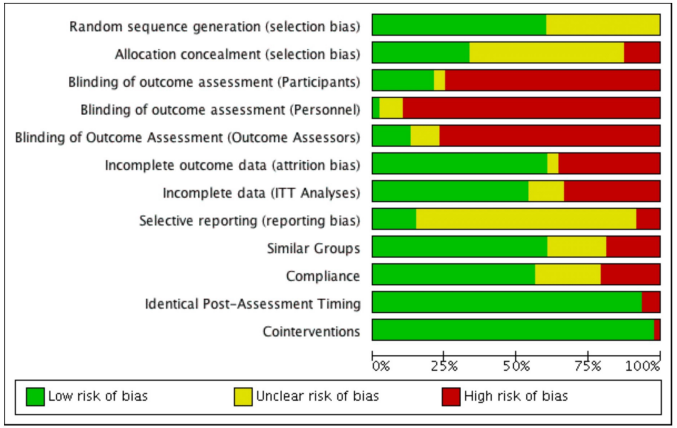
Study Quality & Risk of Bias

- It is common in meta-analysis to also rate and report the quality of the primary studies. The information you need to extract from each study to do this depends on the type of rating system you are using.
- Countless tools to assess the quality of primary studies have been developed in the last decades (Sanderson, Tatt, and Higgins 2007).
- For RCTs, one of the best ways to code the study quality is to use the Risk of Bias Tool developed by Cochrane (Higgins et al. 2011; Sterne et al. 2019).

Study Quality & Risk of Bias

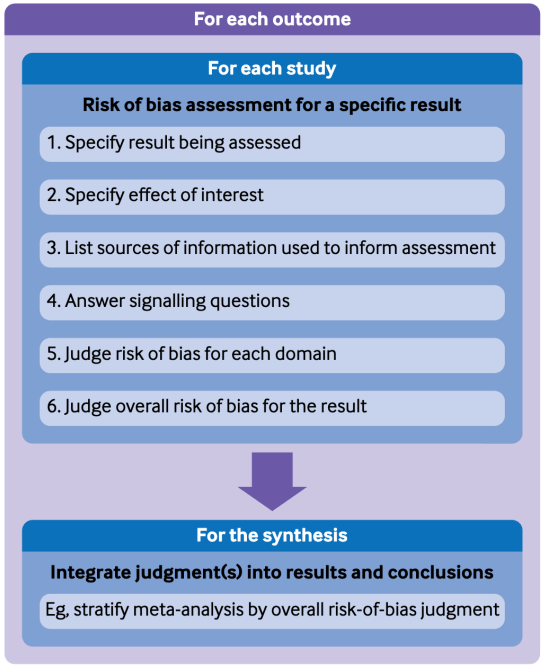
- **Study quality is related, but not identical to risk of bias**
  - "Bias”: systematic errors in the results or interpretation of a study
  - ”Risk of bias”: aspects of the study that may increase the likelihood of such errors.
  - Even studies that apply "state of the art" methods may still be prone to biases.
  - The "risk of bias" concept focuses on whether the output of an intervention study is believable and considers criteria that are conducive to this goal.



Study Quality & Risk of Bias

Version 2 of the Cochrane Risk of Bias Tool ("RoB 2") contains 5 domains:

1. Bias arising from the **randomization** process
2. Bias due to **deviations from intended interventions**
3. Bias due to **missing outcome data**
4. Bias in **measurement of the outcome**
5. Bias in **selection of the reported result**

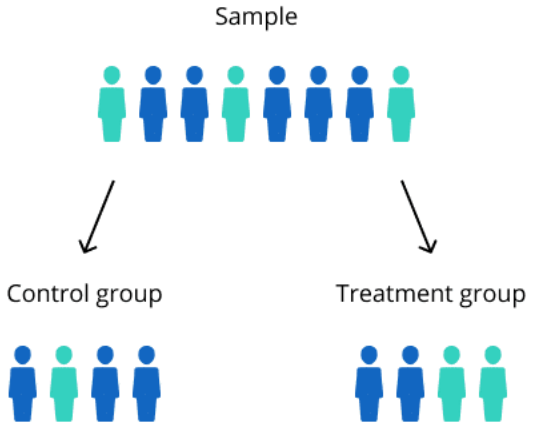


Sterne et al., 2019

Study Quality & Risk of Bias

D1: Bias arising from the randomization process

- In RCTs, randomization removes the influence of prognostic factors on the assignment of participants to intervention groups.
- An **allocation sequence is generated based on chance**, and allocation sequence **concealment is vital to prevent bias** in intervention assignment.
- Allocation sequence concealment is **not the same as blinding of assigned interventions** during the trial, which seeks to prevent bias after assignment and cannot always be implemented in certain types of trials.
- Allocation sequence concealment can be **successfully implemented in any study design or clinical area**, including RCTs of psychological interventions



Study Quality & Risk of Bias

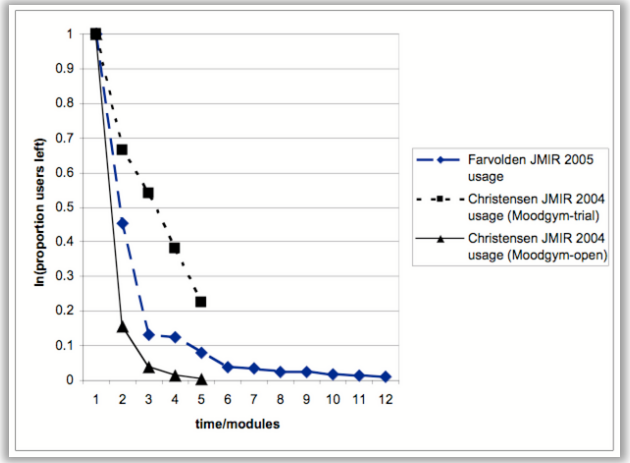
D1: Bias arising from the randomization process

- **Signalling questions:**
  - Was the allocation sequence random?
  - Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
  - Did baseline differences between intervention groups suggest a problem with the randomization process?

Study Quality & Risk of Bias

D2: Bias due to deviations from intended interventions

- E.g., administration of additional interventions, failure to implement protocol interventions, or non-adherence
- Can lead to so-called “performance biases”
- Trial protocols may not fully specify circumstances or changes to interventions → document deviations considered as intended or not.
- Particularly relevant for trials with usual care as the comparator intervention.
- Typical example in digital health care: intervention non-adherence (“law of attrition”; Eysenbach, 2005)



Study Quality & Risk of Bias

D2: Bias due to deviations from intended interventions

- **Signalling questions:**
  - Were deviations likely to have affected the outcome?
  - Were these deviations from intended intervention balanced between groups?
  - Was an appropriate analysis used to estimate the effect of assignment to intervention?
  - Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?

Study Quality & Risk of Bias

D3: Bias due to missing outcome data

- Missing outcome data can lead to bias in the intervention effect estimate.
- Participants may withdraw from the study, miss a visit, not provide data, or data may be lost, leading to missing outcome data.
- If we conduct an analysis of the recorded data (complete case analysis), this can lead to bias.
- Bias can also be introduced by procedures used to impute or account for the missing data.

Study Quality & Risk of Bias

D3: Bias due to missing outcome data

A complete case analysis…

- … is not biased if missingness is unrelated the true value of the missing
- … is biased when missingness depends on the true value of the missing, and on the intervention (e.g. antidepressant trial in which patients without improvements are more likely to drop out, *and* with drug-specific side-effects, which also lead to dropout)
- …is usually biased when missingness depends on the true value of the missing, and if the effect of the treatment differs from the control group (i.e., is effective) (e.g., psychotherapy trial in which patients without persistent depressive symptoms are more likely to drop out, *and* in which psychotherapy affects symptoms of depression)

→ **Bias due to missing outcome data is often likely!**

Study Quality & Risk of Bias

D4: Bias in measurement of the outcome

- Measurement errors can bias intervention effect estimates.
- There are **two types of measurement errors**: differential (between trial groups) and non-differential

Some considerations:

- appropriateness of outcome measurement
- differences in measurement or between groups
- blinding of outcome assessors
- whether the assessment of outcome is likely to be influenced by knowledge of intervention received.

Blinding of outcome assessors is often possible, but difficult for participant-reported outcomes (which are common in mental health research)

Study Quality & Risk of Bias

D5: Bias in selection of the reported result

- bias that arises when a trial's reported result is **selected from multiple estimates** based on direction, magnitude or statistical significance (“cherry-picking”; ”outcome-switching”).
- Considers whether the trial was analyzed according to a pre-specified plan and whether a particular outcome measurement or analysis was selectively reported based on its results.
- Encourages review authors to retrieve pre-specified analysis intentions for each trial and assess the risk of bias in selection of the reported result.
- **Insufficient detail** in some documents may limit the assessment of the risk of bias.

Study Quality & Risk of Bias

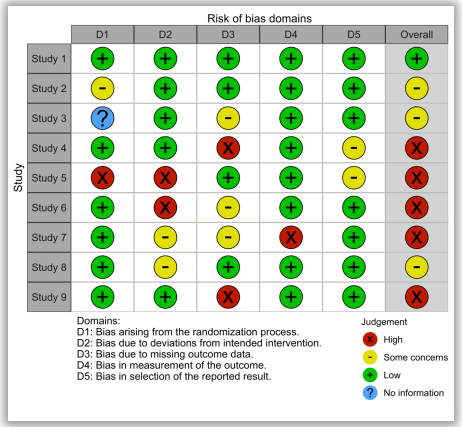
D5: Bias in selection of the reported result

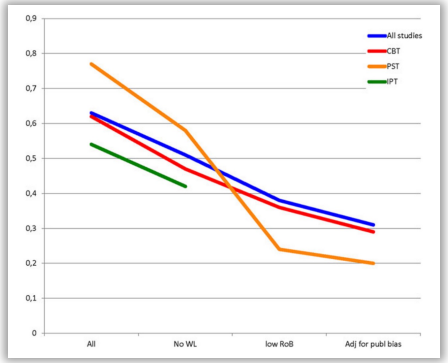
- **Signalling questions:**
  - Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis?
- Is the numerical result being assessed likely to have been selected, on the basis of the results, from:
  - ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?
  - ... multiple eligible analyses of the data?

Domain Judgments & Overall Risk of Bias

- All included studies in a meta-analysis are rated on all 5 domains as either **“low” or “high” risk of bias, or “some concerns”**
- Based on these rating, it can be determined if the study has an overall low or high risk of bias, or shows some concerns
- Typically depicted using a **“traffic light”** or **“summary plot”**
  - In RoB 2, results are additionally weighted by the size of the respective study
- These judgements can be used to conduct stratified analyses, e.g. calculate the pooled effect when only low risk of bias evidence is considered

→ **This typically leads to much lower/conservative effect estimates!**





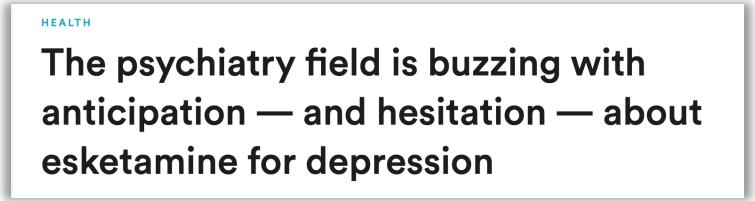
Choose Your Paper!

“How to prove that your therapy is effective, even when it is not: a guideline”

Ioana Cristea

Pim Cuijpers

“History repeating: A roadmap to address common problems in psychedelic science”



→ Read the marked sections & take notes for the discussion!