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Assessing risk of bias in non-randomized studies of exposures: ROBINS-E tool

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…on behalf of the ROBINS-E development team, led by Julian Higgins, Rebecca Morgan, Andrew Rooney, Kyla Taylor, Kristina Thayer and Jonathan Sterne

ROBINS-E tool

Welcome to the website for the ROBINS-E tool (Risk Of Bias In Non-randomized Studies - of Exposures)

Version 20 June 2023

We are pleased to make available a full version of ROBINS-E for follow-up studies.

A Word template is available for completing the tool.

The tool is also available in this ROBINS-E Excel implementation.

About ROBINS-E

Observational epidemiologic studies are key to evaluation of the effects of exposures (including environmental, occupational and behavioural exposures) on human health, because evaluation through randomized controlled trials (RCTs) is not usually feasible. Even when RCTs have been conducted, the evidence that they provide may suffer from limitations. Therefore, the best evidence to guide policymakers and the public will be from observational studies that implement appropriate methods to minimize the risk of bias in their results, and from systematic reviews of such studies.

The **Risk Of Bias In Non-randomized Studies - of Exposure** (ROBINS-E) tool provides a structured approach to assessing the risk of bias in observational epidemiological studies. ROBINS-E is designed primarily for use in the context of a systematic review. It should contribute to a thorough examination of the strength of evidence about the presence of, and/or nature of, a potential effect of an exposure on an outcome. A key feature of the ROBINS-E approach is the specification, for each study, of the causal effect estimated by the result under consideration.

ROBINS-E shares many characteristics with the RoB 2 tool for randomized trials and the ROBINS-I tool for non-randomized studies of interventions, and is informing the further development of ROBINS-I. ROBINS-E includes seven domains of bias, each of which is addressed using a series of signalling questions that aim to gather important information about the study and the analysis being assessed. After the relevant signalling questions have been completed, three judgements are made:

1. The **risk of bias** in the result that arises from this domain.

ROBINS-E: a tool to assess risk of bias in non-randomized studies – of exposures

- ROBINS-E concerns the risk of bias (RoB) in the results of a non-randomized study (observational study) that is…
  - quantitative
  - estimating the effect (harm or benefit) of an exposure
  - making comparisons of exposure groups or exposure levels

Follow-up (cohort) studies

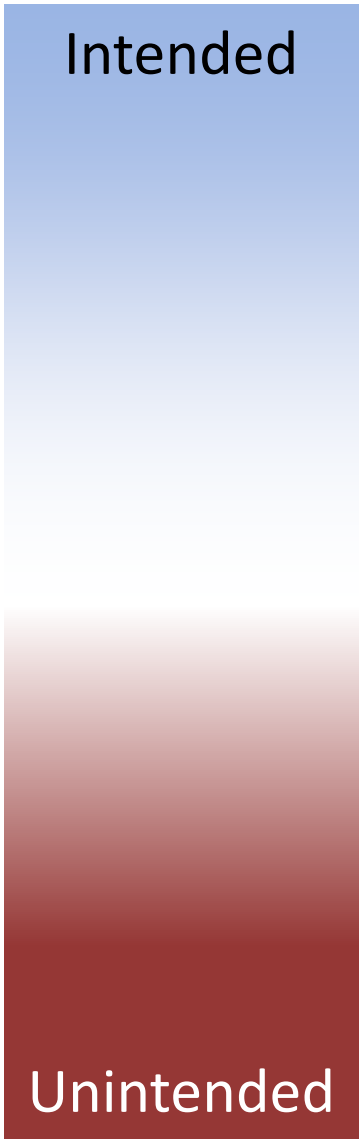
Before/after or time series studies

Case-control studies

Cross-sectional studies

Intervention vs exposure
A continuum

- Interventions
  - by a health professional
  - legislation
- Personal choices
  - type of toothbrush
  - taking a vitamin supplement
  - dietary intake
  - lifestyle, e.g. smoking, exercise
- Exposures
  - occupational
  - environmental
- Traits
  - socioeconomic status
  - biomarkers
  - genetic



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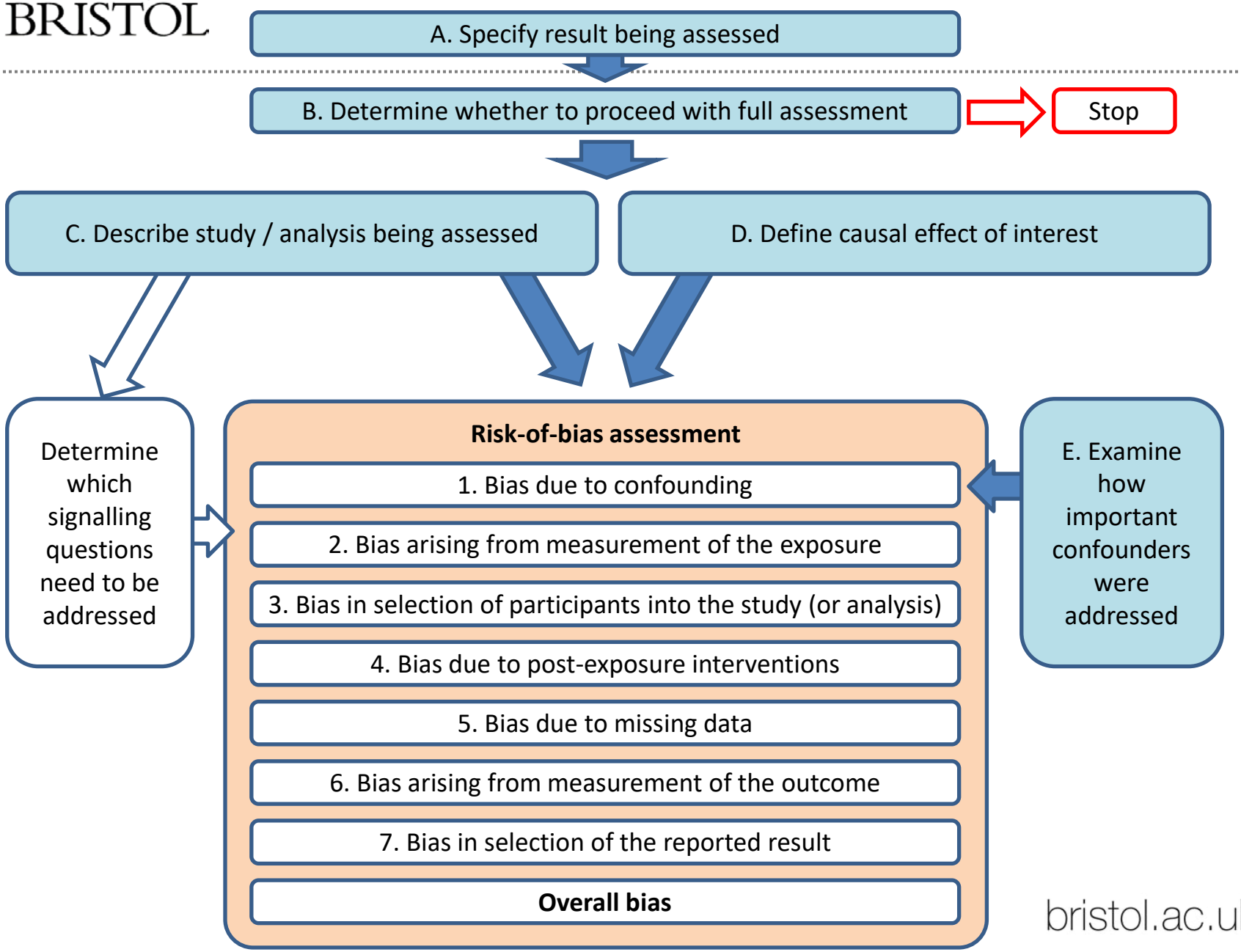
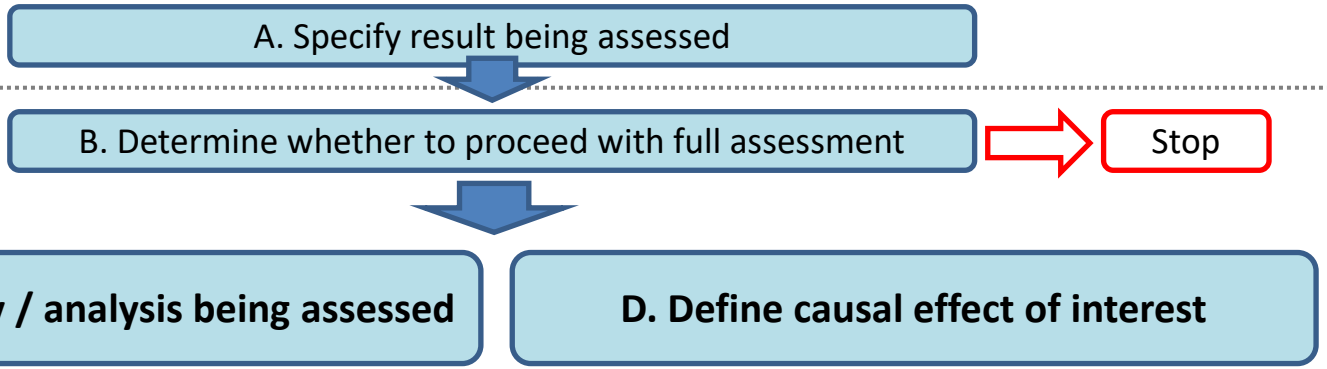
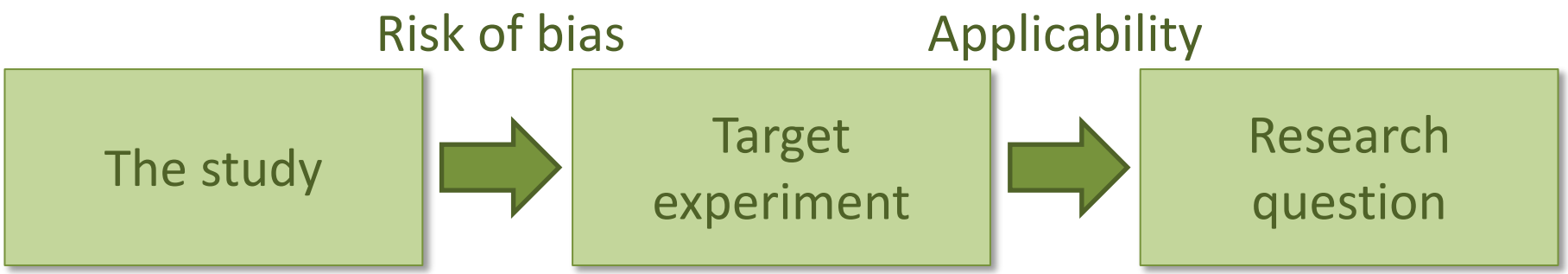




Establishing the causal effect being evaluated



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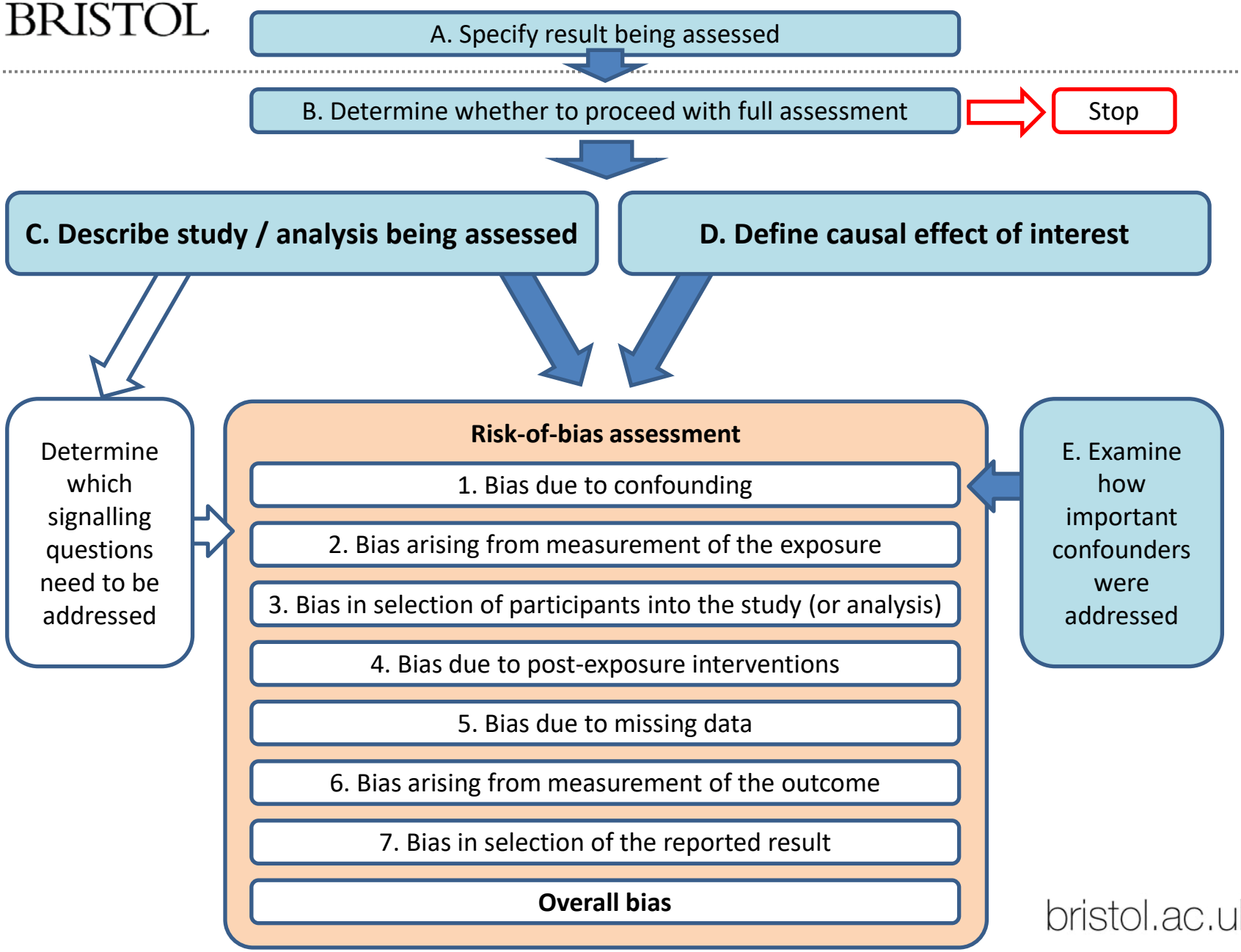

ROBINS-E: signalling questions

- As for ROBINS-I
- We use the WN/SN (or WY/SY) construct for some questions

Yes (Y)	Yes (Y)
Probably yes (PY)	Probably yes (PY)
Probably no (PN)	Weak no (WN) (no, but …)
No (N)	Strong no (SN) (no, and …)
No information (NI)	No information (NI)

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ROBINS-E: risk of bias judgement

Judgement	Interpretation
Low risk of bias	There is little or no concern about bias with regard to this domain
Some concerns	There is some concern about bias with regard to this domain, although it is not clear that there is an important risk of bias
High risk of bias	The study has some important problems in this domain: characteristics of the study give rise to a high risk of bias
Very high risk of bias	The study is very problematic in this domain: characteristics of the study give rise to a very high risk of bias

Judgement	Interpretation
Low risk of bias (except except for concerns about uncontrolled confounding)	There is little concern about bias with regard to confounding, but risk of bias due to uncontrolled confounding cannot be excluded in an observational study

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ROBINS-E: Threat to conclusions

- Whether the risk of bias (arising from each domain) is sufficiently high, *in the context of its likely direction and the magnitude of the estimated exposure effect*, to **threaten conclusions** about whether the exposure has an important effect on the outcome
- Take into account
  - finding of the study (including its magnitude and the strength of evidence around it)
  - broad assessment of bias (through the likelihood of it being present, its likely direction and its likely magnitude)
- Challenging, and detailed guidance has not been developed for this
- Response options: **Yes** / **No** / **Can't tell**

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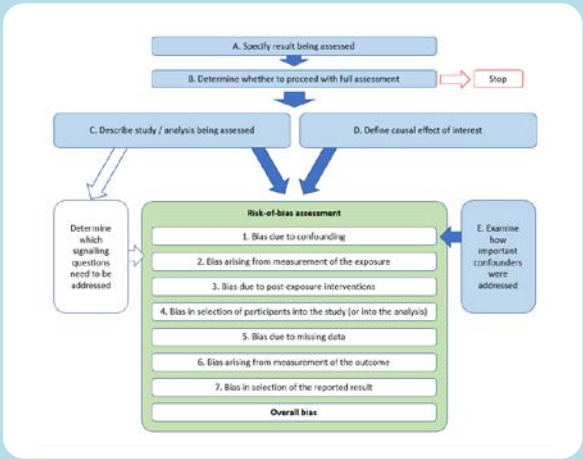
Define research question for the synthesis

Specify eligibility criteria

List important **confounding factors**

Identify studies and eligible results

Perform ROBINS-E assessment for each result contributing to the synthesis



Integrate ROBINS-E judgements into the synthesis
e.g. stratification, sensitivity analysis, triangulation

Draw conclusions, including certainty in the evidence
e.g. using GRADE

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ROBINS-E contributors to date

- Elie Akyl, Carla Ancona, Mohammed Ansari, Bruce Armstrong, Whitney Arroyave, Nancy Berkman, Lisa Bero, Aaron Blair, Abee Boyles, Bert Brunekreef, Paul Demers, Tanja Farmer, Francesco Forastiere, Davina Ghersi, Barbara Glenn, Ali Goldstone, Gordon Guyatt, David Henry, Miguel Hernan, Julian Higgins, Judy LaKind, Juleen Lam, Ruth Lunn, Daniele Mandrioli, Joerg Meerpohl, Rebecca Morgan, Julie Obbagy, Neil Pearce, Andrew Rooney, Kenneth Rothman, Jelena Savović, Mary Schubauer-Berigan, Holger Schünemann, Pam Schwingl, Beverly Shea, Kyle Steenland, Jonathan Sterne, Patricia Stewart, Kyla Taylor, Kris Thayer, Kate Tilling, Jos Verbeek, Roel Vermeulen, Meera Viswanathan, Shelia Zahm

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Assessing risk of bias in non-randomized studies of interventions: ROBINS-I tool

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…with special thanks to Miguel Hernán, Barney Reeves, Jelena Savović, Matt Page and other ROBINS-I collaborators

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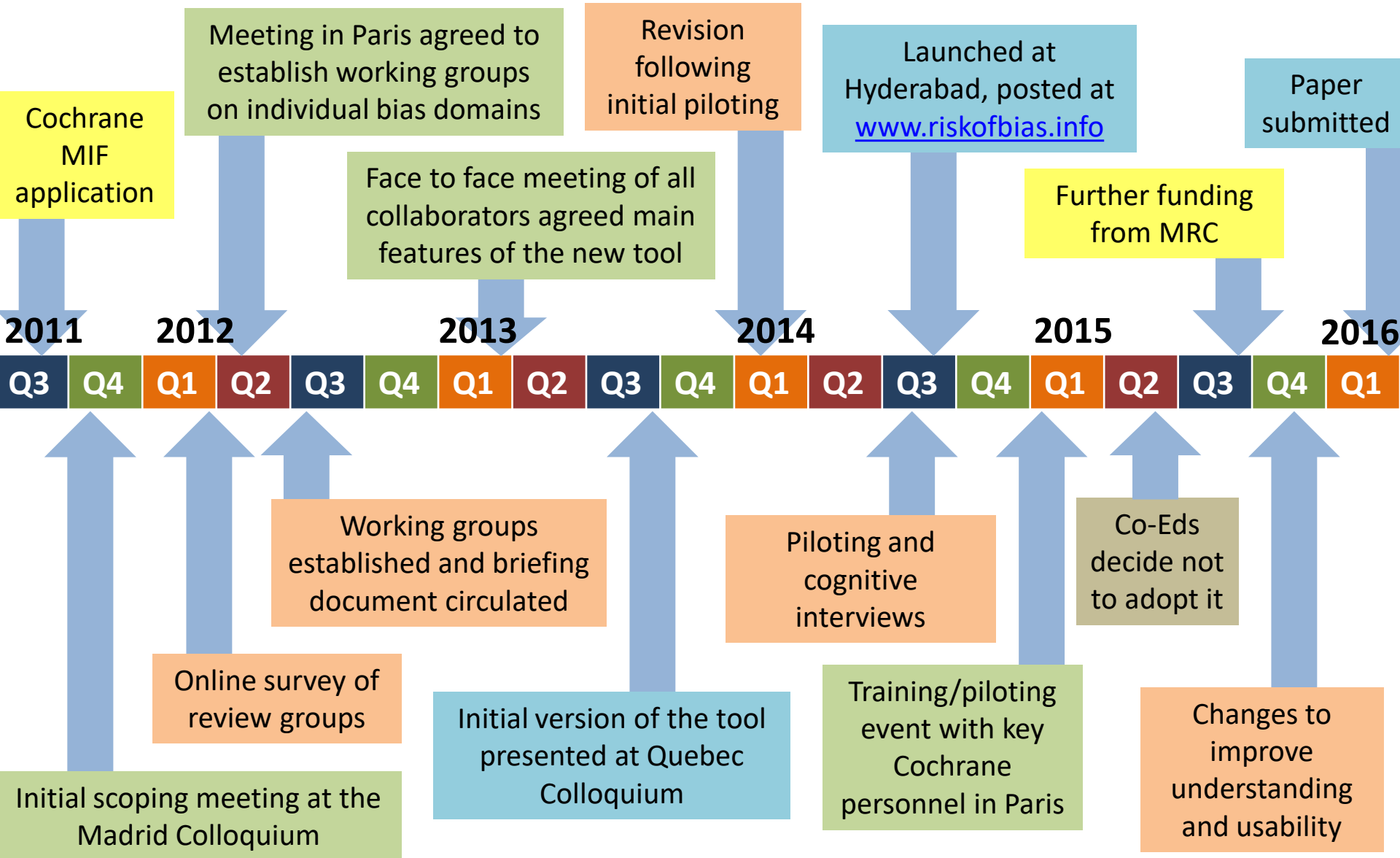
ROBINS-I: development chronology



ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions

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Non-randomised studies of the effects of interventions are critical to many areas of healthcare evaluation, but their results may be biased. It is therefore important to understand and appraise their strengths and weaknesses. We developed ROBINS-I ("Risk Of Bias In Non-randomised Studies - of Interventions"), a new tool for evaluating risk of bias in estimates of the comparative effectiveness (harm or benefit) of interventions from studies that did

such as cohort studies and case-control studies in which intervention groups are allocated during the course of usual treatment decisions, and quasi-randomised studies in which the method of allocation falls short of full randomisation. Non-randomised studies can provide evidence additional to that available from randomised trials about long term outcomes, rare events, adverse effects and populations that are typical of real world practice.[1,2] The availability of linked databases and compilations of electronic health records has enabled NRSI to be conducted in large representative population cohorts.[3] For many types of organisational or public health interventions, NRSI are the main source of evidence about the likely impact of the intervention because randomised trials are difficult or impossible to conduct on an area-wide basis. Therefore systematic reviews addressing the

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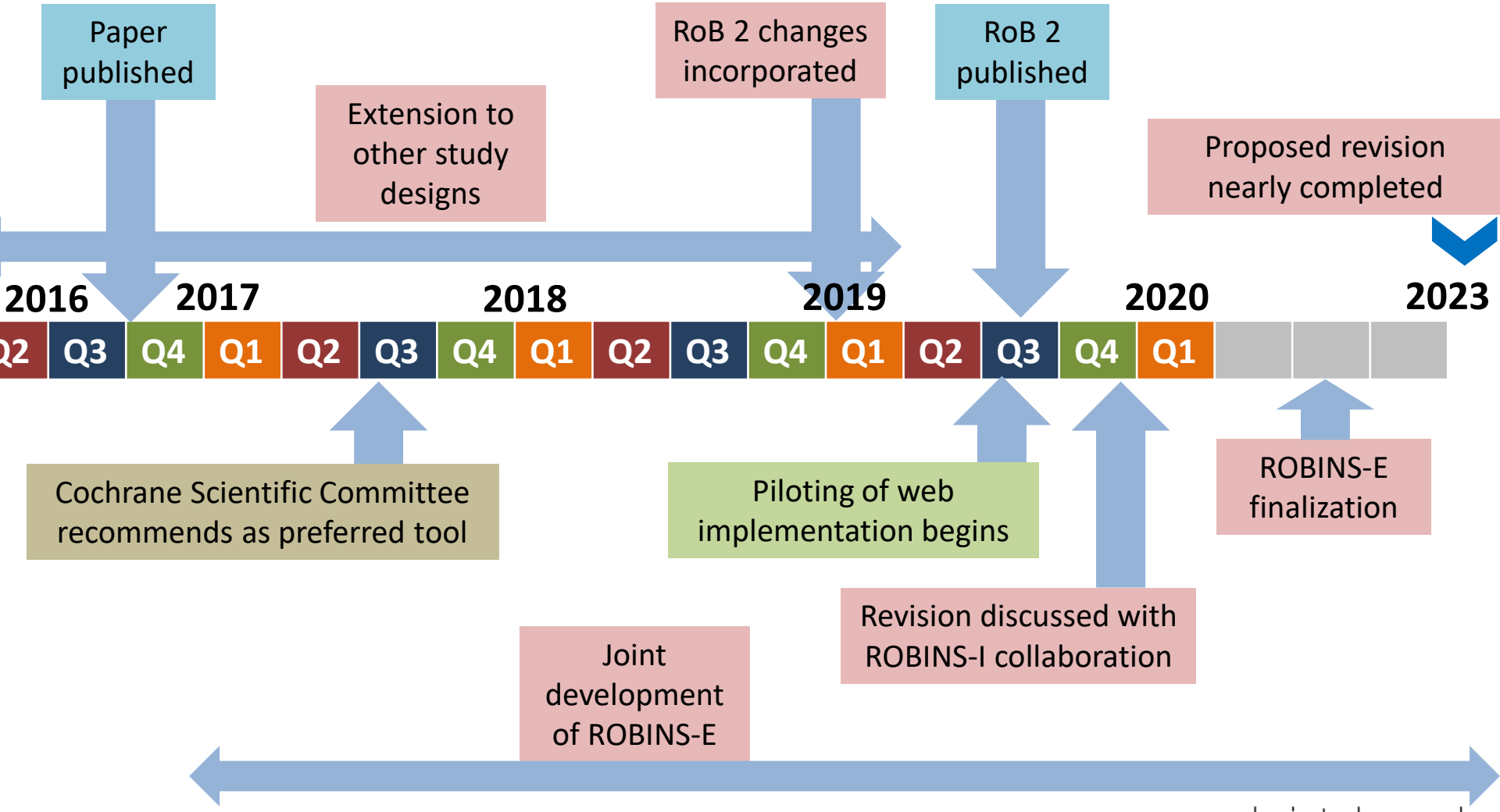
ROBINS-I: development chronology



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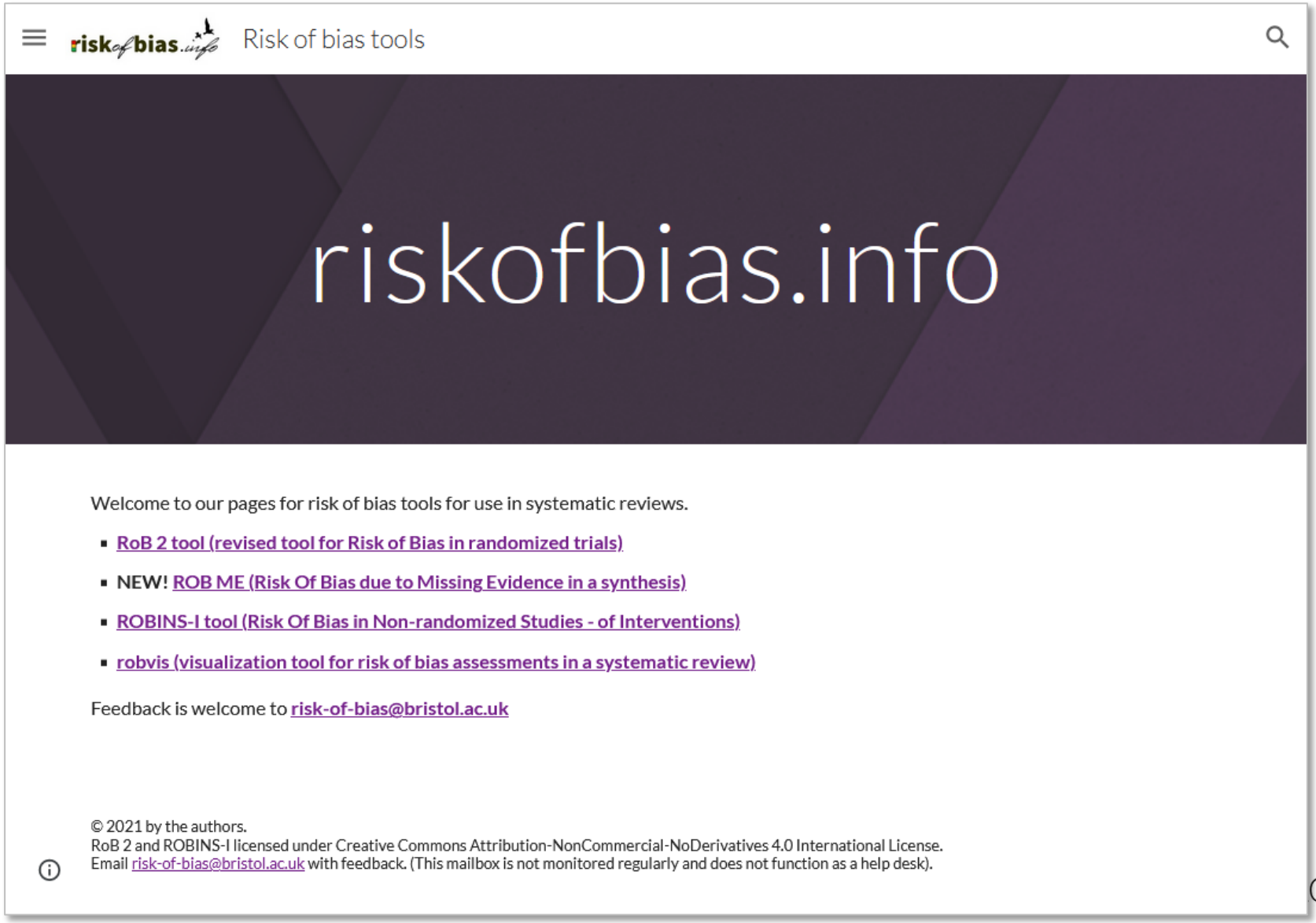

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Overview of the tool

- Preliminary considerations at protocol stage
  - Identify key confounding factors (& co-interventions)
- For each study:
  - Triage questions:
    - decide if a full assessment is warranted
    - determine which version of the Confounding domain to use
  - Target (idealized) randomized trial to match the study
    - PICO; effect estimate of interest (ITT vs per-protocol)
  - Examine key confounding factors (& co-interventions)
  - For each bias domain (result-level assessment)
    - Signalling questions
    - Free text descriptions
    - Risk of bias judgements, proposed by an algorithm
  - Overall risk of bias judgement (result-level assessment)
    - feed into (e.g.) GRADE

Main changes from 2016 version

- Preliminary considerations at protocol stage
  - Identify key confounding factors (& co-interventions)
- For each study:
  - Triage questions:
    - decide if a full assessment is warranted
    - determine which version of the *Confounding* domain to use
  - Target (idealized) randomized trial to match the study
    - PICO; effect estimate of interest (ITT vs per-protocol)
  - Examine key confounding factors (& co-interventions)
  - For each bias domain (result-level assessment)
    - Signalling questions
    - Free text descriptions
    - Risk of bias judgements, proposed by an algorithm
  - Overall risk of bias judgement (result-level assessment)
    - feed into (e.g.) GRADE

Rewritten, with more issues considered

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Bias domains

Domain	Related terms
Bias due to confounding	*Pre- or peri-intervention* features, for which considerations of bias in NRSI are mainly distinct from those in RCTs
Bias in classification of interventions	
Bias in selection of participants into the study	
Bias due to departures from intended interventions	*Post-intervention* features, for which many considerations of bias in NRSI are similar to those in RCTs
Bias due to missing data	
Bias in measurement of outcomes	
Bias in selection of the reported result	

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Bias domains

Domain	Related terms
Bias due to confounding	Versions for (a) baseline confounding only and (b) baseline and time-varying confounding
Bias in classification of interventions	New consideration of immortal time bias arising from definition of intervention groups; More specific consideration of non-differential classification bias
Bias in selection of participants into the study	New consideration of immortal time bias
Bias due to departures from intended interventions	Similar
Bias due to missing data	Much more detailed consideration of when bias arises, including consideration of (i) whether missingness depends on the true value of the outcome and (ii) imputation
Bias in measurement of outcomes	Similar
Bias in selection of the reported result	Additional consideration of analysis plans

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ROBINS-I: contributors

- Core group:
  - **Jonathan Sterne, Barney Reeves, Jelena Savović, Julian Higgins**

- Wider development team and other contributors:
  - **Kate Tilling, Miguel Hernán, Alexandra McAleenan, Roy Elbers, Matthew Page, Luke McGuinness, Isabelle Boutron, Asbjørn Hróbjartsson, Ian Shrier, David Henry, Sasha Shepperd, Hugh Waddington, Su Golder, Jamie Kirkham, Doug Altman, Mohammed Ansari, Nancy Berkman, Belinda Burford, James Carpenter, Jon Deeks, Toby Lasserson, Rachel Churchill, Rebecca Armstrong, An-Wen Chan, Peter Jüni, Terri Piggott, Deborah Regidor, Hannah Rothstein, Lakho Sandhu, Lina Santaguida, Bev Shea, Jeff Valentine, Meera Viswanathan, David Moher, Yoon Loke, Elizabeth Waters, Craig Ramsay, George Wells, Vivian Welch**