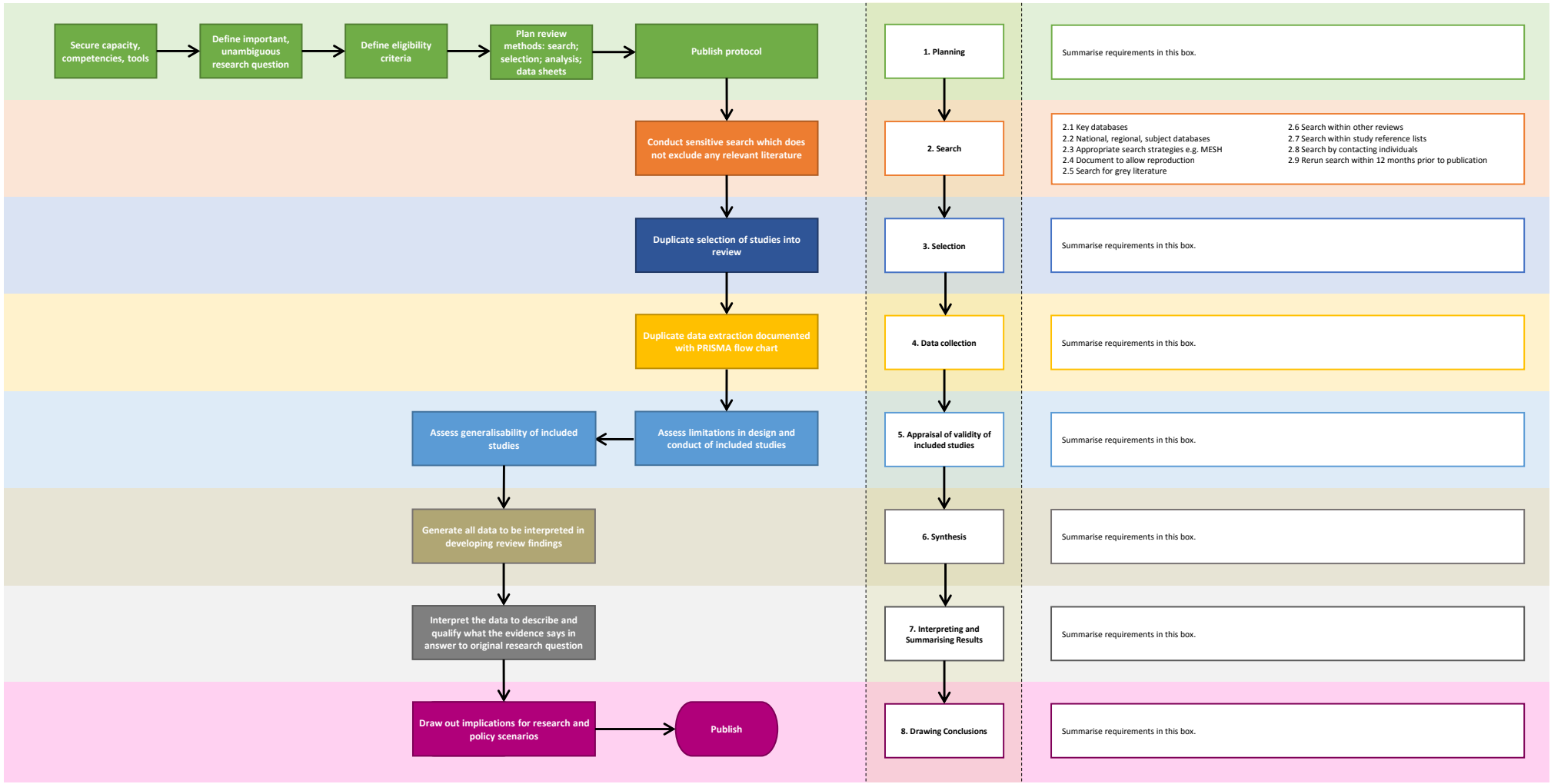
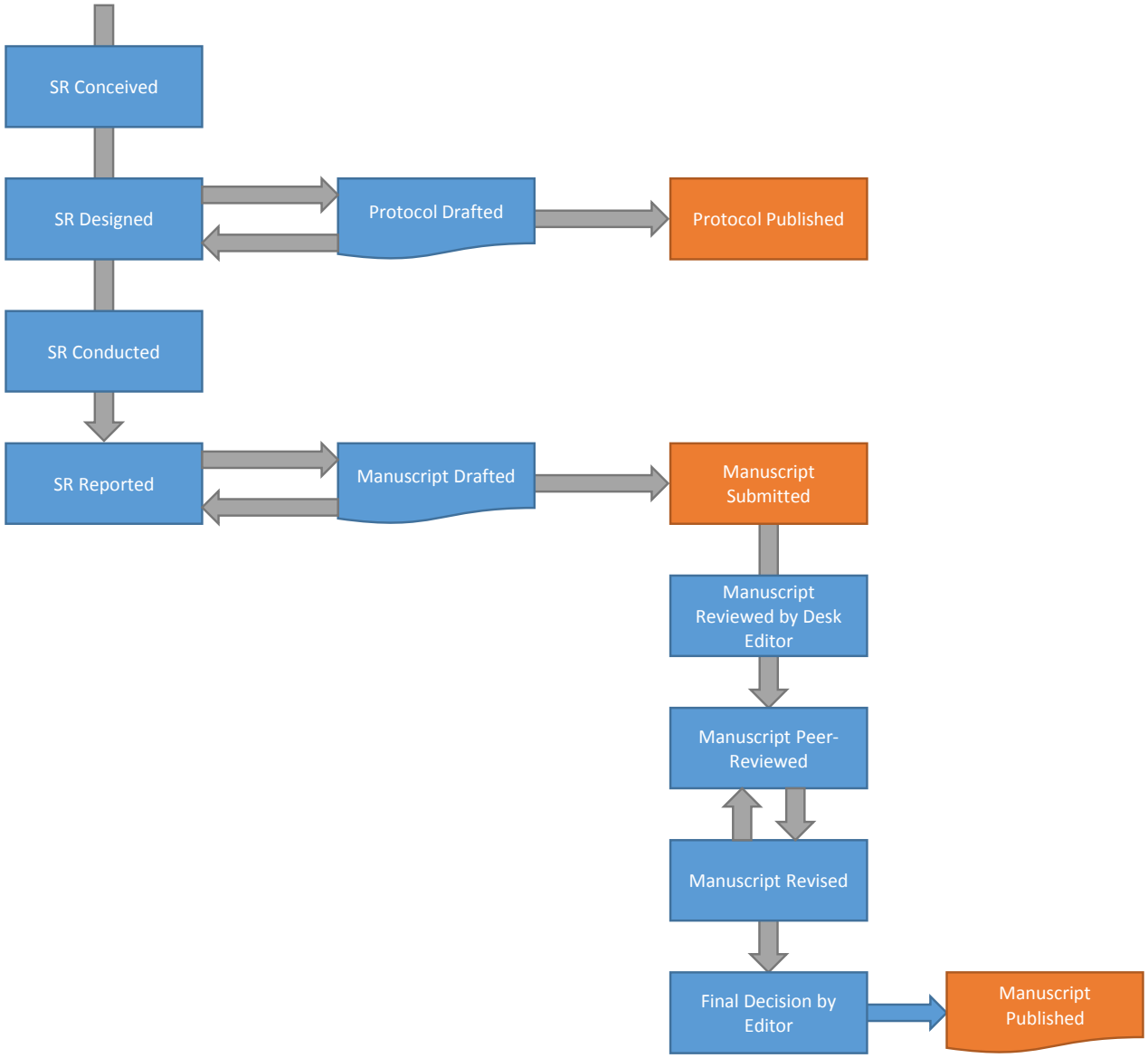
MECIR steps	WWHC Steps	ECoSys-CRA Steps
Setting the research question (s) to inform the scope of the review	Initiation	Conduct of the planning stage
Setting eligibility criteria for including studies in the review	Finding and Appraising Individual Studies	Conduct of the search stage
Selecting outcomes to be addressed for studies included in the review	Synthesising	Conduct of the selection stage
Planning the review methods at protocol stage	Reporting	Conduct of data collection stage
Searching for studies		Conduct of appraisal (internal, external validity) of studies
Selecting studies into the review		Conduct of synthesis
Collecting data from included studies		Conduct of interpreting and summarising results of synthesis
Assessing risk of bias in included studies		Conduct of reaching conclusions
Synthesizing the results of included studies		
Summarizing the findings		
Reaching conclusions		

General Discussion Points
1 Focus, as far as practically possible, on articulating unambiguous standards for conduct of systematic reviews in CRA
2 Consider the extent to which we need to anticipate or describe standards which may only be relevant to SRs conducted for specific sub-disciplines of CRA
3 Address the absence of specific quality control measures at point of internal review, peer-review and/or publication which should prevent inadequate reviews being published
4 Consider whether or not we can stipulate levels of requirement for each clause in our proposed standard, or whether everything should at this stage be "recommended"
5 Address the absence of criteria for systematic appraisal of the generalisability (external validity) of individual included studies and other evidence



The stages of conducting a systematic review



Conduct, Reporting and Publishing Workflow for Systematic Reviews

1. Conduct of Planning Stage of Systematic Review				
Ref.	**Level of Requirement**	**Practice**	**Explanatory notes**	**Points flagged for discussion**
1.1	**Securing capacity, competencies and tools**			
1.1.1		Ensure the review team has expertise in: pertinent risk assessment areas; systematic review methods; librarianship; quantitative methods. Disclose which team members have which expertise.		
1.1.2		Select appropriate software to facilitate conduct of systematic review		e.g. HAWC, DRAGON, Covidence, RevMan etc. Helps ensure integrity of review process, data extraction etc. and no important steps are missed.
1.1.3		Disclose interests (financial, intellectual) and roles of each member of the review team		What about excluding financial COIs? How to manage strong intellectual interests?
1.2	**Setting the research question to inform the scope of the review ("problem formulation")**			
1.2.1		Demonstrate the need for a new review		
1.2.2		Develop a framework which connects the exposure to the outcomes of interest and defines the key questions to be addressed		Not clear exactly how to articulate this but it seems important, particularly in light of e.g. requirement (in some form of wording!) that identification of an endocrine disruptor in EU will necessitate adverse outcome, endocrine activity and outcome being a result of that activity.
1.2.3		Use a PECOS statement or other suitable format to articulate each question		
1.2.4		Prioritise questions according to stakeholder requirements, stating rationale for decision relating to each question		
1.2.5		Consult stakeholders on questions and revise according to input		There is potentially a "publication of question" point of practice here, after which the protocol would be formulated. Flag?
1.2.6		Considerations of equity and specific sub-populations		Quite fundamental in e.g. MECIR. Vulnerable sub-populations should be taken into account in CRA; how to formulate the requirement?
1.3	**Setting eligibility criteria**			
1.3.1		Define unambiguous and appropriate study population criteria for inclusion of studies		
1.3.2		Define how studies with some eligibile and some ineligible participants will be handled		
1.3.3		Define unambiguous and appropriate exposures (or interventions, depending on objectives) and what the exposure will be compared against, for included studies.		

1.3.4		Define unambiguous and appropriate outcomes for inclusion of studies in the review. Keep number to a minimum; define intermediate outcomes; define acceptable outcome measures, inc. hierarchy of measures if there are several available; define timing of outcome measurement.		
1.3.5		Define unambiguous and appropriate criteria for study design, focusing on design features rather than labels, for inclusion of studies in the review		
1.3.6		Include studies irrespective of publication status	Entails grey literature search	
1.3.7		Include studies irrespective of "usable" data		
1.3.8		Unbiased restrictions on publication date and format		
1.3.9		Include studies irrespective of language	Simply removing language filters is insufficient to ensure inclusion of foreign-language research	
1.4	**Planning the review methods**			
1.4.1		Design sufficiently sensitive search which will not exclude studies which meet the inclusion criteria.		Refer to Step 2 for requirements for the search strategy.
1.4.2		Define in advance valid criteria and method for distinguishing studies at higher risk of bias from studies at lower risk of bias		Risk of bias is a fundamental concept; interested in limitations in design and conduct of included studies, which if not accounted for would result in systematic over- or underestimation of true effect size. Do we want to flag that scores and scales are not appropriate?
1.4.3		Design the methods for synthesising the included studies, i.e. qualitative and quantitative methods; assessment of heterogeneity; whater a quantitative synthesis is planned; choice of effect measure (e.g. RR, OR etc.); methods for meta-analysis; pre-defined, appropriate effect modifers for sub-group analysis of minimum number		
1.4.4		Design the "summary of findings" table		More detail is required? The reason for this must be that the summary of findings table determines data extraction requirements, for example.
1.4.5		Design and demonstrate satisfactory usability of data extraction form		This is "design and test" the data extraction form, but making it less ambiguous.
1.5	**Publishing the protocol**			I think we need this (not in MECIR)
1.5.1		Register the protocol	Enough information to show intent to conduct; not necessarily the full protocol	e.g. in Prospero. After decision on question and eligibility criteria?
1.5.2		Publish the protocol for stakeholder comment		
1.5.3		Revise protocol on stakeholder feedback		
1.5.4		Publish final version of protocol in public archive		

2. Conduct of Search Stage of Systematic Review				
Ref.	**Level of Requirement**	**Practice**	**Explanatory notes**	**Points flagged for discussion at workshop**
2.1		Search all the key databases for the field		Which ones: PubMed, EMBASE, Ovid, WoS … ?
2.2		Search appropriate national, regional and subject-specific databases	Foreign-language DB searches are essential for limiting language bias effects	
2.3		Structure search strategies as appropriate for each database. Use "AND" and "OR" as sole Boolean operators; terms for outcome and exposure only; appropriate controlled vocabulary e.g. MESH; "exploded" terms; free-text terms such as truncations, alternative spellings etc.; give consideration to designed-and-tested search filters.	Maximises sensitivity (NOT is an insensitive exclusion - better to manually screen; population can be manually screened from outcome - again, a matter of insensitivity of database search methods; ditto study designs)	
2.4		Document search process in sufficient detail to render it reproducible		
2.5		Search for grey literature	Minimise risk of publication bias	
2.6		Search within other reviews	Identify maximum amount of relevant evidence	
2.7		Search within reference lists of included studies	Identify maximum amount of relevant evidence	
2.8		Search by contacting relevant individuals and organisations	Minimise risk of publication bias, identify maximum amount of relevant evidence	
2.9		Rerun all searches within 12 months prior to publication of the review or review update	Either fully incorporate new data, or at least list studies and flag as "awaiting classification"	

3. Conduct of Selection Stage of Systematic Review				
Ref.	**Level of Requirement**	**Practice**	**Explanatory notes**	**Points flagged for discussion at workshop**
3.1		Determination of whether a study meets inclusion criteria conducted by two people working independently, with a third person settling disputes	Initial screening off title, abstract; full text review for most cases is ideal.	
3.2		Document decisions in enough detail to allow PRISMA flow chart and table of "characteristics of excluded studies"		
3.3		Collate multiple reports of the same study, treat them as a single study (do not exclude multiple reports)	Each report can contain important methodological information, therefore collate do not exclude	

4. Conduct of Data Collection Stage of Systematic Review				
Ref.	**Level of Requirement**	**Practice**	**Explanatory notes**	**Points flagged for discussion at workshop**
4.1		Collect characteristics of the included studies in sufficient detail to populate the planned "characteristics of included studies" table		Reinforces how fundamental is the planning of the "characteristics of included studies" table. Say more about it somewhere (elucidation notes?)
4.2		Extraction of **study characteristics** to be conducted by at least two peope working independently, with disagreements resolved by a third party		
4.3		Extraction of of **outcome data** to be conducted by at least two peope working independently, with disagreements resolved by a third party		
4.4		Collect and utilise the most detailed numerical data possible.		
4.5		Examine any relevant retraction statements and errata for information		
4.6		Obtain unpublished data which is missing from reports and studies		
4.7		Check accuracy of numeric data in the review		

5. Conduct of Appraisal of Limitations in Design and Conduct, and Generalisability, of Individual of Included Studies Stage of Systematic Review				
Ref.	**Level of Requirement**	**Practice**	**Explanatory notes**	**Points flagged for discussion at workshop**
5.1	**Internal Validity / risk of bias / limitations in design and conduct of included studies**			
5.1.1		Assess risk of bias per outcome rather than per study		Should we have a note on directly assessing risk of bias, as some tools (e.g. Newcastle Ottawa scale) do not necessarily do this, while other tools conflate external and internal validity assessment, and so forth?
5.1.2		Assess risk of bias in duplicate, with third party to settle disagreements		
5.1.3		Comment on likely direction and magnitude of effect of bias		Even if it is not possible to anticipate this (e.g. for lack of empirical support), comment anyway?
5.1.4		Provide appropriate explanation for judgement of risk of bias, with supporting quotes from report and study manuscripts		
5.2	**External Validity / Generalisability of findings of included studies**			There should be a way of systematising this, explicitly drawing out relevance of each PECOS domain in each individual study to the overall objective, though I am not aware of any formal methods for doing this. Regardless, systematically referring to each component seems sensible.
5.2.1				
5.2.2				
5.2.3				
???				

6. Conduct of Synthesis Stage of Systematic Review

Note: There is a general issue of conducting each step, and interpreting the results of each step (e.g. doing the meta-anaysis, assessing heterogeneity, then interpreteing the heterogeneity), then summarising that work. There is not necessarily a clear division between when one process ends and another starts. Here, the split is made between undertaking the synthesis (step 6) and interpreting and summarising the results (step 7).

Ref.	Level of Requirement	Practice	Explanatory notes	Points flagged for discussion at workshop
6.1		Combine all scales (where appropriate) into common measures of outcome, explaining how each scale has been reinterpreted in the review		
6.2		Undertake (or display) only meaningful meta-analyses, where populations, exposures, comparisons and outcomes are sufficiently similar to render the combined result meaningful		
6.3		Validly assess statistical heterogeneity (presence and extent of between-study variation) when undertaking meta-analysis		
6.4		Address missing outcome data		This generates the results for interpretation in step 7 (intepretation), but needs clarification in terms of detail
6.5		Address skewed data		This generates the results for interpretation in step 7 (intepretation), but needs clarification in terms of detail
6.6		Address risk of publication bias in the data		This generates the results for interpretation in step 7 (intepretation), but needs clarification in terms of detail
6.7		Address risk of bias in the synthesis (present analysis stratified according to summary risk of bias, or restricted to studies at low risk of bias); qualitative or quantitative approach		
6.8		Conduct subgroup analyses using a formal statistical test to compare them, following the plan in the protocol	Does not preclude use of sensible post-hoc subgroup analysis	
6.9		Test the robustness of the results using sensitivity analyses		
6.10		Perform dose-response analysis		This is for GRADE-style appraisal of strength of evidence but how should we specify it?
6.11		Assess observational studies for plausible confounding		This is for GRADE-style appraisal of strength of evidence but how should we specify it? Does it belong in stage 5 (internal validity)?
6.12		Describe strength of association between exposure and outcome		This is for GRADE-style appraisal of strength of evidence but how should we specify it?

7. Conduct of Interpretation and Summarising Stage of Systematic Review				
Ref.	**Level of Requirement**	**Practice**	**Explanatory notes**	**Points flagged for discussion at workshop**
7.1		Interpret subgroup analyses (do not selectively report), without placing undue emphasis on particular findings.		
7.2		Take into account internal validity (risk of bias - direction and magnitude) when interpreting results		
7.3		Interpreting external validity (generalisability) of the evidence base: ???		
7.4		Interpreting consistency: Take into account statistical heterogeneity and explainable variation between studies when interpreting results, through the sub-group and sensitivity analyses.		
7.5		Interpret the precision of the result of the synthesis.	Interpret a statistically non-significant P-value as a finding of uncertainty (not of no effect) unless confidence intervals are sufficiently narrow to rule out an important magnitude of effect	Prevents absence of evidence of effect being interpreted as evidence of absence of effect.
7.6		Magnitude of effect (for observational evidence)		???
7.7		Plausible confounding (for observational evidence)		???
7.8		Dose-response relationship		???
7.9		Interpret the potential effects of reporting and publication biases (e.g. missing outcome data, unpublished studies etc.) on the results of the review / meta-analysis		
7.10		Include a "summary of findings" table		
7.11		Summarise the quality of the evidence into an appropriate overall statement of confidence in the results of the synthesis [for GRADE: justifying all assessments and rationale for upgrade and downgrade and no-change decisions]		GRADE is an option but there may not be consensus on this as best method.

8. Conduct of Drawing Conclusions Stage of Systematic Review				
Ref.	**Level of Requirement**	**Practice**	**Explanatory notes**	**Points flagged for discussion at workshop**
8.1		Draw implications based only on findings from the synthesis of studies included in the review	Don't draw conclusions on evidence which has not been systematically reviewed	
8.2		Describe implications for research based on PECOS formula	So recommendations are tightly associated with how research problems in EH should be formulated	
8.3		Describe policy implications scenarios rather than making specific policy recommendations	Because the review has dealt with the evidence only, not e.g. people's attitudes towards the implied problems which motivated the review	