Evidence In Practice Webinar Series Lecture #4

When the Bias is Baked-In?

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The University of Alberta respects the sovereignty, lands, histories, languages, knowledge systems, and cultures of First Nations, Métis and Inuit

Leading with Purpose.

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First, decide which cake you are interested in!

Quickly
Read the **abstract**
(and some methods) to
choose most **relevant**

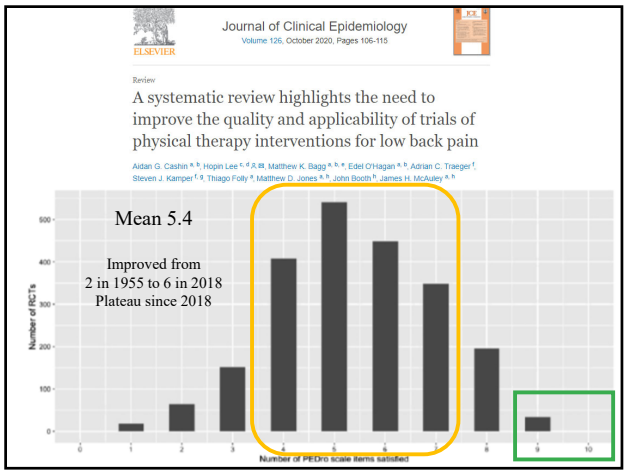
2

Judging relevance to your clinical question! Did they study…

- **patients** similar to yours?
  - Severity? Diagnoses? Age? Sex? Race?
- **intervention** you are interested in?
  - Feasible?, Defined clearly?
- similar **therapists** to you or could you train to achieve their expertise?
- A **clinical setting** similar to yours?
  - Funding vs dose? Space and equipment availlable?, Accessibility? Motivation?
- The **outcomes** you care about? At the right follow-up time?

IF NOT close enough, THEN possibly

3



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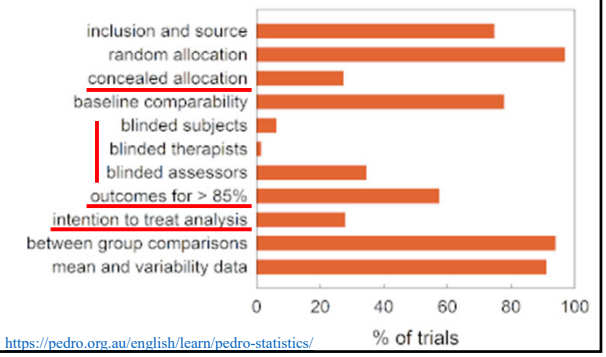
Most common sources of bias in PT trials based on RCT pedro scores



https://pedro.org.au/english/learn/pedro-statistics/

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We should not demand perfection from clinical research because it is not generally attainable.

Instead, we should look for studies that are good enough for clinical decision-making

Herbert et al.
Chapter 5,
Practical Evidence-Based Physiotherapy 2005

Let's not throw the baby out with the bath water.

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Rather than merely annihilating the work, your goal is to identify areas of strength as well as areas for improvement.

…
And to understand their impact on the results

On Quality appraisal
Hurley et al Research Methods A framework for evidence-based clinical practice. 2011

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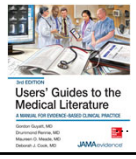
Identifying Common Sources of Bias in Intervention Effectiveness Studies

PEDro
Physiotherapy Evidence Database

- https://pedro.org.au/english/resources/pedro-scale/
- https://training.pedro.org.au/ (50 AUD)

RoB 2 tool
A revised Cochrane risk of bias tool for randomized trials

- https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2,



- https://jamaevidence.mhmedical.com/Book.aspx?bookId=847
- https://jamaevidence.mhmedical.com/DownloadMultimedia.aspx?multimediaID=6548467

…

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There are appraisal guides for all types of research studies

Prognosis
Diagnostic
Guidelines
Etiology
Systematic reviews
Harms
Prediction rules
INTERVENTIONS
Quality improvement

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*Identifying Common Sources of Bias in **Systematic reviews and Meta-analyses***

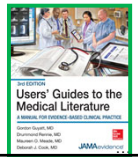
RESEARCH METHODS AND REPORTING

Cite this as: BMJ 2017;358:j4008
http://dx.doi.org/10.1136/bmj.j4008

AMSTAR 2 a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

Beverley J Shea,[1,2,3] Barnaby C Reeves,[4] George Wells,[3,5] Micere Thuku1,[2] Candyce Hamel,[1] Julian Moran,[6] David Moher,[1,3] Peter Tugwell1,[2,3,7] Vivian Welch,[2,3] Elizabeth Kristjansson,[8] David A Henry[9,10,11]

- https://amstar.ca/Amstar-2.php



- https://jamaevidence.mhmedical.com/content.aspx?bookid=847&sectionid=69031500
- https://jamaevidence.mhmedical.com/DownloadMultimedia.aspx?multimediaID=6548468

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RoB 2 tool

A revised Cochrane risk of bias tool for randomized trials

5 RISK OF BIAS domains

1. Randomization
2. Deviations from the intended interventions (assignement / adhering)
3. Missing outcome data
4. Measurement of the outcome
5. Selection of the reported results

Each domain has signaling questions to judge as

Low risk of bias;
Some concerns; or
High risk of bias.

The highest risk of bias for a domain determines the risk for the study.

- high risk in at least one domain Or
- some concerns for multiple domains lowers confidence in the result.

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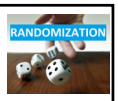
Randomization



- Should ensure groups have the same prognosis before the intervention because it balances the known and unknown prognosis factors between groups.
  - **allocation sequence generation**.
  - **allocation sequence concealment**. (Always possible!!!)
    - Bias if authors could reject/choose patients for a specific intervention
    - Bias if authors could manipulate who enters the trial at a given time to control what intervention they received.

- SUBOPTIMAL IF
  - know the assignment rule (alternation, date of birth or admission)
  - know the sequence of assignments, (if openly posted on a bulletin board);
  - able to predict assignments based on previous assignments.

IF bias = ↑ 7-10%

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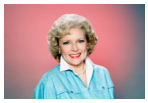
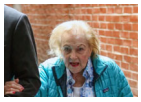
Assessing prognosis balance

- **HOW = Compare the baseline descriptives characteristics of each group.**
- **Do not** limit yourself to a statistical comparison of characteristics between groups at baseline:
  - Study was not planned for this comparison and it may be underpowered to detect differences that are important.
  - e.g. If you know that age is related to an outcome targeted by the intervention then ask:
    - Could imbalance in age or severity at baseline explain the results or do I trust that the effect is due to the intervention?
      - CTRL: usual care Age 85 gain 30m on 6 Min walking distance
      - TREATED with more rehab Age 65 gain 50m





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Deviations from intended interventions

- Participants receive additional interventions NOT in the trial protocol,
  - Control participants seeks exercises outside of the study.
  - Stroke patients benefiting from walking more back and forth to therapy in the intervention group even if intervention is not very effective
- failure to implement the interventions as planned,
  - Participants complete more sets and reps than prescribed
- participants do not adhere to their assigned intervention.
  - Participants only completed 50% of prescribed exercises

If Bias =
Or Depends

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Assessments of 'Bias due to deviations from interventions' depend on your goal.

(1) **intention-to-treat (ITT) effect**: What is the effect for patients assigned to each group? *(regardless of whether the interventions are received during follow-up);*

to inform health policy about whether to recommend an intervention in a **particular health system**

or

(2) **per-protocol effect**: What is the effect for participants **adhering to** intervention as specified in the trial protocol

inform a care decision by an **individual patient**

They differ when some participants do not receive or deviate from the assigned intervention after baseline

Per-protocol = overestimates

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Assessing the effect of adherence to intervention

(1) were participants, carers and people delivering the interventions **blinded**;

(2) if participants, or people delivering the interventions were not blinded, were important co-interventions **balanced** across intervention groups;

(3) were intervention implemented successfully, and did participants **adhere to** the assigned intervention;

(4) if deviations, was an appropriate **analysis** was used.

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Risk of bias if

- Patients and therapists aware of intervention
- There were deviations OR non-adherences
- Possibly affecting outcomes
- Imbalanced between groups
- Absence of appropriate analysis

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Bias due to missing outcome data

<u>Possible reasons</u>:

- 'loss to follow-up' or 'dropout';
- Did not attend an evaluation visit;
- Attended evaluation but did not provide data;
- data lost or unavailable for other reasons;
- participants can no longer experience the outcome (EG died).

IF bias = DEPENDS

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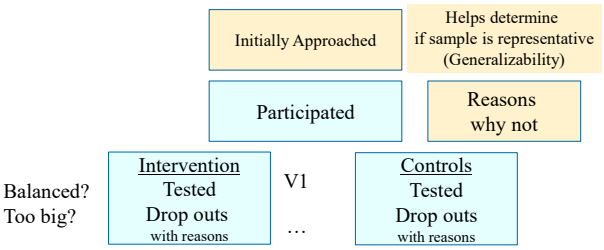
Judging if Data is missing?

- Was participant flow (e.g., patients, clinicians, hospitals) through the study explicitly reported?



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Risk of missing outcome bias if

- Incomplete data
- No evidence provided to reassure you of no bias
  - Analyses with and without missing data not provided
  - Results that do not change provide greater confidence
- Missingness could depend on true value
- Missingness likely depend on true value
  - Different between groups
  - Reasons for missing related to true value
  - Or; Reported reasons differ between groups.

IF bias = DEPENDS

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Bias in measurement of the outcome

- Bias arise when the measured values do not equal the true or underlying values

Risk of bias depends on:

1. Is the outcome measurement **method appropriate**?
2. Is there a **difference** in outcome measurements between intervention groups (EG more visits.)
3. **Who** is the outcome **assessor**? (Participant, provider, assessor)
4. Is the assessor **blinded** to intervention assignment
   Participant-reported outcomes are not blinded by assessor blinding
   Outcomes that reflect decisions made by provider need blinding (EG discharge date or destination, …)
5. Can the outcome measurement **be influenced** by knowing the intervention received.
   - Bias will depend on the observers' belief and if judgement is involved in assessing an outcome.
     - More risk if comparator is no treatment than usual care.
     - Lower risk if assessor was not involved in care.

IF bias = ↑ 34%

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Biased selection of reported results

- If the reported result reported is **selected** (based on its direction, magnitude or statistical significance) from among multiple intervention effect estimates available to the trialists.

- **reporting of a particular outcome measurement** from an outcome domain; and
- **reporting only a subset of time points** at which the outcome was measured
  EG. only the effect at 3 weeks after baseline despite testing at 6 and 8 weeks;
- **reporting of a particular analysis** from multiple analyses of a specific outcome measurement.
  - (i) the unadjusted or (ii) the adjusted effect
    - only one or a subset of multiple analyses adjusting for different prognostic factors

IF bias = DEPENDS

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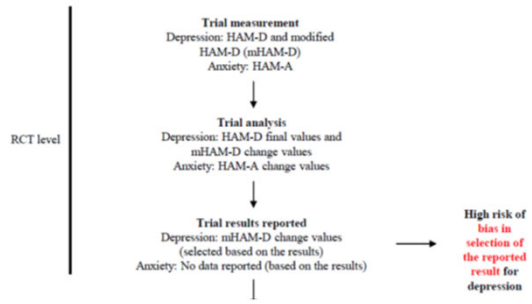
Figure 6. Examples of bias in selection of the reported result and outcome non-reporting bias



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Where did you get info to identify bias!

NIH U.S. National Library of Medicine
ClinicalTrials.gov

- ☐ **Journal article(s)**
- ☐ Trial protocol
- ☐ Statistical analysis plan
- ☐ Trial registry record
- ☐ 'Grey literature' (e.g. unpublished thesis)
- ☐ Conference abstract about the trial
- ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary
- ☐ Personal communication with trialist or sponsor

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Not all Bias suggest the study as a whole is invalid

- some causes of bias apply
  - to the whole study;
  - to the outcome domain being measured;
  - to the outcome measurement method used;
  - to a specific result.

- Try to predict the **likely direction of bias**
  - No bias / Favours experimental / Favours comparator / Unpredictable
- Try to predict the **magnitude of the worst bias**
  - No bias / Small or large effect!
- Then, judge the value of the study **for you**.

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Thank you!
Questions?

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