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RoB 2 Domain 5: Bias in selection of the reported result

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Outline

- Selective reporting vs selective non-reporting
- Types of bias in selection of the reported result
- *Questions*
- How to spot bias in selection of the reported result?
- *Questions*
- Assessing the risk of bias in selection of the reported result in RoB 2
- Examples
- *Questions and discussion*

Risk of bias in randomized trials

Bias arising from the randomization process

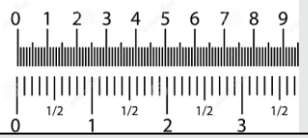
Bias due to deviations from intended intervention

Bias due to missing outcome data

Bias in measurement of the outcome

Experimental

Comparator



Outcome

Outcome

1.02 3.87
2.20 4.32
1.38 5.44

Bias in selection of the reported result

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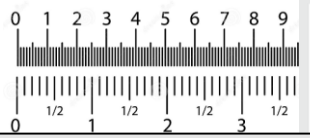

Outcome

Outcome

1.02	3.87
2.20	4.32
1.38	5.44

Bias in selection of the reported result

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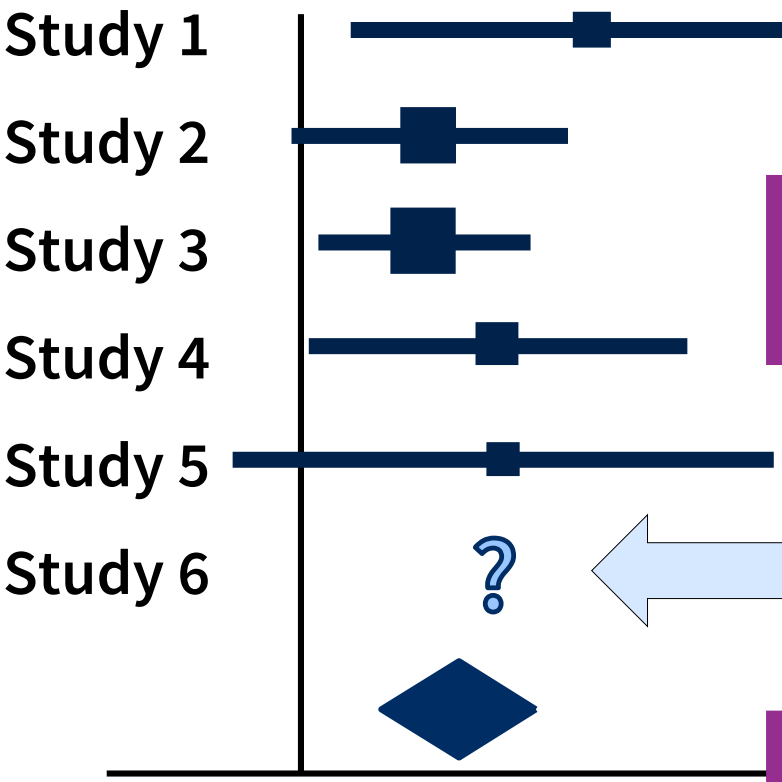
Poll

- Have you ever used the original Cochrane risk of bias tool for randomized trials?

Selective reporting vs selective non-reporting



1 result reported from among 3 scales used for the same clinical outcome

Potential bias in selection of the reported result: Domain 5 in RoB 2

Not reported, because “P > 0.05”

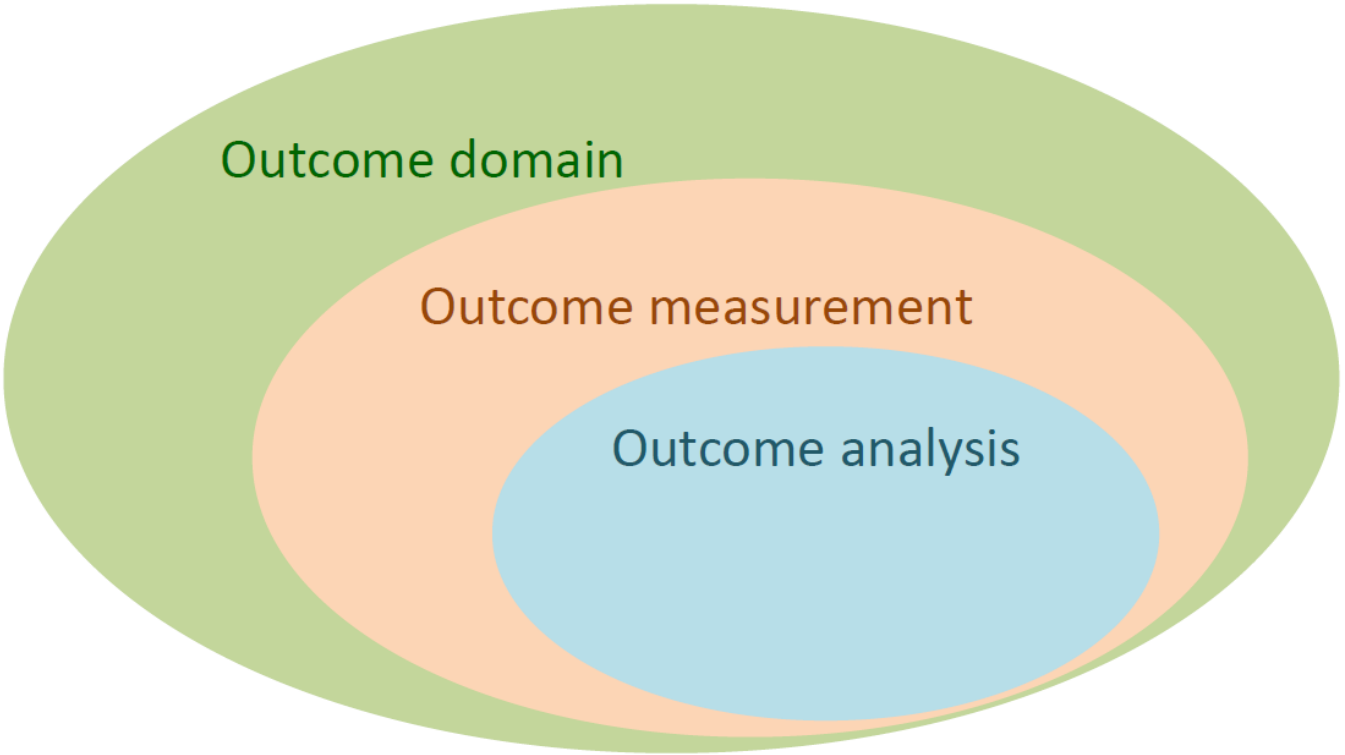
Potential bias in the meta-analysis: ROB-ME tool

Selective non-reporting

- Selective non-reporting addressed in the ROB-ME ("Risk Of Bias due to Missing Evidence") tool
- ROB-ME integrates assessment of risk of bias in ***meta-analyses*** due to:
  - Missing studies (publication bias)
  - Missing results (selective non-reporting bias)

- beta version of ROB-ME tool to be launched October 27 at riskofbias.info

Bias in selection of the reported result

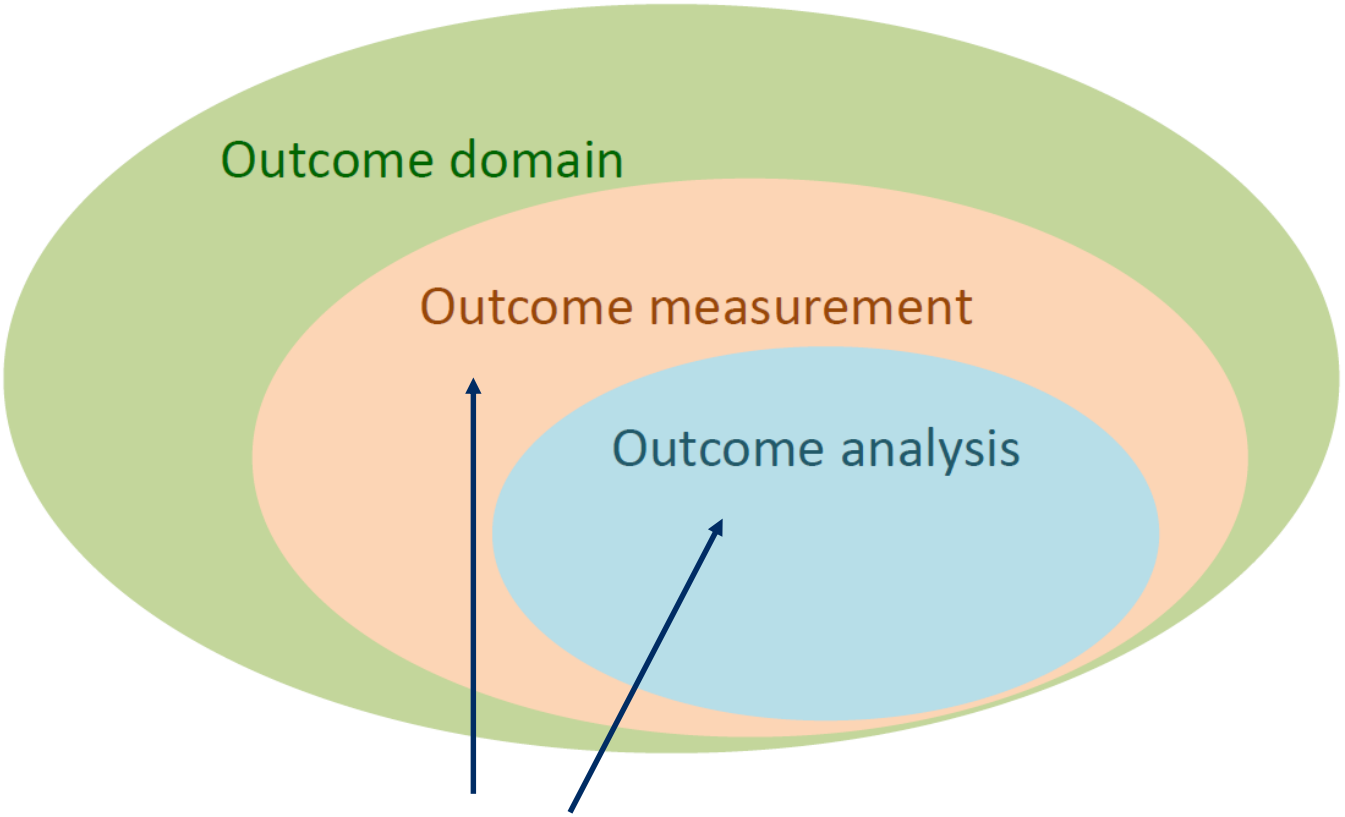


e.g. severity of depression

e.g. Hamilton rating scale after 6 weeks

e.g. difference in mean change in Hamilton score from baseline to 6 weeks

Bias in selection of the reported result



e.g. severity of depression

e.g. Hamilton rating scale after 6 weeks

e.g. difference in mean change in Hamilton score from baseline to 6 weeks

There are multiple possible results that could be generated for a domain, each of which are eligible for the synthesis we want to undertake.

Bias in selection of the reported result

Bias may arise when results are selected based on their magnitude, direction or P value, from:

- multiple outcome ***measurements*** within the outcome domain, e.g.
  - multiple scales
  - multiple definitions of/criteria for an event
  - multiple time points

Bias in selection of the reported result

Bias may arise when results are selected based on their magnitude, direction or P value, from:

- multiple ***analyses*** of the outcome measurement, e.g.
  - unadjusted *vs* adjusted models
  - different sets of covariates in adjusted models
  - final values *vs* change from baseline *vs* analysis of covariance
  - continuous scale converted to categorical data with different cut-points

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Questions

How to spot bias in selection of the reported result

- Preliminary considerations

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ☐ Journal article(s) with results of the trial
- ☐ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

How to spot bias in selection of the reported result

- ideally, we have a pre-specified analysis plan
  - a trial protocol (even a detailed trial registry record) may be sufficient
  - statistical analysis plan (SAP) often provides the most detail
- check for any amendments or updates to plans
  - usually date-stamped in trials registry or journal publication

How to spot bias in selection of the reported result

- analysis plan should be date-stamped, confirming that planned analyses were finalised before unblinded outcome data were made available for analysis

Protocol Number Code:	**DMID Protocol: 20-0006**
Development Phase:	Phase 3
Products:	Remdesivir Placebo
Form/Route:	IV
Indication Studied:	COVID-19
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	February 21, 2020
Clinical Trial Completion Date:	Trial Ongoing
Date of the Analysis Plan:	April 20, 2020
Version Number:	1.0

How to spot bias in selection of the reported result

- If there is an analysis plan, check the trial report agrees with it:
  - outcome measures changed?
  - analysis methods changed?
  - any explanation for the changes?

- Reminder: focus only on changes relating to the trial result(s) being assessed for risk of bias

How to spot bias in selection of the reported result

- Some differences between analysis plan and trial report may be due to legitimate changes to the protocol:
  - planned cut-points for a continuous outcome needed to be modified because the distribution of data differed to what was anticipated
  - timing of follow-up was delayed because the measurement device was broken
  - plans were modified before conducting any analyses, yet protocol not updated
- Contact trialists for clarification

How to spot bias in selection of the reported result

- what if there is no pre-specified analysis plan?
  - compare ‘Methods’ with ‘Results’ – look for:
    - whether outcome measurements or analyses reported match what was described in the ‘Methods’ section
    - any measurements or analyses added that were apparently not planned

How to spot bias in selection of the reported result

- what if there is no pre-specified analysis plan?
  - consider the following questions:
    - were outcome measures and analyses consistent across multiple reports relating to a study?
    - are subscales aggregated in an unusual manner?
    - have the researchers categorized continuous outcome measures in an unusual way?
    - has an unusual combination of unanticipated adverse events been categorised as “serious” and “minor” adverse events?

How to spot bias in selection of the reported result

- Take all sources (e.g. protocol, journal article, clinical study report, results supplied by authors) into consideration when reaching a judgement of risk of bias
- No reason for concern if, *across all sources*, you have access to results of all planned analyses

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Questions

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Assessing the risk of bias in selection of the reported result

Bias in selection of the reported result

5.1. Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?
Reponses: Y/PY/PN/N/NI

Analysed in accordance with pre-specified plan?

Is the numerical result being assessed likely to have been selected, on the basis of the results, from...

5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?
Reponses: Y/PY/PN/N/NI

5.3 ... multiple eligible analyses of the data?
Reponses: Y/PY/PN/N/NI

Reported result likely selected on the basis of the results?

Is the numerical result being assessed likely to have been selected, on the basis of the results, from...
- multiple eligible outcome measurements
- multiple analysis

'No' or 'Probably no':

- All reported results are consistent with what was planned.
- Only one possible way in which the outcome domain can be measured / analyzed
- All inconsistencies are explained and not related to the results.

'Yes' or 'Probably yes' :

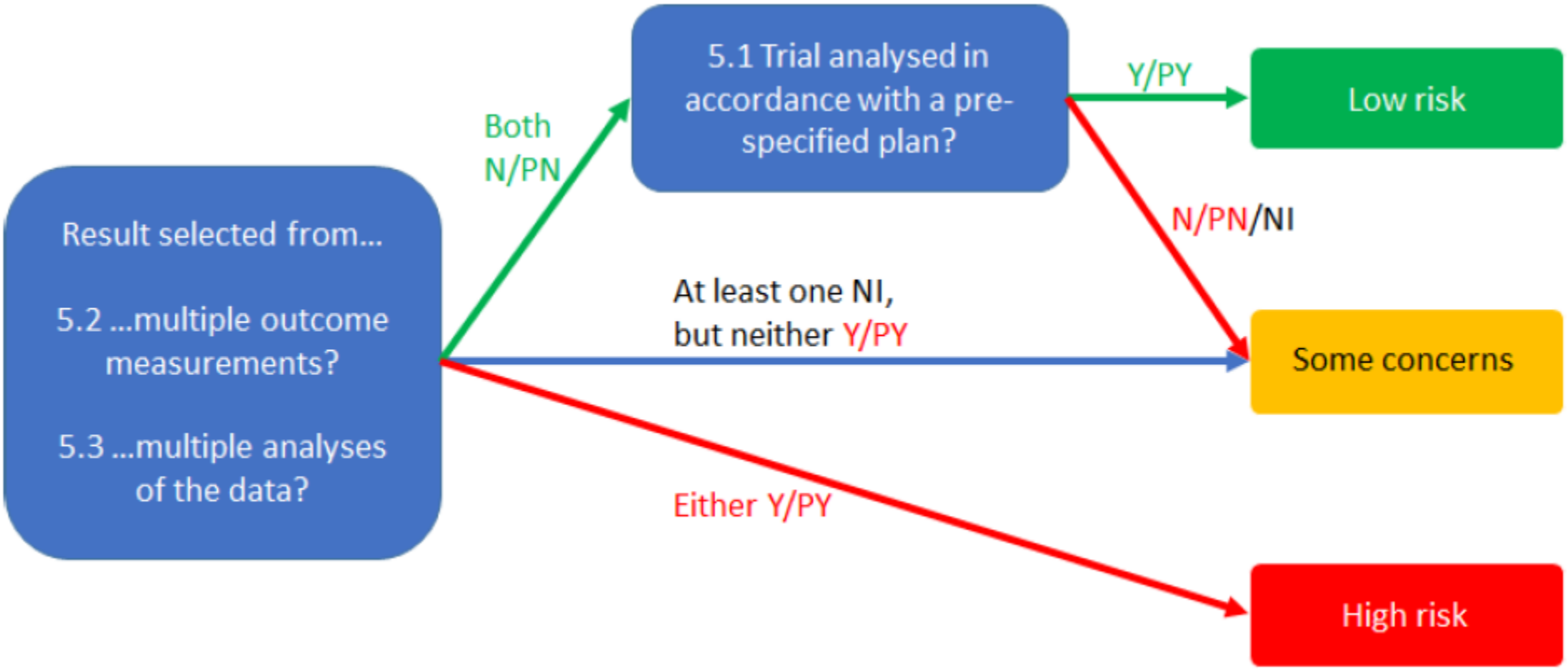
- Clear evidence that the results reported were selected on the basis of the results (e.g., statistically / non statistically significant).

Bias in selection of the reported result

Signalling question			Domain level judgement
5.1	5.2	5.3	Default risk of bias
In accordance with plan?	Selected from multiple outcomes?	Selected from multiple analyses?	
Y/PY	N/PN	N/PN	Low
N/PN/NI	N/PN	N/PN	Some concerns
Any answer	N/PN	NI	Some concerns
Any answer	NI	N/PN	Some concerns
Any answer	NI	NI	Some concerns
Any answer	Either 5.2 or 5.3 Y/PY		High

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Bias in selection of the reported result



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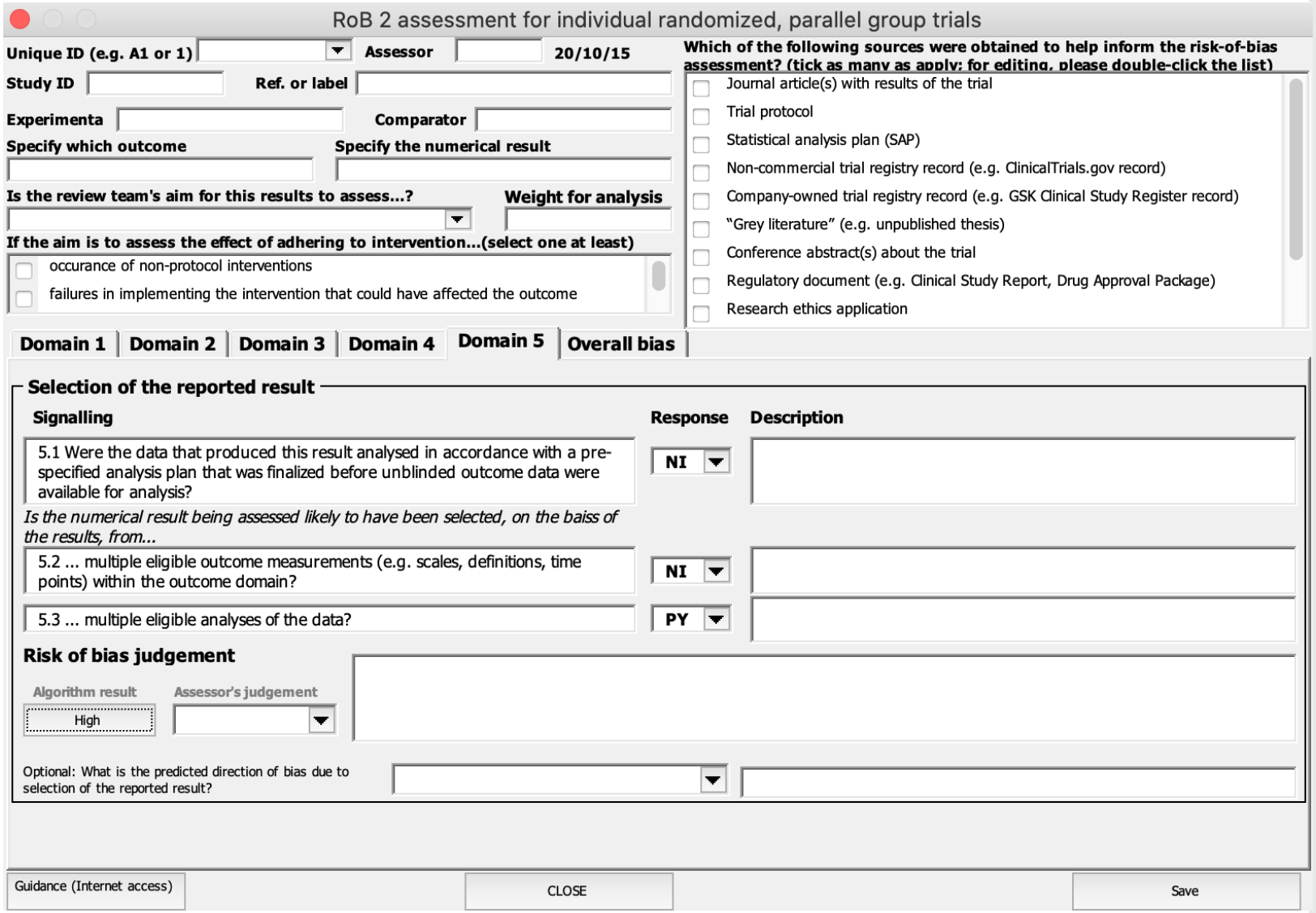


Bias in selection of the reported result

Low risk of bias

- prespecified trial analysis plan is available
- eligible outcome measures (and analyses) reported according to trial analysis plan, irrespective of the results

High risk of bias

- evidence (or strong hint) that the reported outcome measure (or analysis) was selected on the basis of the results

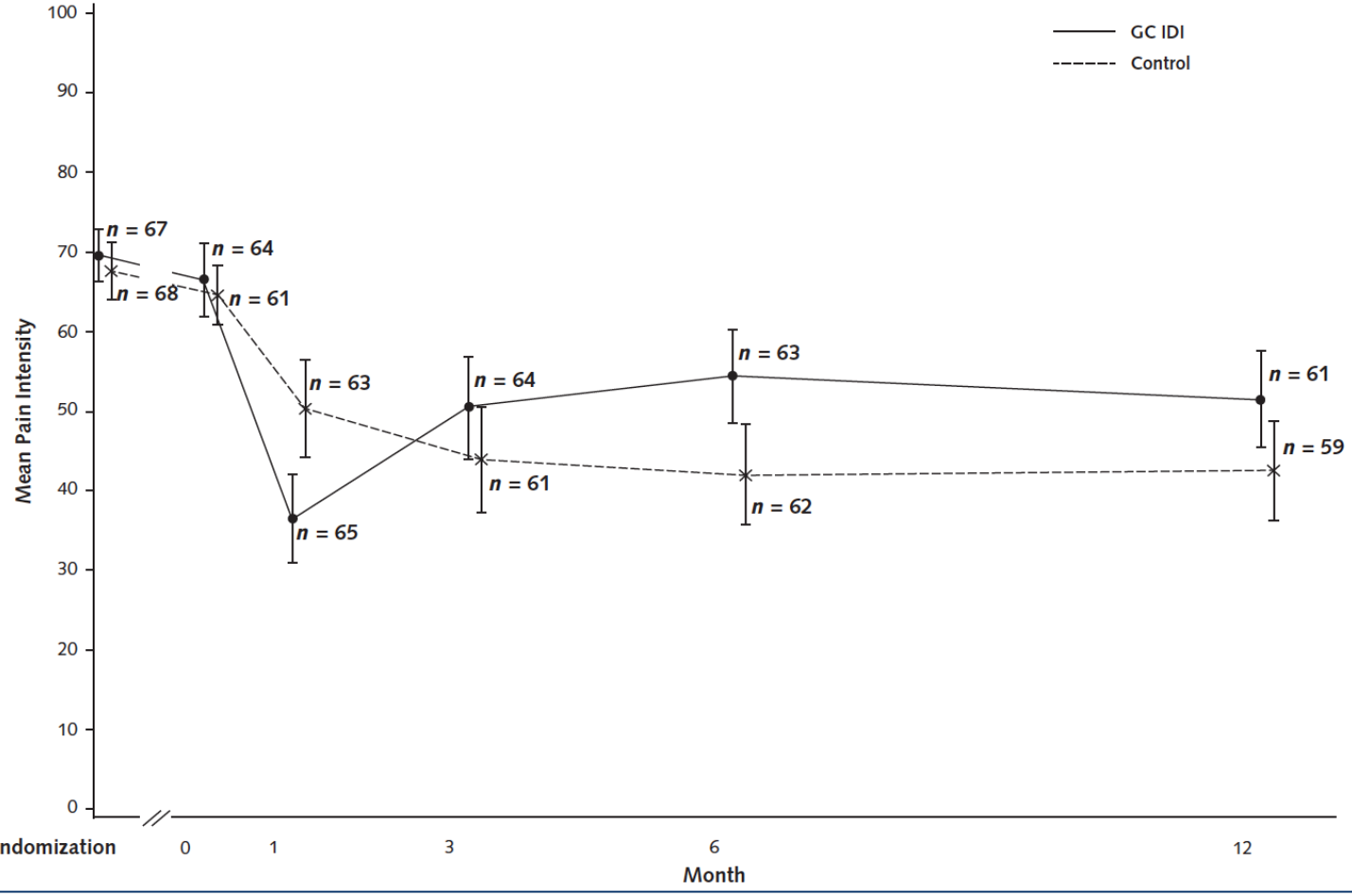
Some concerns

- many trials will be judged in this category

Examples

Randomized controlled trial evaluating intradiscal injection of steroid in patients with low back pain

Figure 2. Mean lumbar pain intensity in previous 48 h, by intervention group.



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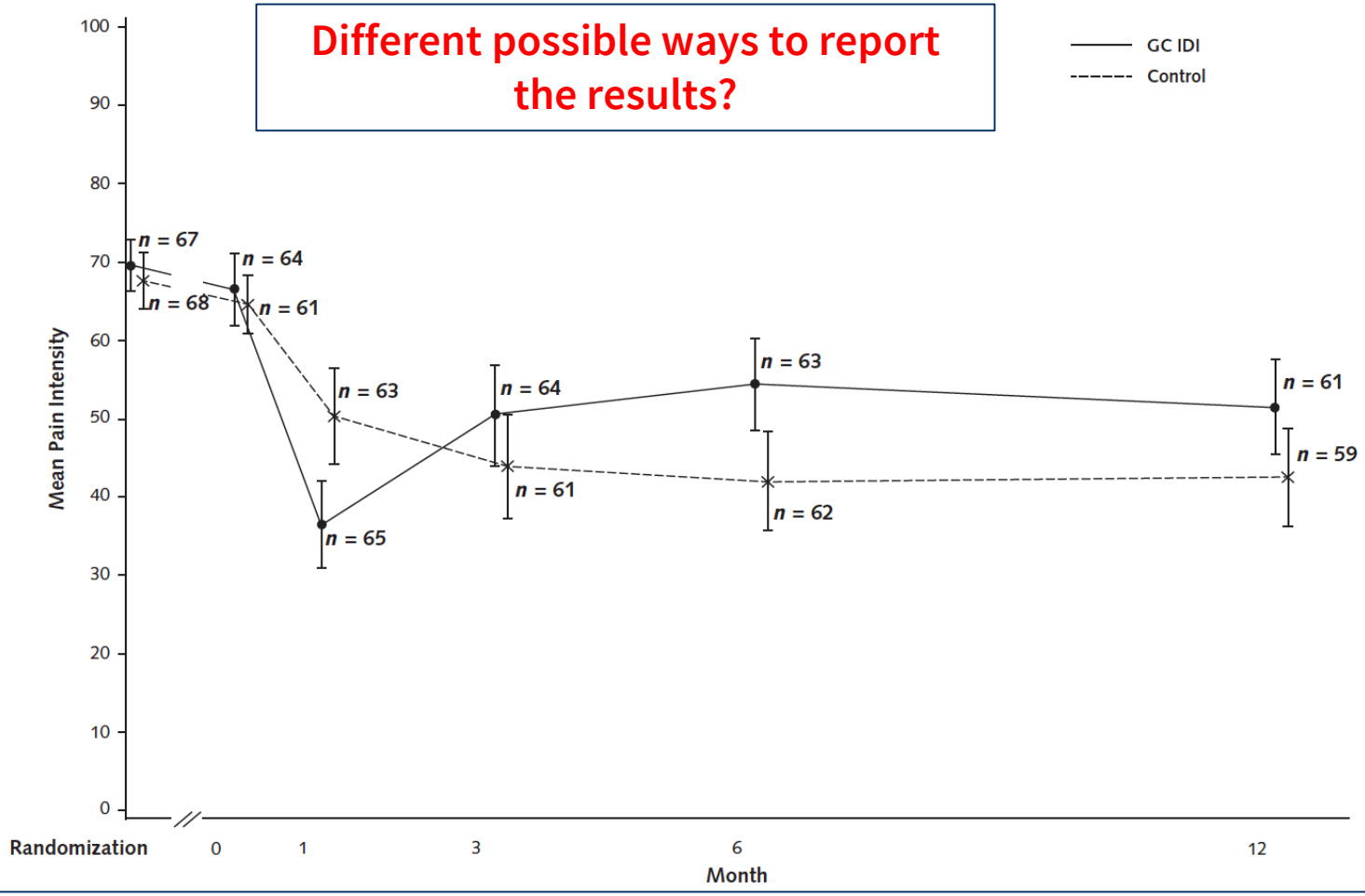
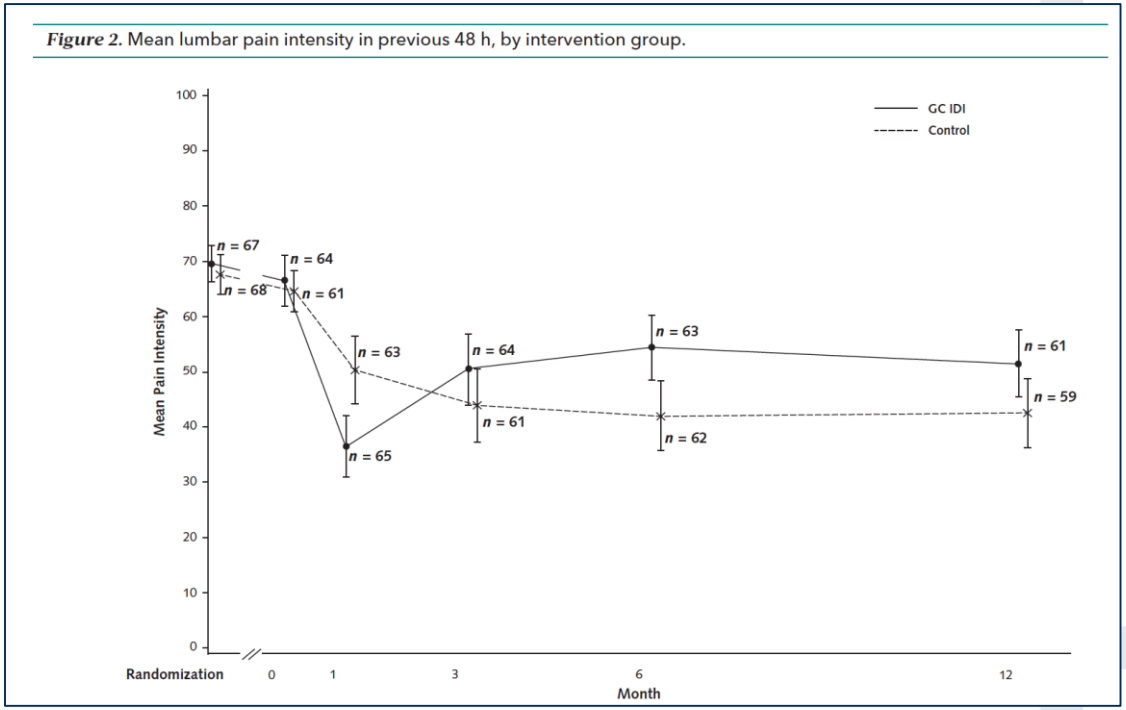


Reporting of results?

- Mean at M1
- Mean at M6
- Mean at M12



- Mean change from baseline at M1
- Mean change from baseline at M6
- Mean change from baseline at M12

Dichotomization

- Success is defined as less than 40/100 on pain numeric scale
- Success is defined as less than 35/100 on pain numeric scale
- Success is defined as less than 30/100 on pain numeric scale
- Etc…

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Outcome in the registry/Protocol/SAP (blinded and before the analysis)

Primary Outcome Measures : Back pain level assessed on a 11-point numeric scale (0-100) at 1 month. Success is defined as less than 40 on pain numeric scale at 1 month [Time Frame: 1 month]
CT.gov

Outcome in the publication

The primary outcome was the percentage of patients with LBP intensity less than 40 on an 11-point numerical rating scale (0 [no pain] to 100 [maximum pain] in 10-point increments) in the previous 48 hours at 1 month after the intervention. The main secondary outcomes were LBP intensity and

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Low risk of bias

Analysed in accordance with a prespecified plan

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Outcome in the registry/Protocol/SAP

Primary outcome: Back pain level assessed on a 11-point numeric scale (0-100) at 12 month

Outcome in the publication

The primary outcome was the percentage of patients with LBP intensity less than 40 on an 11-point numerical rating scale (0 [no pain] to 100 [maximum pain] in 10-point increments) in the previous 48 hours at 1 month after the intervention. The main secondary outcomes were LBP intensity and

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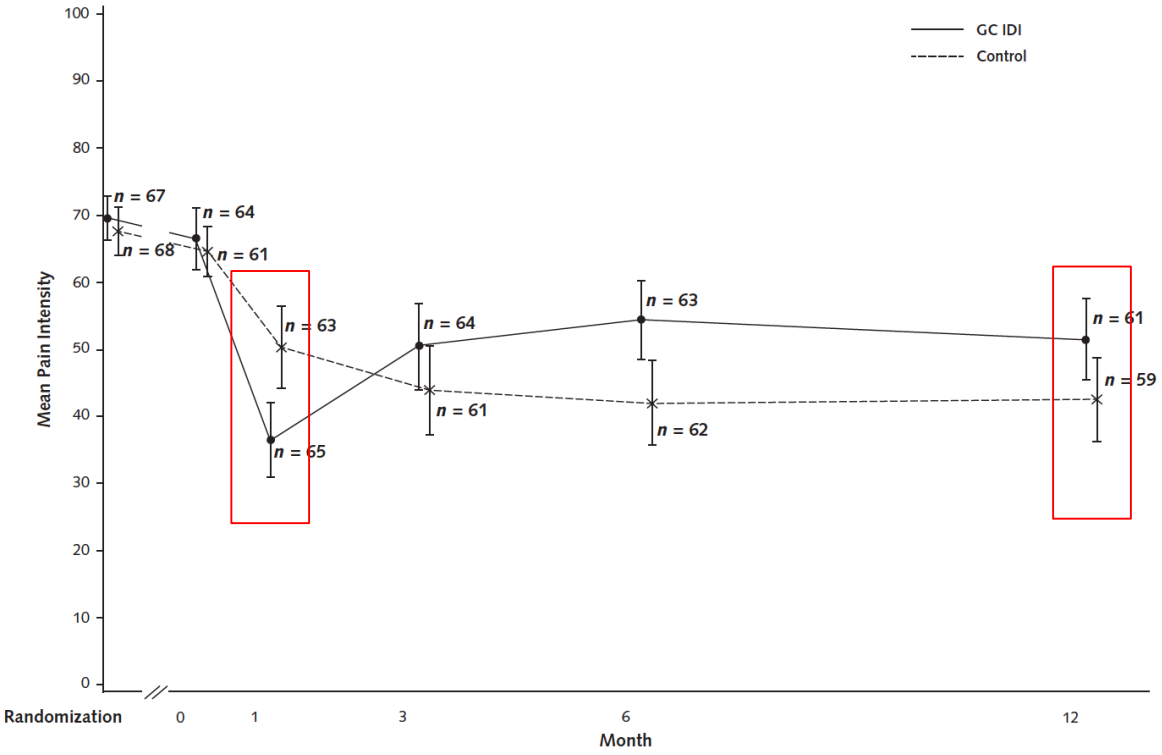

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High risk of bias

The numerical result being assessed likely to have been selected on the basis of the results

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COVID example
Horby P, Lancet, 2020

Outcomes
- **Mortality (day 28)**
- **Time to discharge from hospital**

Resources
- **Protocol – Yes**
- **Statistical Analysis Plan - Yes**
- **Registry entry (prospective registration)- Yes**

- **All resources are consistent**

2.6 Definitions of primary and secondary outcomes

Outcomes will be assessed at 28 days and then 6 months after randomisation. Analysis of longer-term outcomes collected beyond this will be described in a separate Statistical Analysis Plan.

2.6.1 *Primary outcome*

Mortality (all-cause)

2.6.2 *Secondary clinical outcomes*

- Time to discharge from hospital
- Use of mechanical ventilation/Extra Corporal Membrane Oxygenation (ECMO) or death (among patients not on ventilation or ECMO at baseline)

2.6.3 *Subsidiary clinical outcomes*

- Cause-specific mortality (COVID-19; cardiovascular; non-vascular; other)
- Use of renal dialysis or haemofiltration
- Serious cardiac arrhythmia (recorded in a subset)

- Use of ventilation (overall and by type)
- Duration of ventilation (overall and by type)

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Horby P, Lancet, 2020

Outcomes

- Mortality (day 28)
- Time to discharge from hospital

Resources

- Protocol – Yes
- Statistical Analysis Plan - Yes
- Registry entry (prospective registration)- Yes

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Low risk of bias

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- Duration of ventilation (overall and by type)

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COVID example

Outcomes

- Time to clinical improvement
- Time to viral negative conversion
- Incidence of clinical improvement (day 14)

Sources

- Protocol – no
- Statistical Analysis Plan - no
- Registry entry – Yes

Analysis planned /reported

- All outcomes are reported completely in the registry and consistently in the publication

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COVID example

Outcomes

- Time to clinical improvement
- Time to viral negative conversion
- Incidence of clinical improvement (day 14)

Sources

- Protocol – no
- Statistical Analysis Plan - no
- Registry entry – Yes

Analysis planned /reported

- All outcomes are reported completely in the registry and consistently in the publication
- However the registration was not done prospectively

Some concerns.

NI on the prespecified plan

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Questions and discussion