How to reach consensus for integration of randomized and non-randomized studies of interventions (RWE) into next-generation health guidelines

EAACI is leading the way towards a sustainable management programme for allergy and asthma ensuring better health and outcomes at a lower cost

Current landscape

Adaptation processes have been increasingly used to develop clinical guidelines, especially under the pressure to incorporate real-world data (RWD) such as data from registries, electronic health records or patient generated data.

This is believed to facilitate the implementation of the guidelines.

However, there is confusion about what RWE is and how it can be generated and integrated in evidence to decision processes

Case study: EAACI Guidelines for the use of biologicals in severe asthma

"Is the treatment with biologicals (i.e., benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) efficacious and safe for patients with uncontrolled severe eosinophilic asthma?"

"Is treatment with benralizumab, dupilumab and omalizumab efficacious and safe for patients with allergic asthma?"

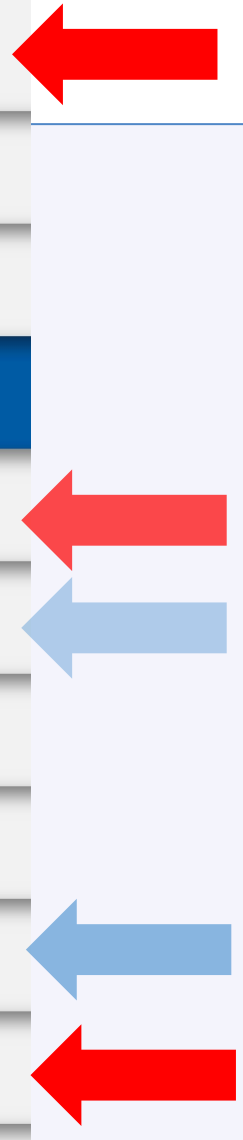
"Is the treatment with dupilumab efficacious and safe for patients with severe asthma?"

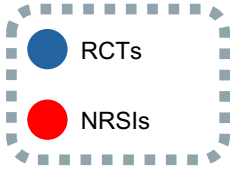
Agache I et al. Allergy. 2021 ;76(1):14-44

Methodology
Separate systematic reviews on eosinophilic asthma (benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab), allergic asthma (benralizumab, dupilumab, omalizumab) and severe T2 asthma (dupilumab) were conducted to inform the recommendations
A GRADE SOF table was provided for each PICO question. The quality of evidence was evaluated based on GRADE quality assessment criteria
The quality of evidence for each outcome was rated as high, moderate, low or very low.
The GDG framed a separate cost-effectiveness question to assess the economic impact of the biologicals versus standard of care
The criteria in the EtDs require different types of evidence to answer the relevant question including observational evidence and priority setting surveys
In support of formulated recommendations, the GDG performed narrative reviews collecting evidence on phase IV and NRSI for the clinical questions not addressed by the SRs

GRADEpro

1. **Problem**
   Is the problem a priority?
2. **Desirable Effects**
   How substantial are the desirable anticipated effects?
3. **Undesirable Effects**
   How substantial are the undesirable anticipated effects?
4. **Certainty of evidence**
   What is the overall certainty of the evidence of effects?
5. **Values**
   Is there important uncertainty about or variability in how much people value the main outcomes?
6. **Balance of effects**
   Does the balance between desirable and undesirable effects favor the intervention or the comparison?
7. **Resources required**
   How large are the resource requirements (costs)?
8. **Certainty of evidence of required resources**
   What is the certainty of the evidence of resource requirements (costs)?
9. **Cost effectiveness**
   Does the cost-effectiveness of the intervention favor the intervention or the comparison?
10. **Equity**
    What would be the impact on health equity?
11. **Acceptability**
    Is the intervention acceptable to key stakeholders?
12. **Feasibility**
    Is the intervention feasible to implement?





Evidence to Decision Criteria

- Randomized designs applicable to many of these criteria
- Non-randomized designs definitely for baseline risk, priority of the problem

The goal is to go further and do better

Case study: EAACI Guidelines for the use of biologicals in severe asthma

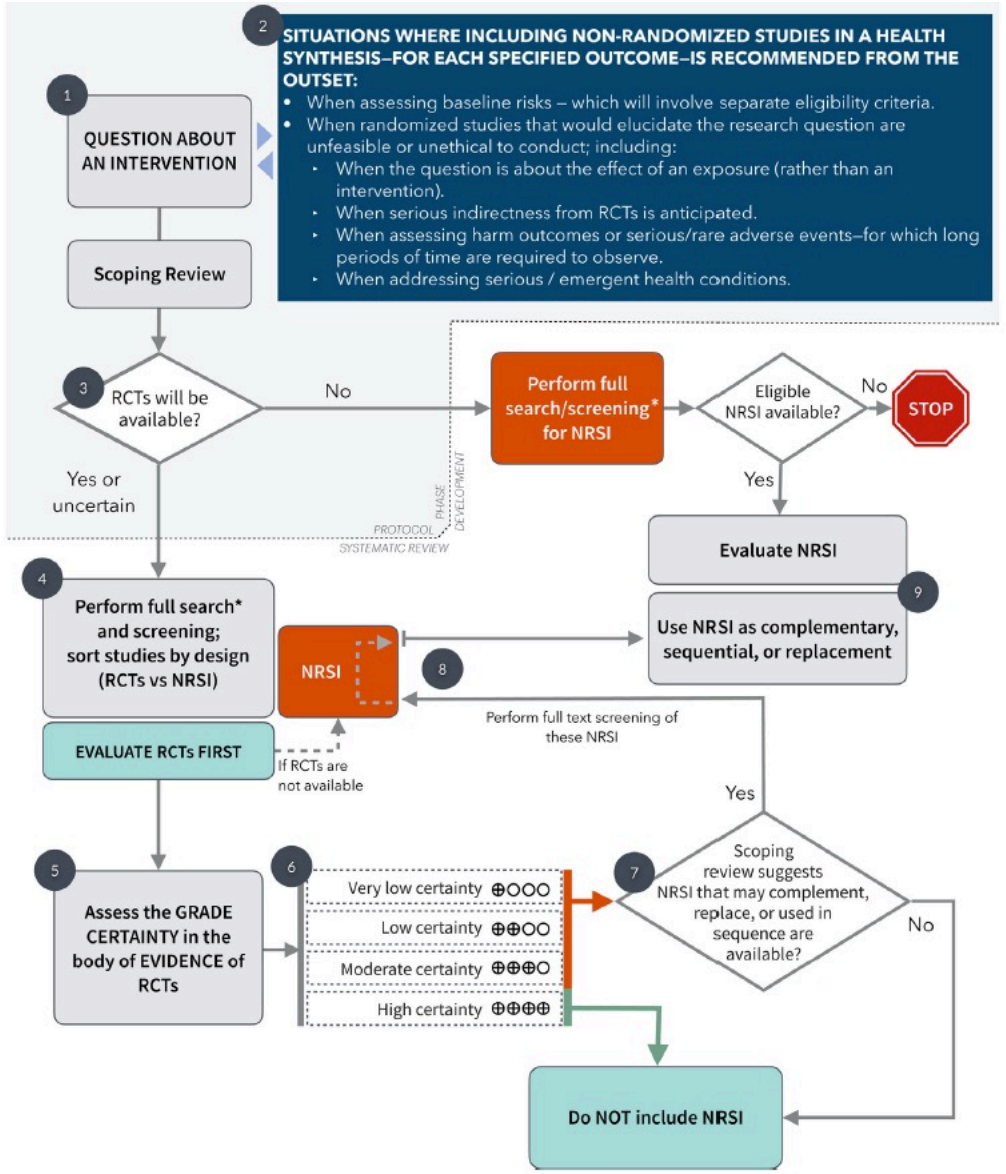
Formulating the recommendations
The recommendations followed the data included in the EtD tables and took into consideration 1. the balance of desirable and undesirable consequences 2. quality of evidence
3. patients' values and preferences, 4. feasibility, and acceptability of various interventions 5. use of resources paid for by third parties, equity considerations 6. impacts on those who care for patients 7. public health impact
The benefit- harm ratio was the key driver for formulating a strong or a conditional recommendation
However, the underlying values and preferences played a key role as well
The perspective chosen when formulating recommendation was mainly that of the HCPs and of the patient, although the healthcare system perspective was also evaluated
Recommendation is provided per product, per subgroups and per outcomes

How should these be weighted in the decision process?

Perspective of the guideline/implementation setting…

Agache I et al. Allergy. 2021 ;76(1):14-44

New GRADE methodology



Cuello-Garcia CA, et al. J Clin Epidemiol. 2022;142:200-208

EAACI-REG initiative

- Critically appraise the current guidelines adaptation processes
- Align on the “quality threshold” of NRSI
- Discuss the incorporation of NRSI into EtD frameworks
- Specific recommendations for using NRSI in the context of randomized trials

Applies to:

Health guidelines
Regulators
Health policy

2 WS (March and October 2023)

- All major allergy and respiratory international societies
- Regulators: EMA, FDA, PEI, NICE
- Patient organisations
- Guidelines developers: Guidelines International Network (GIN), GINA, ARIA, GOLD

How to position NRSI

Non-randomized studies (NRS)

as COMPLEMENT

Additional information on:
- Whether or not an intervention works in different populations
- Different estimates of baseline risk

RCT → CoE in X population

NRS → CoE in Y population

used in SEQUENCE

NRS may provide information on outcomes not (yet) obtained from RCTs:
- Rare / long-term outcomes that are not available yet from RCTs

RCT + NRS → CoE

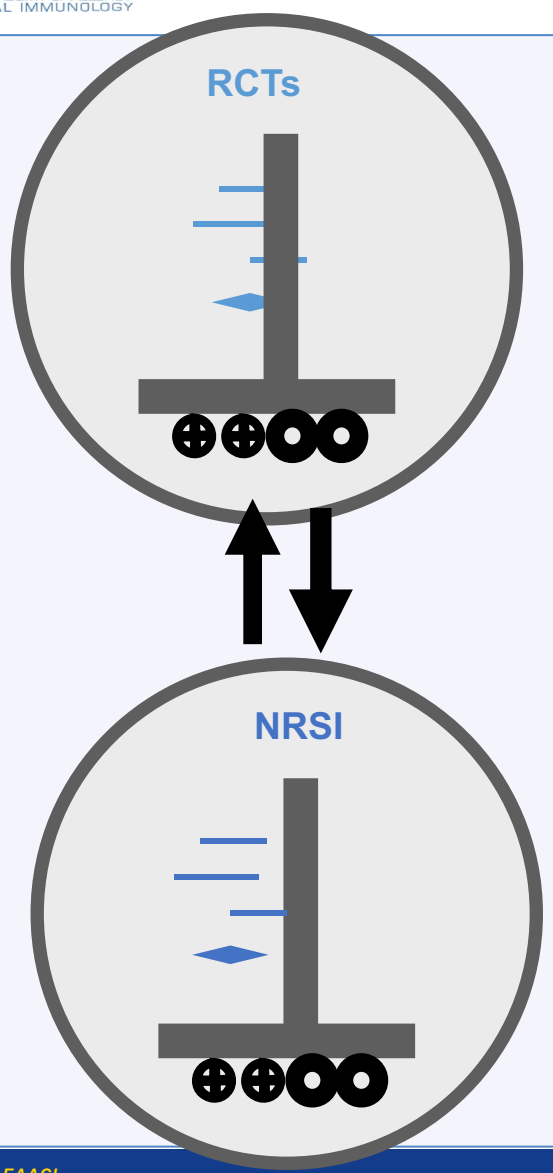
as REPLACEMENT

NRS are used instead of RS:
- NRS provide the best available evidence due to the absence of RCTs, or…
- Higher CoE in NRS substitute that from RCTs

NRS → CoE

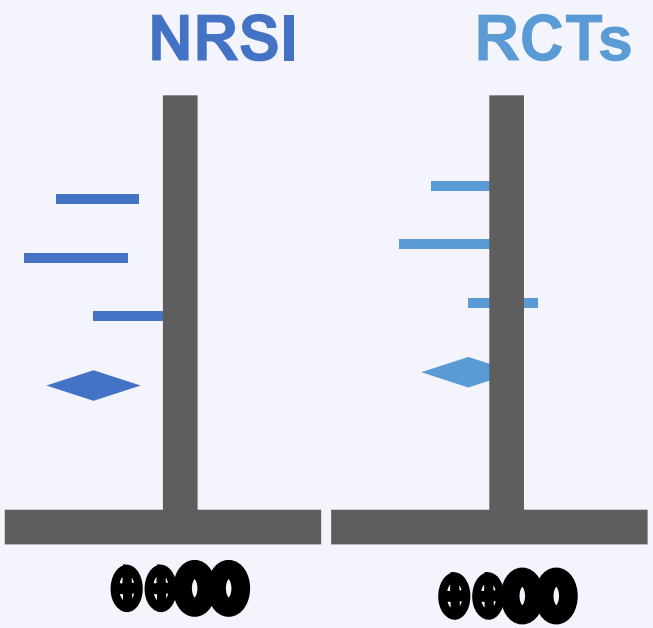
Schünemann 2013

How to position NRSI

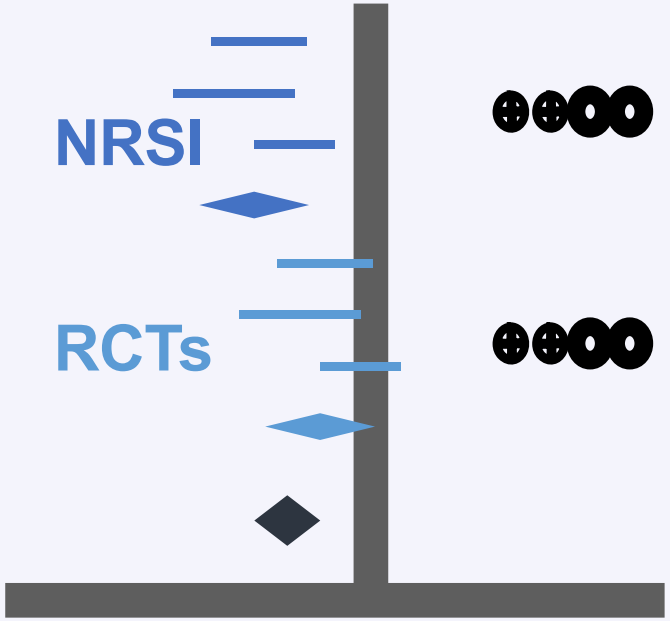


- Do they agree?
- What is the CoE on each?
- Which GRADE domains are affected?
- What is the effect of the CoE in one over the other
- What is the final effect on recommendations/decisions?
- How to use/present them?

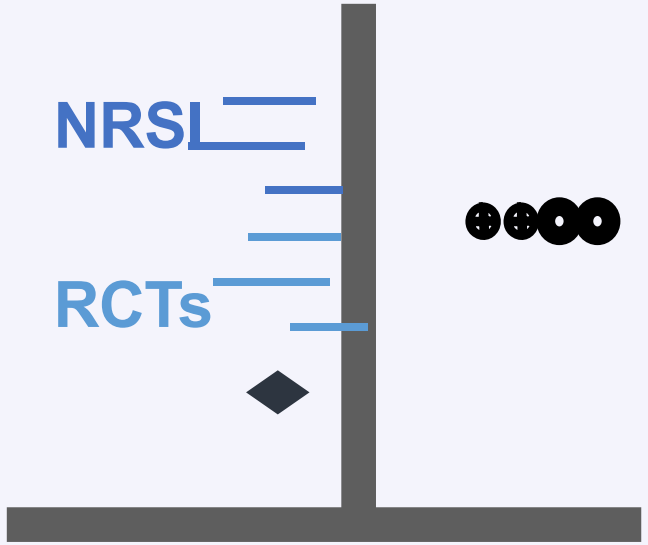
How to use/present them



Keep them separated?



Keep them together?



Combine (pool effects)?

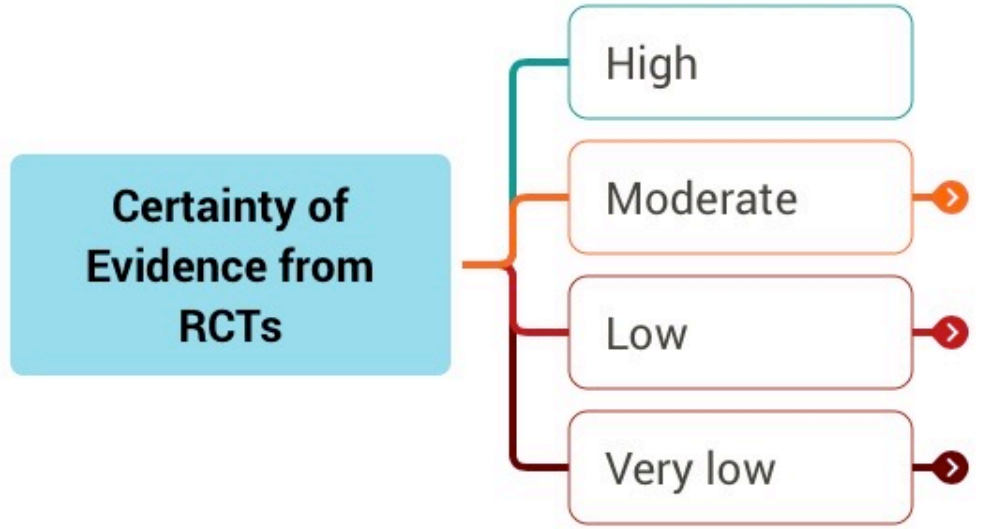
Strategy for a pragmatic approach to integrating RCT and NRSI evidence

1. Use the RCTs as starting point

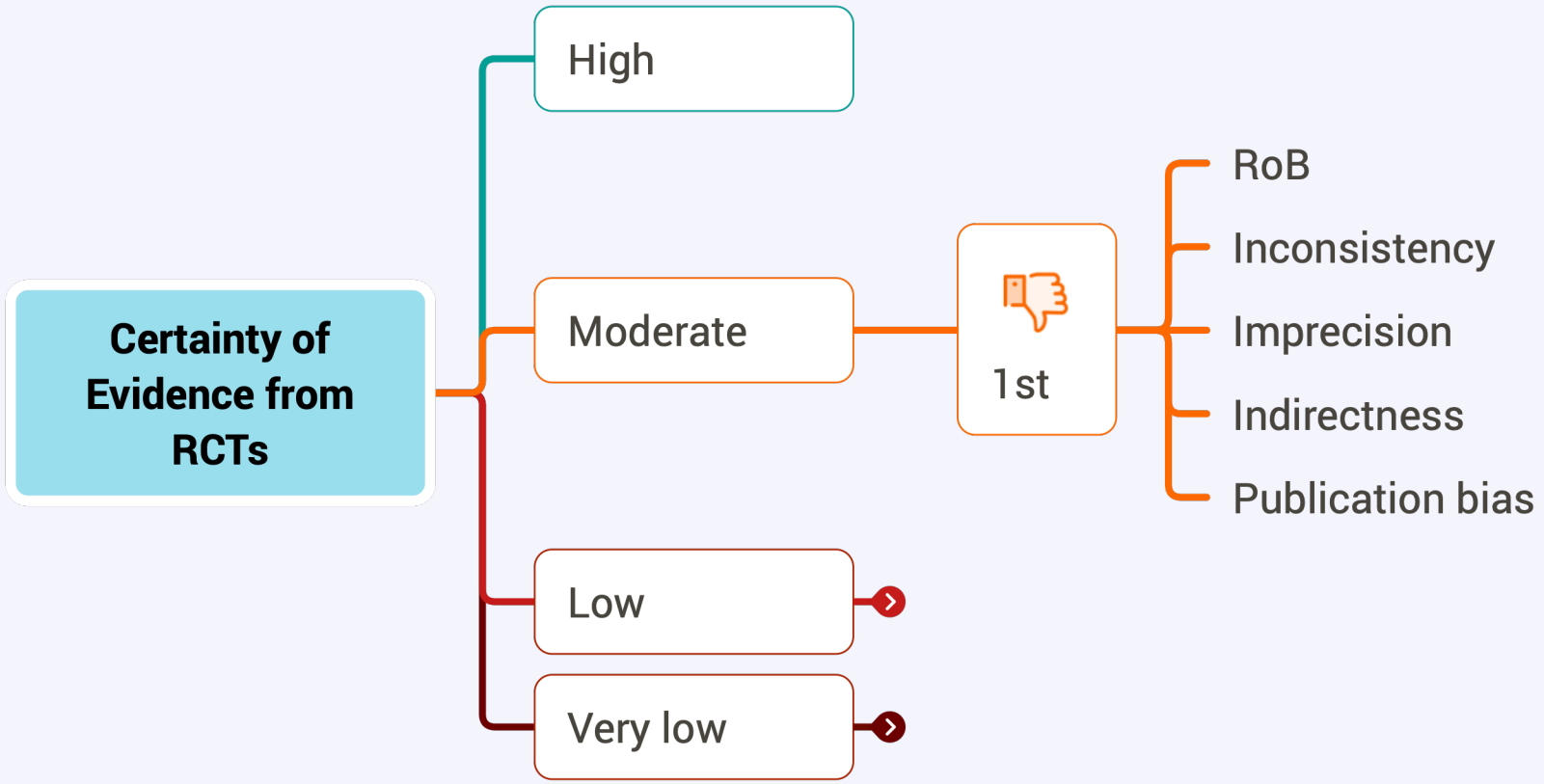
2. What is the CoE in the RCTs?

3. Then, what is the CoE in NRSI?

4. Can NRSI help ameliorate uncertainty in RCTs as replacement, sequential or complementary evidence – **the concept of congruency**

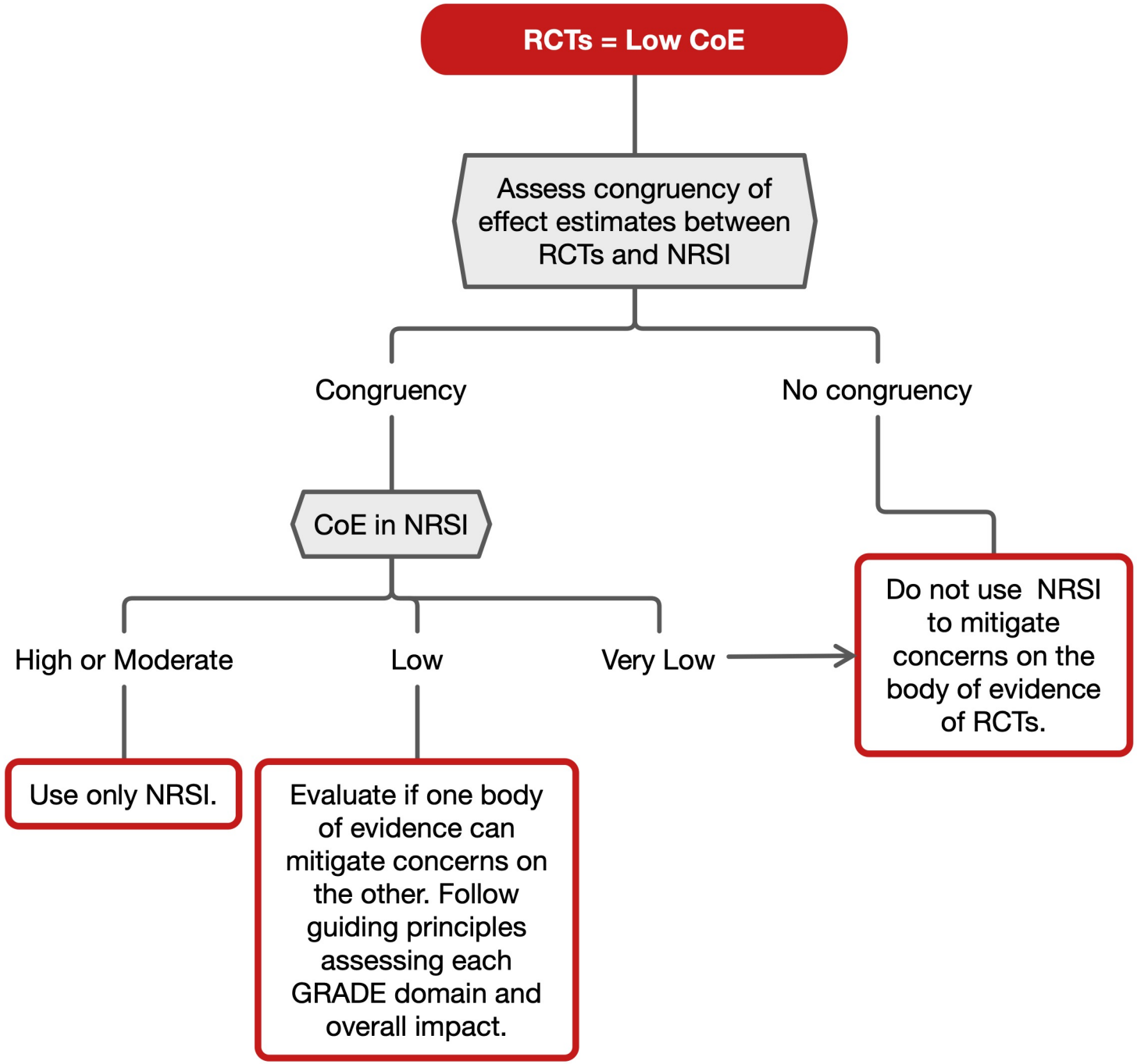


Strategy for a pragmatic approach to integrating RCT and NRSI evidence

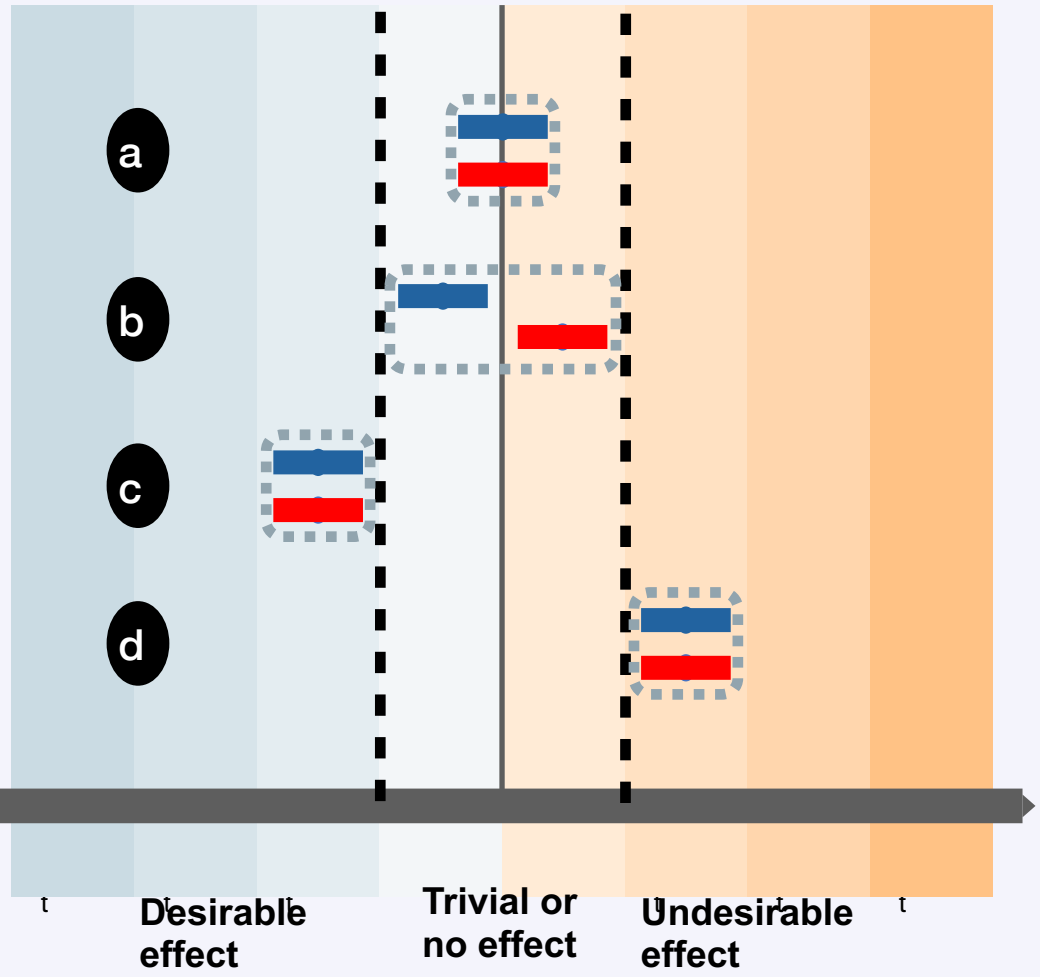


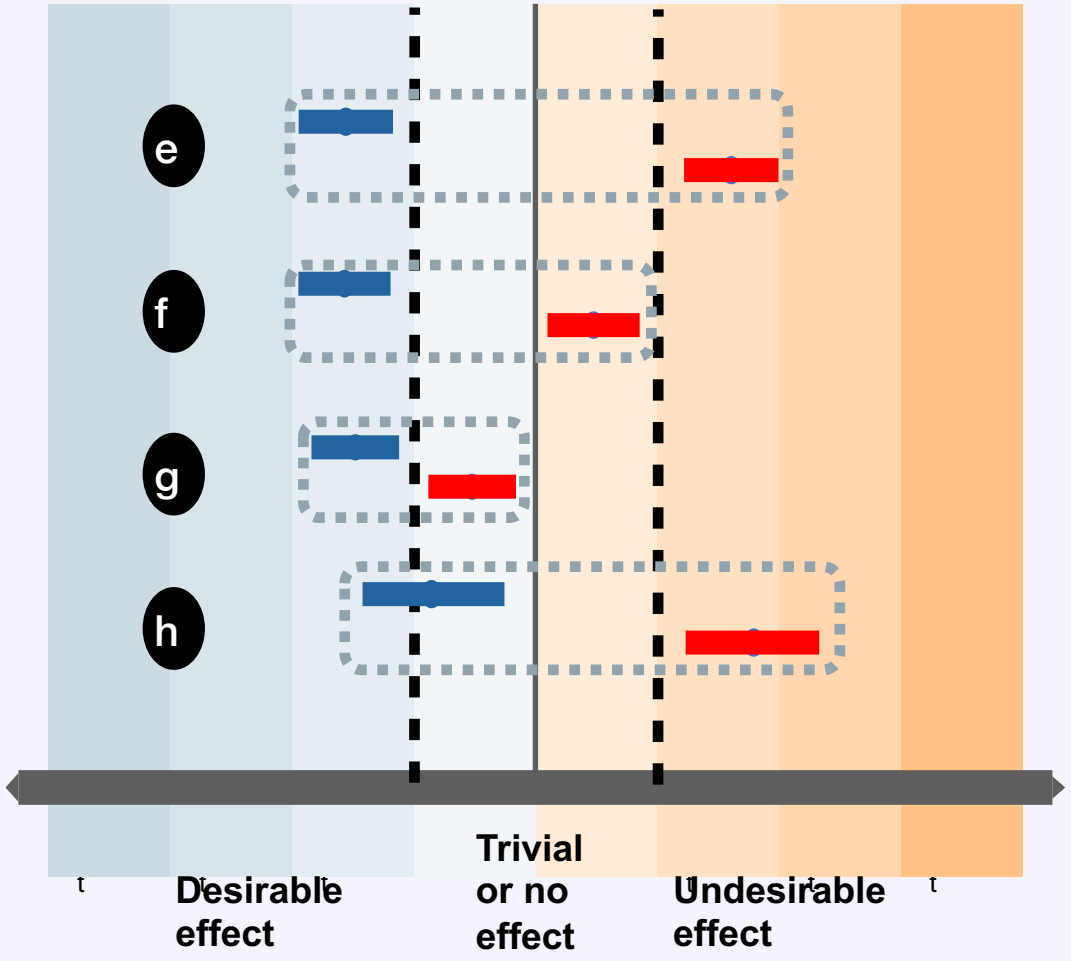
Assess which domain is affected.

Can NRSI help ameliorate the uncertainty?

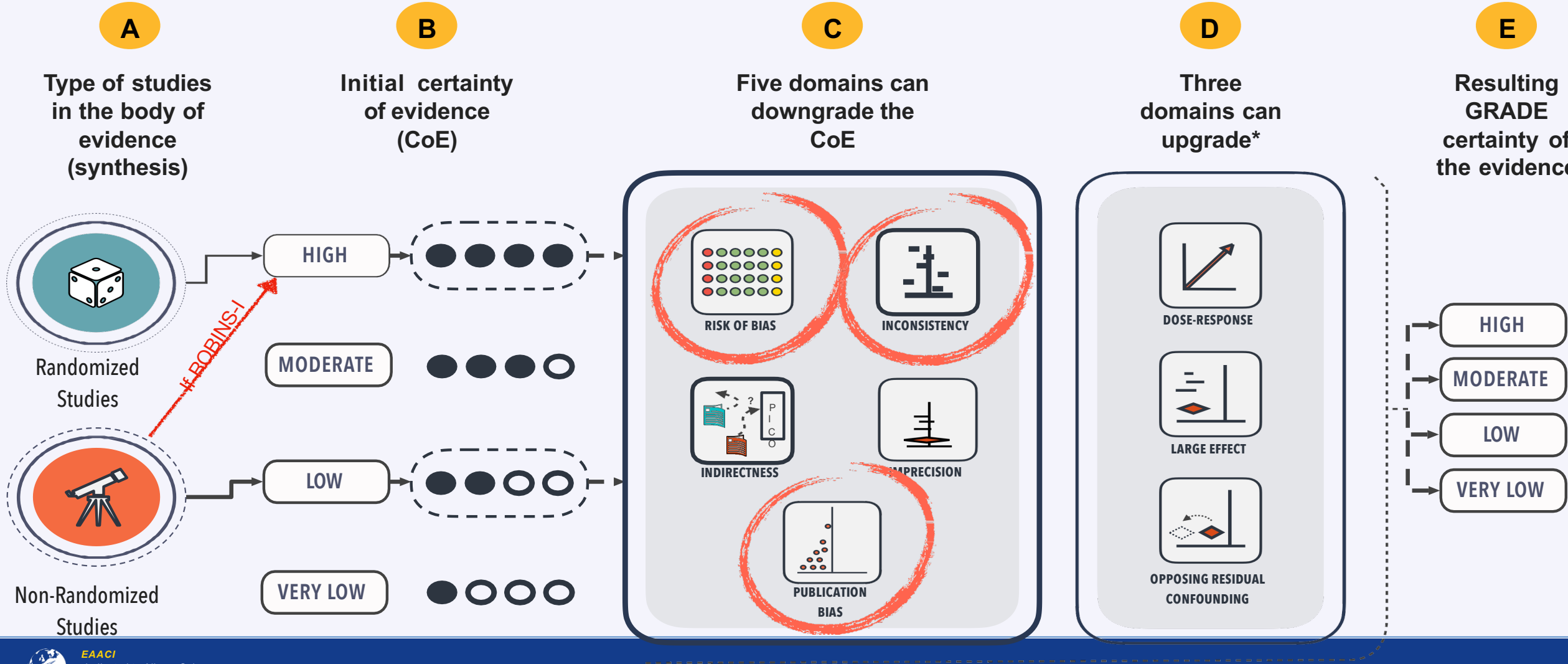

RCTs = Low CoE
Assess congruency of effect estimates between RCTs and NRSI
Congruency
No congruency
CoE in NRSI
High or Moderate
Low
Very Low
Do not use NRSI to mitigate concerns on the body of evidence of RCTs.
Use only NRSI.
Evaluate if one body of evidence can mitigate concerns on the other. Follow guiding principles assessing each GRADE domain and overall impact.

Congruency and thresholds





Has the study been registered affects risk of bias, inconsistency and publication bias



Next steps

1. Publish a detailed methodological guidance incorporating feedback from all stakeholders

2. Simplify to a pragmatic approach for all end-users

3. Add a glossary of terms to support the guidance

4. Develop educational modules on how to use the new methodology