Implications for Guideline Developers/Users: Guideline developers can use GRADE and these methods when there is no evidence or low/very low quality evidence from RCTs.

Methods The authors used an iterative process of suggesting guidance and obtaining feedback to arrive at a proposed approach.

Results For participants with missing data, systematic reviewers can use a range of plausible assumptions in the intervention and control arms. Extreme assumptions include ‘all’ or ‘none’ of the participants had an event, but these assumptions are not plausible. Less extreme assumptions may draw on the incidence rates within the trial (e.g., same incidence in the trial control arm) or in all trials included in the meta-analysis (e.g., highest incidence among control arms of all included trials). The primary meta-analysis may use either a complete case analysis or a plausible assumption. Sensitivity meta-analyses to test the robustness of the primary meta-analysis results should include extreme plausible assumptions. When the meta-analysis results are robust to extreme plausible assumptions, inferences are strengthened. Vulnerability to extreme plausible assumptions suggests rating down confidence in estimates of effect for risk of bias.

Conclusions This guide proposes an approach to establishing confidence in estimates of effect when systematic reviewers are faced with missing participant data for binary dichotomous outcomes in randomised trials.

Background Systematic reviewers including all randomised participants in their meta-analyses need to make assumptions about the outcomes of those with missing data.

Objectives To provide systematic review authors with guidance on dealing with participants with missing data for dichotomous outcomes.

Methods The authors used an iterative process of suggesting guidance and obtaining feedback to arrive at a proposed approach.

Results For participants with missing data, systematic reviewers can use a range of plausible assumptions in the intervention and control arms. Extreme assumptions include ‘all’ or ‘none’ of the participants had an event, but these assumptions are not plausible. Less extreme assumptions may draw on the incidence rates within the trial (e.g., same incidence in the trial control arm) or in all trials included in the meta-analysis (e.g., highest incidence among control arms of all included trials). The primary meta-analysis may use either a complete case analysis or a plausible assumption. Sensitivity meta-analyses to test the robustness of the primary meta-analysis results should include extreme plausible assumptions. When the meta-analysis results are robust to extreme plausible assumptions, inferences are strengthened. Vulnerability to extreme plausible assumptions suggests rating down confidence in estimates of effect for risk of bias.

Conclusions This guide proposes an approach to establishing confidence in estimates of effect when systematic reviewers are faced with missing participant data for binary dichotomous outcomes in randomised trials.
NONRANDOMISED STUDIES AS A SOURCE OF COMPLEMENTARY, SEQUENTIAL OR REPLACEMENT EVIDENCE FOR RANDOMISED CONTROLLED TRIALS IN SYSTEMATIC REVIEWS AND GUIDELINES

OBJECTIVES To offer conceptual and practical guidance to those judging directness and using research evidence from non-randomised studies (NRS).

Methods We used a literature review and feedback from participants of a workshop funded by the Agency for Healthcare Quality and Research and the Cochrane Collaboration.

Results Guideline developers can use NRS as a source of complementary, sequential or replacement evidence for randomised controlled trials (RCTs) by focusing on judgements about the population, intervention, comparison and outcomes. They use NRS to complement judgements about inconsistency, the rationale and credibility of subgroup analysis, baseline risk estimates for the determination of absolute benefits and downsides, and the directness of surrogate outcomes. Authors use NRS as sequential evidence to provide evidence when the evidence from RCTs is insufficient (e.g. long-term harms). Use of evidence from NRS may also replace RCT evidence when RCTs provide indirect evidence but NRS provide overall higher quality, direct evidence. We developed a simple tool and algorithm to make judgements about indirectness more transparent.

Discussion These judgements need to be made in the context of other quality of evidence domains.

Implications for Guideline Developers/Users The transparency of the framework will support interaction with those making health care decision and policy.

GUIDELINE IMPLEMENTABILITY APPRAISAL (GLIA) IN US NATIONAL GUIDELINES

Objectives To explore to what extent using GLIA during the development process would result in guideline revision before publication.

Methods The development process of the European hyponatremia guideline -coordinated by European Renal Best Practice - was our study context. Using the GLIA web-tool, eleven clinicians and methodologists from eight countries individually appraised 27 guideline statements. In a face-to-face consensus meeting, four GLIA panelists and one guideline development group (GDG) representative summarised potential implementability issues. The GDG discussed these issues, and revised the guideline if deemed necessary.

Results We identified 33 issues; the GDG accepted 26 as potentially hampering implementability. This resulted in statement reformulation with (n=5) and without (n=10) influencing clinical content, adding or (re)moving entire statements (n=8), and adding information to tables or rationales (n=3). The majority of issues declined by the GDG (n=7) addressed clinical situations that were covered elsewhere in the guideline or were considered to be uncommon.

Discussion Using GLIA during the development process resulted in a revised guideline. We felt that GDG representation in the consensus meeting optimize our appraisal process.

Implications for Guideline Developers/Users Guideline organizations may want to consider incorporating GLIA into their development process. This may raise GDGs’ awareness of potential implementability issues, and allow revision of the guideline accordingly prior to publication. Future research should explore the effect of GLIA-based revisions on implementability as assessed by guideline users.