Useful Evidence Synthesis Methods in Early HTA

Ottawa Methods Centre,
Clinical Epidemiology Program
Ottawa Hospital Research Institute (OHRI)

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

Clinical Research at OHRI

Improving patient care at TOH and beyond

- OHRI has developed a world-class Clinical Epidemiology Program
- Includes >40 Scientists dedicated to practice-changing research
- >600 clinical investigators, staff and trainees
- Development of the Ottawa Methods Centre has further enabled and enhanced the quality of research at The Ottawa Hospital (TOH)/ OHRI
- Co-location of >75% OF Scientists and staff situated at the Centre for Practice-Changing Research
- Ottawa Methods Centre – is home to our Knowledge Synthesis Group (team of 20+ experience research personnel dedicated to production of systematic reviews and related methodologies)

Recent HTA initiatives at OHRI/TOH

- TOHTAP: The Ottawa Hospital Technology Assessment Program
- MaRS EXCITE Program (designated Methods Centre)

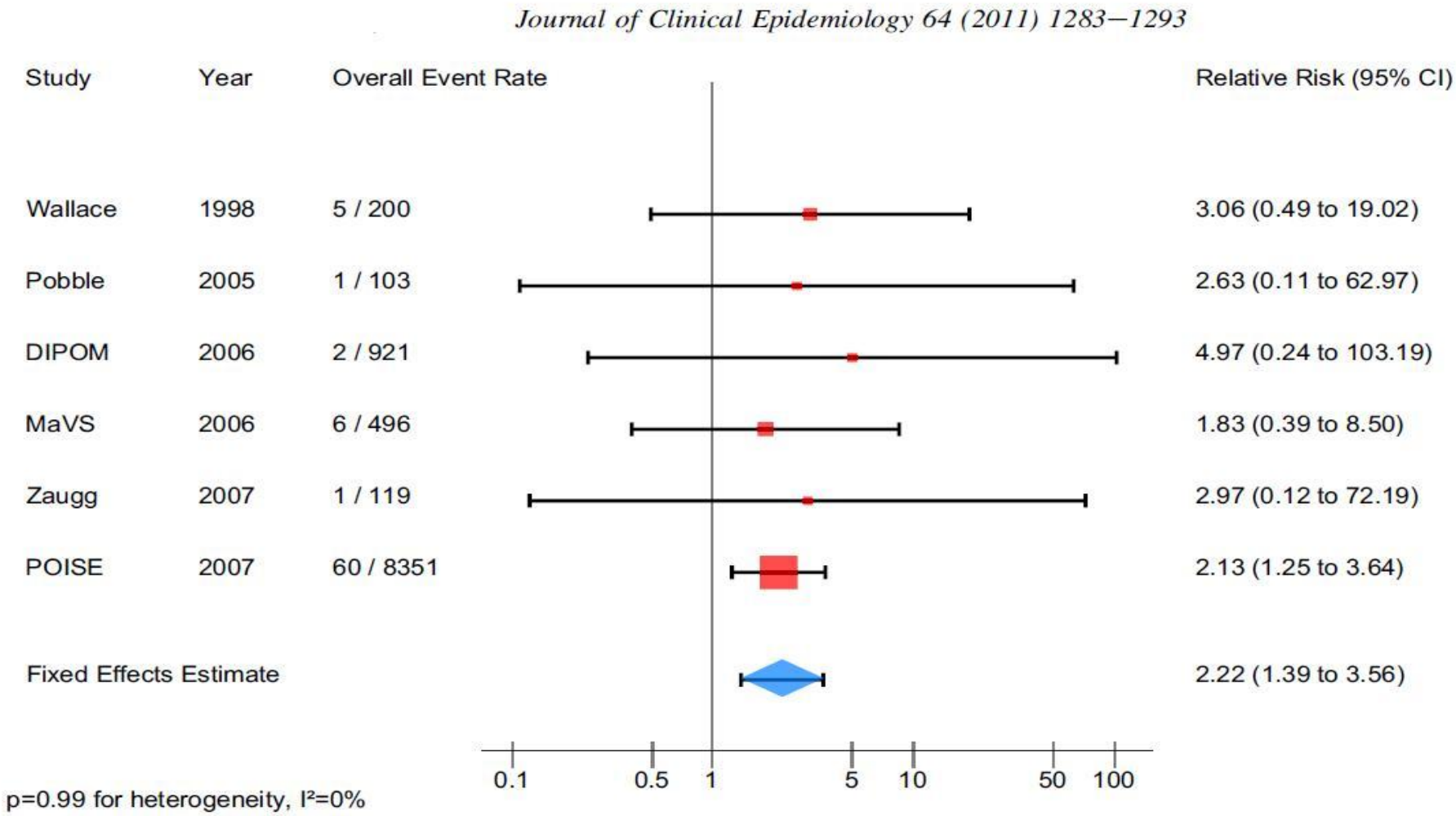
Other initiatives at OHRI (KSG Group)

- Rapid Reviews portfolio:
  - TOHTAP
  - Cochrane Innovations Rapid Response
  - Rapid reviews for requesting clients
- Drug Safety and Evaluation Network designated Network Meta-Analysis Collaborating Centre (CIHR/Health Canada)
- Updating methodology – signal detection
- Cochrane Bias Methods Group
- CONSORT/PRISMA initiatives

Decision-making in Health

- Evidence-based – systematic reviews
- Stakeholder involvement and patient-centredness
- Determinants
  - Quality of Evidence
  - Uncertainty about the balance between desirable and undesirable effects
  - Uncertainties in values and preferences
  - Uncertainties whether the technology represents wise use of resources.
  - *Implementation and uptake barriers*

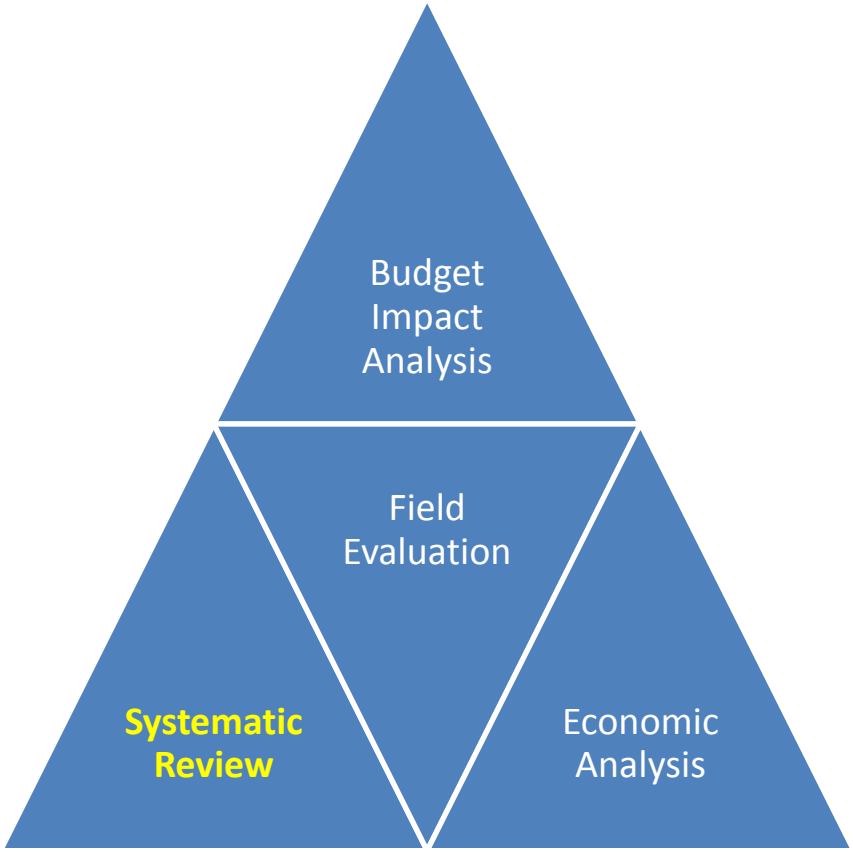
Meta-analysis of beta blockers in noncardiac surgery -- outcome, stroke



Determinants of the Quality of Evidence

- Internal validity/risk of bias
- Applicability in terms of patient, intervention, comparator and patient-centredness of outcomes (i.e. directness or indirectness of evidence) and indirectness of analysis
- Consistency/inconsistency of evidence
- Imprecision
- Publication bias
- Others (dose-response, large magnitude, residual confounding underestimates true effect)

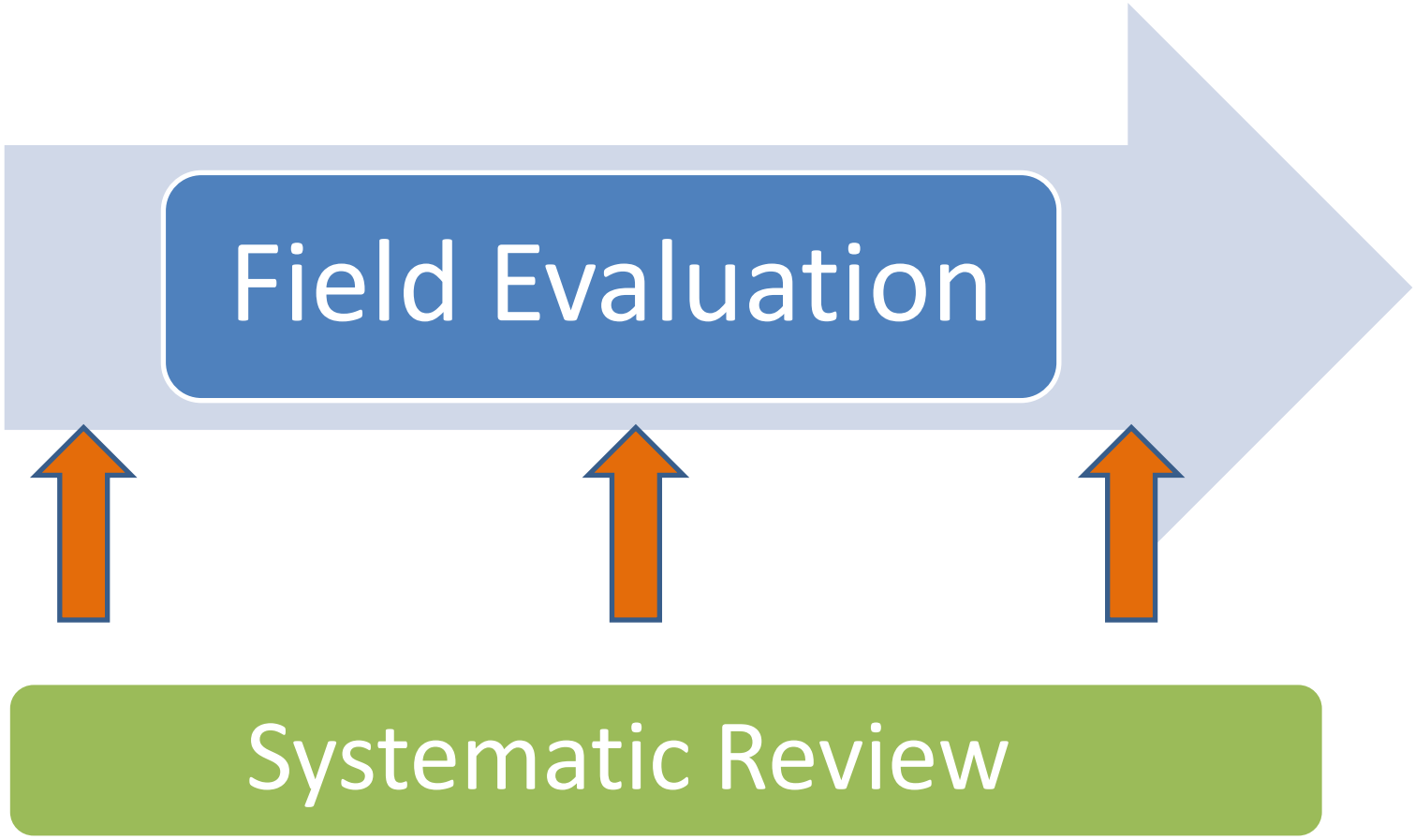
MaRS EXCITE Package



Systematic Reviews in Early HTAs

- Objectives
  1. Benchmarking or clinical potential assessment in the translational phase – to provide literature review of technologies currently in use to inform:
     - Efficacy/effectiveness,
     - Safety, and
     - Costing data
  2. To synthesize the current evidence base estimating effectiveness and safety of the new technology when compared with those in current use
  3. To inform:
     - Design of the prospective field evaluation, including which outcomes to measure, and
     - Economic analyses

Iterative vs. Linear Approach



Practical Issues

Because focus is on emerging technologies in the pre-market phase, we may be faced with limitations when conducting the evidence synthesis:

1) For emerging technologies, body of evidence may be immature at point of evaluation (sparse evidence impacting its quality)

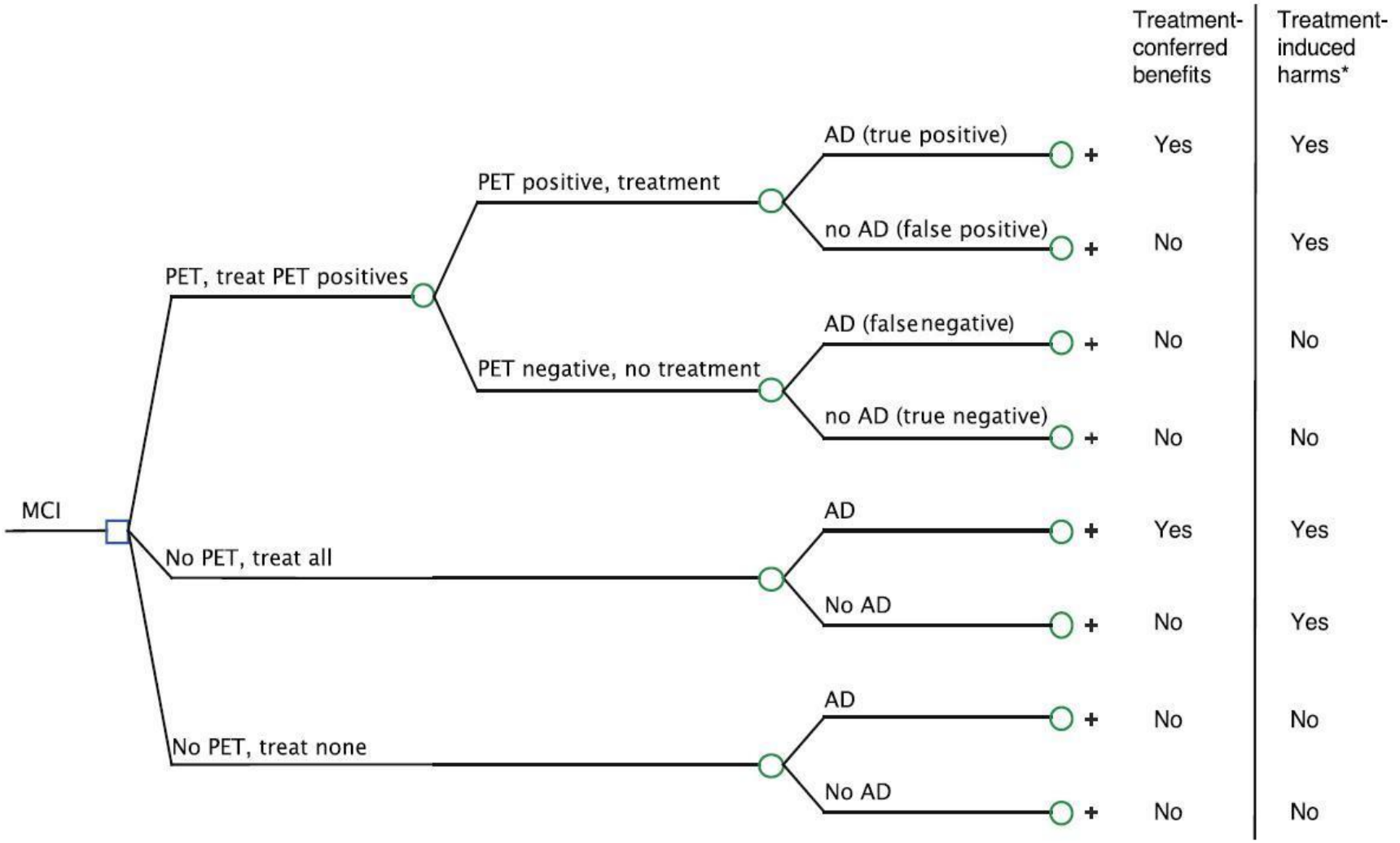
2) Similar/comparator technologies - established literature base (plethora of evidence)

3) Conditions encompassed by the technologies will also impact the fluidity of the evidence base

Immature evidence base

- Asking the right question – contextualizing, Analytic Framework and Key Informant input
- Searching – all data from the industry, preferably a registry of IPD
- Screening – flexible study design, population and outcome eligibility criteria
- Analysis
  - Individual participant data meta-analysis - reduced risk of reporting bias (longer follow-ups, more outcomes), consistent eligibility criteria (excluded can be included), accounting for missing data and overlapping participants, appropriate adjustments, subgroup effects.
  - Beyond standard meta-analysis (pair-wise comparisons)
  - Indirect comparison or network meta-analysis
  - Risk adjusted meta-analysis -- Combining RCTs and Observational evidence (Shrier I et al. Am J Epidemiol, 2007)
  - Multiparameter synthesis (decision modelling) -- The approach is Bayesian, focuses on uncertainty in the parameters rather than the data, and involves Markov chain Monte Carlo simulation from a joint posterior distribution. Example, effectiveness of a diagnostic test.

Management options for mild cognitive impairment

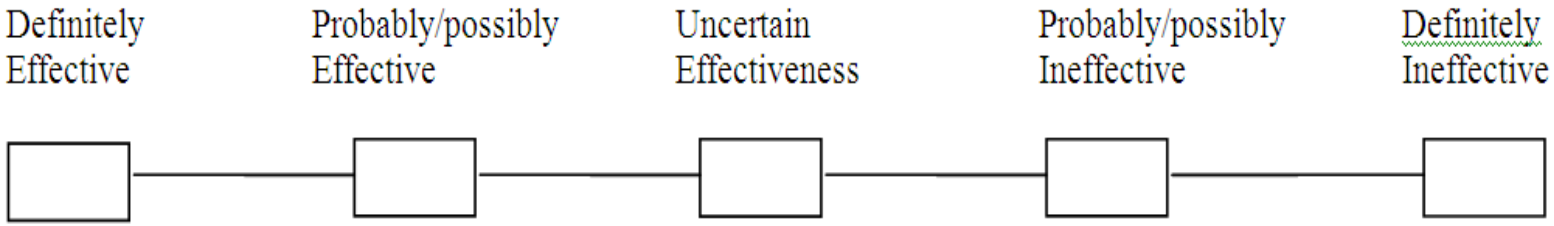


Immature evidence base – surveillance and updating

- Also, because the immature evidence will be rapidly evolving, systematic reviewers of emerging technologies should:
  - Establish a means of surveillance of emerging evidence (regular monitoring of trial registries, alerts issued by regulatory authority and relevant literature databases) to evaluate the currency of previous findings
  - Employ methods to detect signals of change in evidence. For example the Ottawa-RAND approach (which, besides qualitative signals includes the forward cumulative meta-analysis for quantitative signals) and the *new participant ratio* (the ratio of the actual number of participants in new studies to the predicted number required to obtain statistical significance for null meta-analyses) of Barrowman et al.
  - Be cognizant of changes required in their SR protocol as a results of possible changes in endpoints and study design of interest – technology evolution and improvement

Updating Signal Detection

- Expert opinion
- Qualitative signals (pivotal trial)
  - Potentially invalidating change in evidence (opposing findings, substantial harm, superior new intervention)
  - Major change in evidence (changes short of opposing findings, clinically important expansion of treatment, important caveat – important subgroup effect, way in which treatment is delivered, sustainability of evidence, new harms that do not undermine the use altogether), opposing findings from a nonpivotal trial)



Updating Signal Detection

- Quantitative signals
  - Change in effect size of at least 50%
  - Change in Statistical Significance

Fixed Effects update					Logic											
									Line of effect crossed?			Size of Δ ≥50%?		Pt estimate = sig diff	
RR	95%CI low	95%CI high	Old CI (high-low)	New CI (high-low)	New/Old CI	New/Old RR	z	borderline p value?	Lower	Upper	Robust	CI width	Pt estimate	z	
0.910	*0.820*	*1.030*	*0.21*	*NA*	*NA*	*NA*	*-1.621413*	*no*	*NA*	*NA*	*NA*	*NA*	*NA*		
0.901	0.805	1.009	0.21	0.2039026	0.970965	*0.990152*	-1.808962	no	no	no	no	no	no	0.120898	no
0.886	0.795	0.987	0.21	0.1923324	0.915868	*0.973341*	-2.194641	no	no	yes	yes	no	no	0.336718	no
0.897	0.811	0.994	0.21	0.1830113	0.871482	*0.986157*	-2.084364	no	no	yes	yes	no	no	0.178762	no
0.902	0.836	0.973	0.21	0.136753	0.651205	*0.990734*	-2.680449	no	no	yes	yes	no	no	0.133298	no

Mature evidence base - established

- Perhaps useful to consider ways to simplify the systematic review process vs. starting de novo. For example,

  A. Evidence Mapping:

  - Term often used synonymously with **'scoping review'**
  - At a general level, an overview of available evidence underpinning a research area that describes the volume, nature, and characteristics of the available literature
  - Tends to address broader topics vs. narrow questions
  - Usually guided by requirement to find all relevant literature regardless of study design

Mature evidence base – est. Continued...

B. Rapid Reviews (6-12 weeks):

- An abbreviated and accelerated version of current systematic review methods with certain concessions made in relation to the systematic process in order to accommodate expedited turnaround time
- Although not intended to replace a full systematic review, rapid review intended to retain transparency to ensure replication, preference for highest quality studies
- May include both primary studies and relevant systematic reviews, HTAs, and/or clinical practice guidelines
- In addition to a narrative synthesis, meta-analysis conducted if deemed appropriate

Mature evidence base – est. Continued…

C. Overview of Existing Systematic Reviews

- New approach to summarizing evidence, synthesizing results from multiple systematic reviews in a single, useful document
- Overviews identify high-quality, reliable systematic reviews and explore consistency of findings across reviews
- Particularly important in areas with overlapping review
- More efficient approach versus diving immediately into the primary literature

THANK YOU!