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COLLEGE OF APPLIED HEALTH SCIENCES

Assessing Risk of Bias in Randomized Controlled Trials

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My research interests

- Home telemonitoring for patients with heart failure
- Use and effectiveness of mobile health (mHealth) interventions and wearable technologies on self-management of chronic diseases (e.g. heart failure, cardiac rehabilitation, and diabetes)
- Systematic reviews and meta-analysis of IT-based interventions
- Literature reviews and evidence synthesis methods

Typology of literature reviews

Typology of literature review types.

Overarching goal	Theoretical review types	Scope of questions	Search strategy	Nature of primary sources	Explicit study selection	Quality appraisal	Methods for synthesizing/ analyzing findings
Summarization of prior knowledge	Narrative review	Broad	Usually selective	Conceptual and empirical	No	No	Narrative summary
	Descriptive review	Broad	Representative	Empirical	Yes	No	Content analysis/ frequency analysis
	Scoping review	Broad	Comprehensive	Conceptual and empirical	Yes	Not essential	Content or thematic analysis
Data aggregation or integration	Meta-analysis	Narrow	Comprehensive	Empirical (quantitative only)	Yes	Yes	Statistical methods (meta-analytic techniques)
	Qualitative systematic review	Narrow	Comprehensive	Empirical (quantitative only)	Yes	Yes	Narrative synthesis
	Umbrella review	Narrow	Comprehensive	Systematic reviews	Yes	Yes	Narrative synthesis
Explanation building	Theoretical review	Broad	Comprehensive	Conceptual and empirical	Yes	No	Content analysis or interpretive methods
	Realist review	Narrow	Iterative and purposive	Conceptual and empirical	Yes	Yes	Mixed-methods approach
Critical assessment of extant literature	Critical review	Broad	Selective or representative	Conceptual and empirical	Yes or no	Not essential	Content analysis or critical interpretive methods

Pare, G., Trudel, MC., Mirou, J., Kitsiou, S (2015) Synthesizing information systems knowledge: A typology of literature reviews, Information and Management, Vol 52: 183-199.

Objectives of this seminar

- Learn about the different types of bias in clinical trials and why they are important
- Learn how to detect bias when reading a medical article using validated criteria and methods
- Learn how to critically appraise studies, identify, and record risks of bias in clinical trials when conducting a systematic review
- Gain a better understanding of how studies should be designed and importantly what information authors should report in the study publication to enable readers form a judgement on the evidence presented

What is a systematic review?

- *"A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods that are selected to minimize bias, thus providing reliable findings from which conclusions can be drawn and decisions made"* *(Liberati et al., 2009).*

- *"**Meta-analysis** is the use of statistical methods to summarize and combine the results of independent studies. Many systematic reviews contain meta-analyses, but not all"* *(Liberati et al., 2009).*

Steps of a systematic review

- Preparation (team and resources)
- Define the review question → Register title with PROSPERO
  International prospective register of systematic reviews
  http://www.crd.york.ac.uk/PROSPERO/)
- Plan eligibility criteria
- Plan methods → Publish protocol
- Search for studies
- Apply eligibility criteria in the selection of studies
- Extract data from each study
- Assess risk of bias in included studies
- Analyze and present results
- Interpret results and draw conclusions

Assessing risk of bias in clinical trials

- What is bias?
  - Systematic error or deviation from the truth in results or inferences
- Systematic reviews depend on included studies
  - Incorrect or biased studies = misleading reviews
  - Should I believe the results? A study may have overestimated or underestimated the effect
- Assess each study for “Risk of bias” (RoB)
- Look for methods shown to minimize risk

Bias is not the same as

Imprecision

Random error due to sampling variation (small studies with large uncertainty)

Reflected in the confidence interval

Quality

Bias can occur in RCTs and well conducted studies

Not all methodological flaws introduce bias and not all bias have the same impact on results

Reporting

Good methods may have been used but not well reported

The fact that a study claims to be a randomized controlled trial does not necessarily mean that randomization was properly performed

A common classification scheme for bias

Type of bias	Description
Selection bias	Systematic differences between baseline characteristics of the groups that are compared.
Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.
Attrition bias	Systematic differences between groups in withdrawals from a study.
Detection bias	Systematic differences between groups in how outcomes are determined.
Reporting bias	Systematic differences between reported and unreported findings.

Quality scales and checklists

- Many scales and instruments available
- Not supported by empirical evidence
- Different scales, different conclusions
- May include criteria related to reporting not actual bias
- Numerical weighting not justified
- Difficult for readers to interpret the score

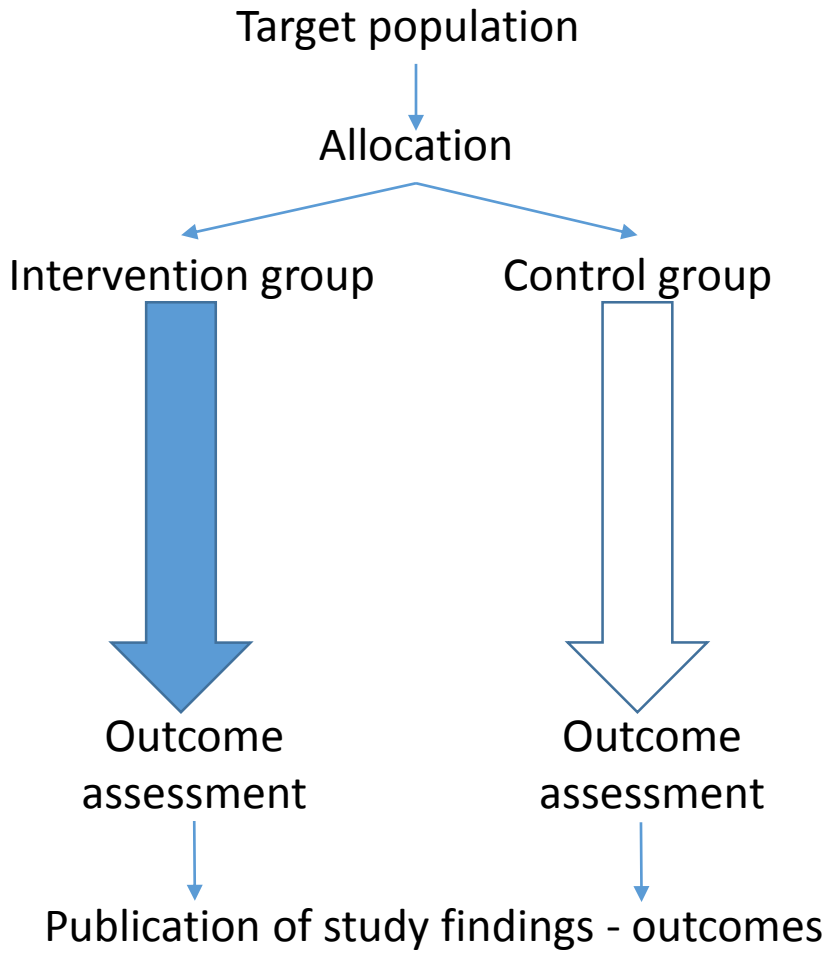
Domains to address in risk of bias assessments

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other bias

Higgins JPT, Altman DG. Assessing Risk of Bias in Included Studies. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. Chichester, UK: John Wiley & Sons, Ltd; 2008:187-241.

Sources of bias and assessment criteria

- Selection bias
  - Random sequence generation
  - Allocation concealment
- Performance bias
- Detection bias
- Attrition bias
- Reporting bias



Random sequence generation

- Occurs at the start of a trial before allocation of participants
- Avoids **selection bias**
- Determines a random order of assigning people into intervention and control groups
- Avoids systematic differences between groups
- Accounts for known and unknown confounders

Random sequence generation

Question: Was the allocation sequence adequately generated?

Low risk - unpredictable

- Random number table
- Computer random number generator
- Stratified or block randomization
- Low tech approaches: coin toss, shuffling cards or envelopes, throwing dice, drawing lots

High risk – predictable

- Quasi-random – date of birth, day of visit, ID or clinical record number, alternate allocation
- Non random – choice of clinician or participant, test results, availability

Unclear

- Insufficient information about the sequence generation process to permit judgement of “Yes” or “No”

Random sequence generation

Example A: “Subjects were enrolled after being seen by the triage nurse, before being seen by a physician and were randomly assigned to the Intervention (I) or Control (C) group.”

Example B: “Adolescents were then randomized into the TeenScreen-ED intervention group or the standard mental health referral control group in blocks of 10. A computerized random number generator was used to derive a list for randomization”

Allocation concealment

- Occurs at the start of the trial during allocation of participants
- Avoids selection bias
- When a person is recruited to the study, no-one can predict which group they will be allocation to
- Ensures the strict implementation of the random sequence
  - Prevents changing the order
  - Prevents selecting who to recruit

Allocation concealment

Question: Was the allocation adequately concealed?

Low risk - unpredictable

- central allocation (phone, web, pharmacy)
- sequentially numbered, sealed, opaque envelopes
- sequentially numbered, identical drug containers
- **High risk – predictable**
- random sequence known to staff in advance
- envelopes or packaging without all safeguards
- non-random, predictable sequence
- **Unclear**
- Insufficient information to permit judgement of “Yes” or “No”

Allocation concealment

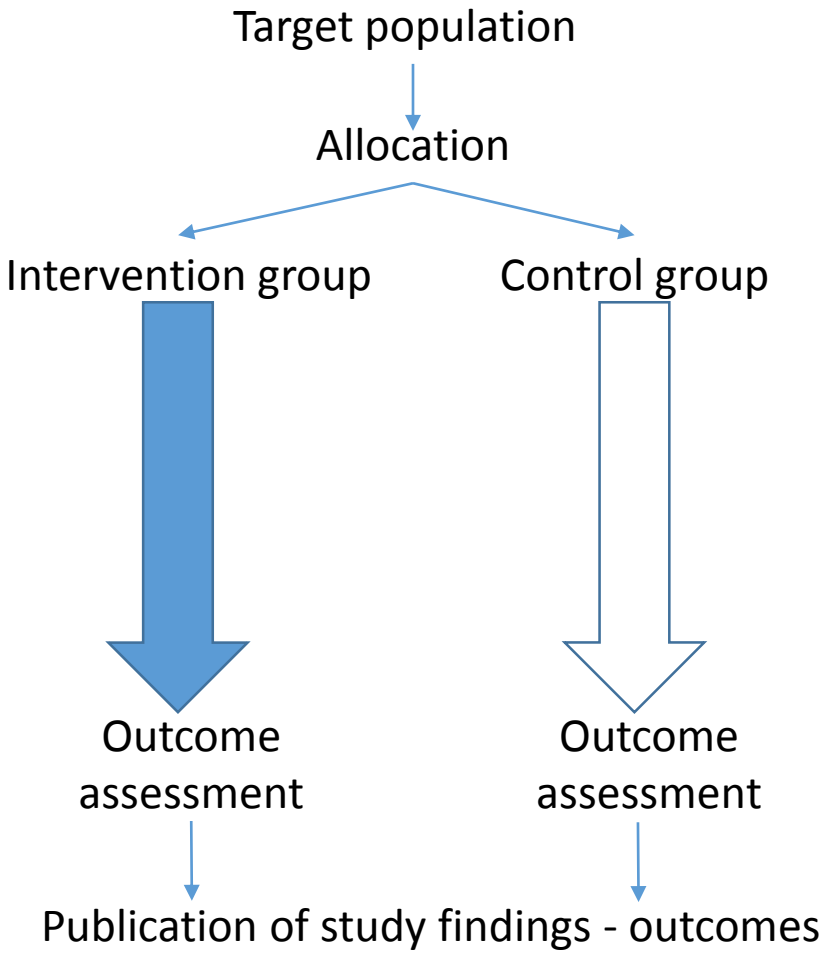
- Example A: “Randomization occurred in blocks of 20 families with the use of sealed and shuffled opaque envelopes prepared by staff unconnected with the trial”

- Example B: “After oral consent was obtained, eligible children were randomized by day to group 1 (no skin test) or group 2 (skin test) using a random number table… A single investigator previously trained to administer the skin tests enrolled all eligible children during the times she was present in the PED”

Sources of bias and assessment criteria

- Selection bias
- Performance bias
- Detection bias
- Attrition bias
- Reporting bias

Blinding of participants and personnel



Blinding of participants and personnel

- Avoids performance bias
  - Differential behaviors across intervention groups (e.g. differential drop out, differential administration of co-interventions)
  - Lack of expectations in a control group
  - Lack of blinding could bias the results by affecting the actual outcomes
- Terms like “single blinding” and “double blinding” are not informative and should be avoided
- Assess carefully the likelihood that blinding was broken
- Consider the impact of non blinding
  - Assessment should be by outcome of interest
  - Objective vs. Subjective outcomes (e.g. mortality vs. pain or quality of life)

Blinding of participants and personnel

Question: Was knowledge of the allocated intervention adequately prevented during the study?

Low risk - unpredictable

- Blinding occurred and unlikely that the blinding could have been broken
- no blinding or incomplete blinding, but outcome unlikely to be influenced or patients were treated according to a strict protocol

High risk – predictable

- No blinding, incomplete or broken blinding, and outcome likely to be influenced

Unclear

- Insufficient information to permit judgement of “Yes” or “No”
- The study did not address this criterion

Blinding of participants and personnel

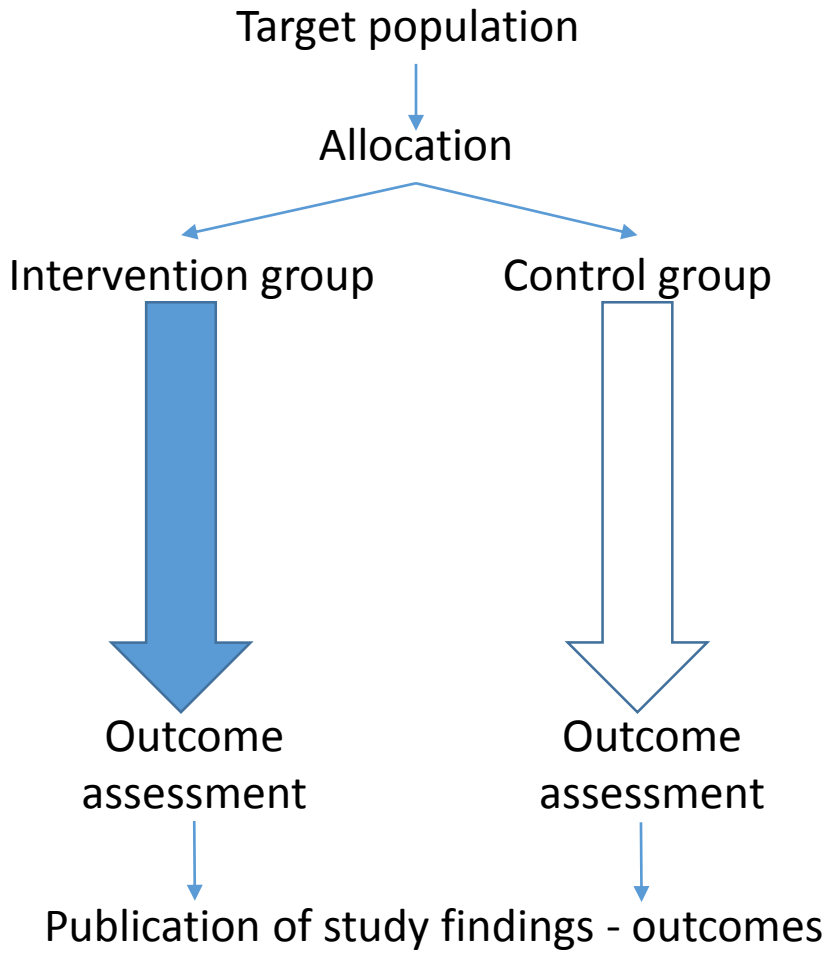
- **Example A** (Hip protectors for preventing hip fractures): “The staff were mostly positive about the hip protectors. They felt that the patients could be left to walk around more freely because the consequences of possible falls were less severe”

- **Example B:** “The patient, treating physician, and primary care outpatient center were blinded to the group assignment”

Sources of bias and assessment criteria

- Selection bias
- Performance bias
- Detection bias
- Attrition bias
- Reporting bias

Blinding of outcome assessment



Blinding of outcome assessment

- Avoids detection bias
  - Measurement of outcomes affected by knowledge of the intervention received
- Assess carefully
  - Avoid terms like “single blinding” and “double blinding”
  - Is it likely that blinding was broken?
  - may be feasible even where blinding of participants and care providers is not
  - remember that participants and personnel may also be outcome assessors

Blinding of outcome assessment

Question: Was knowledge of the allocated intervention adequately prevented during outcomes assessment?

Low risk - unpredictable

- Blinding occurred and unlikely that the blinding could have been broken
- no blinding, but measurement unlikely to be influenced

High risk – predictable

- no blinding or broken blinding, and measurement likely to be influenced

Unclear

- Insufficient information to permit judgement of “Yes” or “No”

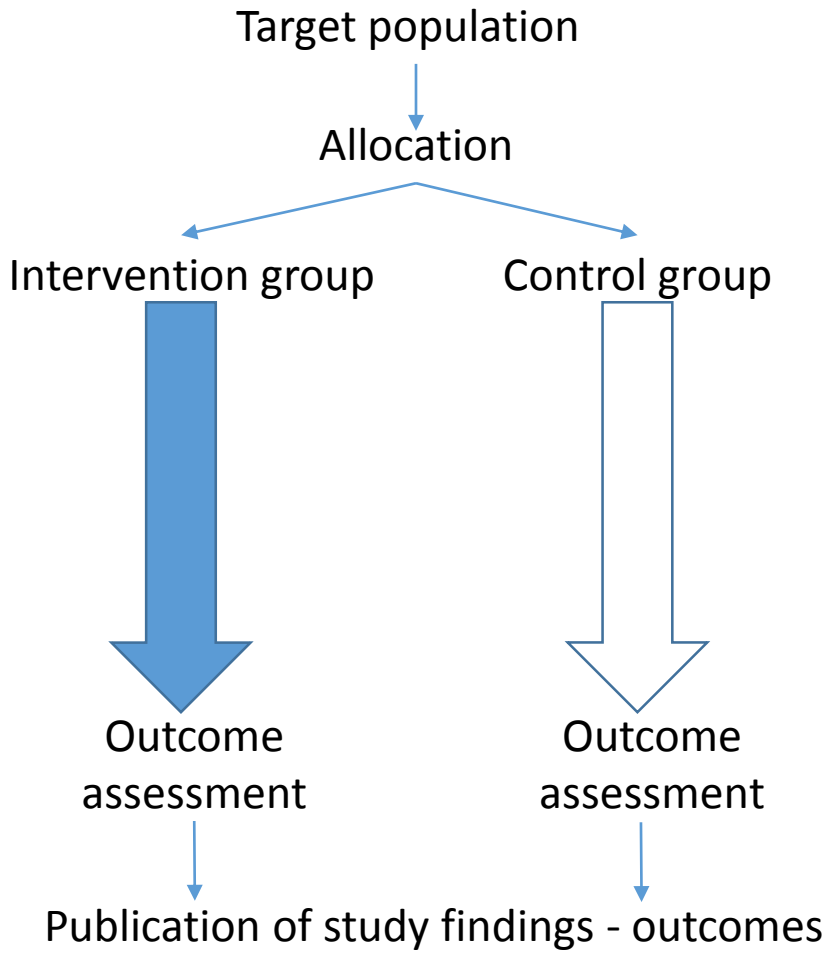
Assessing blinding by outcome

- may reach different conclusions for different outcomes
  - measurement of only some outcomes may be blinded
  - subjective outcomes may be more vulnerable to bias e.g. death vs quality of life
- may apply to both **performance bias** and **detection bias**
- Design your assessment/table with two or more outcome groups for these categories

Sources of bias and assessment criteria

- Selection bias
- Performance bias
- Detection bias
- **Attrition bias**
- Reporting bias

Incomplete outcome data



Incomplete outcome data

- when complete outcome data for all participants is not available for your review
  - attrition - loss to follow up, withdrawals, other missing data
  - exclusions – some available data not included in report
- Can lead to attrition bias
- Considerations
  - How much data is missing from each group?
  - Why is it missing?
  - How were the data analyzed?

How much is too much missing data?

- No simple rule or cut-off point
- Enough missing to meaningfully affect the results
  - Overall proportion of missing data
  - Rate of event risks between intervention and control groups (dichotomous outcomes)
  - Plausible effect size (continuous outcomes)
- Reasons related to study outcomes
  - e.g. adverse events, technological issues, refusal
  - Reasons can have different meaning in each group
- Missing data or reasons not balanced between groups

Intention-to-treat analysis

- all participants analyzed in the groups randomized regardless of what happened during the study
- Issues that may arise
  - Per protocol analysis
    - Non-compliers excluded from analysis
  - As treated analysis
    - Non-compliers moved between groups
  - Imputation of missing values
    - Assumptions may be inappropriate – consult a statistician

Assessing incomplete data by outcome

- May reach different conclusions for different outcomes
  - may be more missing data at different time points
  - some outcomes may have more missing data e.g. sensitive questions, invasive tests
- Option to review and assess studies with two or more outcome groups for ‘incomplete data’

Incomplete outcome data

Question: Were incomplete outcome data adequately addressed?

Low risk - unpredictable

- No missing data
- Reasons for missing data not related to outcome
- Missing data balanced across groups, and reasons similar
- Proportion missing or plausible effect size not enough to have a clinically relevant effect

High risk – predictable

- Reasons related to outcome, and imbalance in numbers or reasons
- Proportion missing or plausible effect size enough to have a clinically relevant effect
- ’as-treated’ analysis with substantial departure from allocation
- Inappropriate use of imputation

Unclear

- Insufficient information to permit judgement of “Yes” or “No”

Sources of bias and assessment criteria

Selection bias

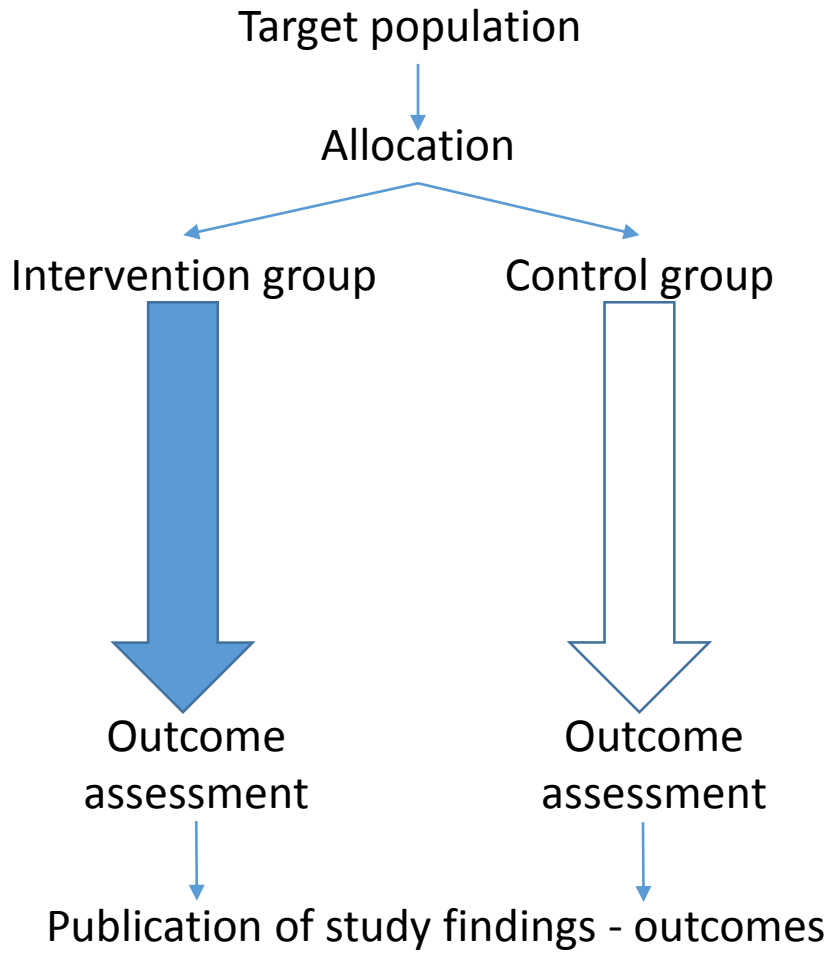
Performance bias

Detection bias

Attrition bias

Reporting bias

Selective reporting



Selective reporting

- Can lead to reporting bias
- Statistically significant results more likely to be reported
- Selective reporting is difficult to determine

Compare methods to results for

- Outcomes measured (or likely to be measured) but not reported
- Outcomes added, statistics changed, presentation of subgroup results only
- Reporting that cannot be used e.g. stating non-significance without numerical results
- Refer to study protocol or trial register

Selective reporting

Question: Are reports of the study free of suggestion of selective outcome reporting?

Low risk - unpredictable

- protocol is available and all pre-specified outcomes of interest are reported in the pre-specified way
- protocol not available but it is clear that all pre-specified and expected outcomes of interest are reported

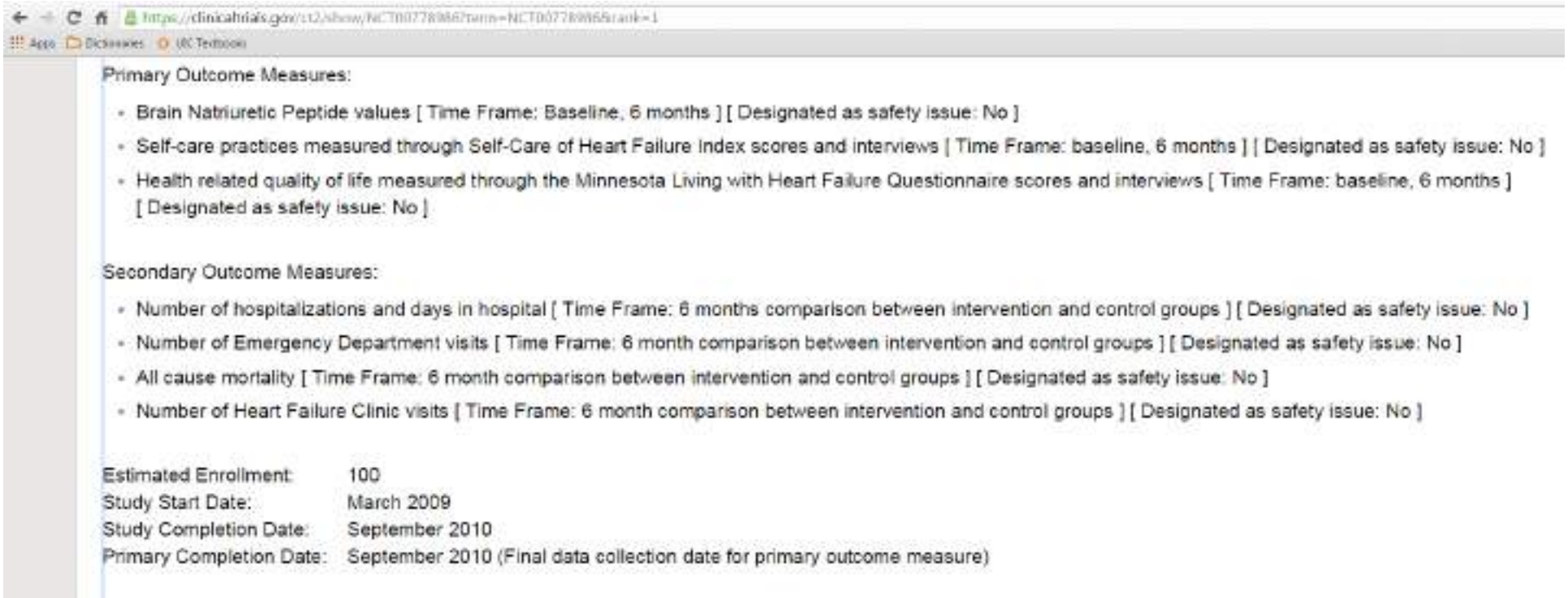
High risk – predictable

- Outcomes not reported as pre-specified or expected e.g. missing, added, subsets, unexpected measurements or methods such as “adjusted ratios”
- Outcomes reported incompletely

Selective reporting

Example of a home telemonitoring trial for heart failure*: **(J Med Internet Res 2012;14(1):e31)*** doi:10.2196/jmir.1909

- "Hospital readmissions, number of nights in hospital, and mortality were secondary outcome measures because the study was underpowered to detect differences between groups for these metrics."



Primary Outcome Measures:

- Brain Natriuretic Peptide values [Time Frame: Baseline, 6 months] [Designated as safety issue: No]
- Self-care practices measured through Self-Care of Heart Failure Index scores and interviews [Time Frame: baseline, 6 months] [Designated as safety issue: No]
- Health related quality of life measured through the Minnesota Living with Heart Failure Questionnaire scores and interviews [Time Frame: baseline, 6 months] [Designated as safety issue: No]

Secondary Outcome Measures:

- Number of hospitalizations and days in hospital [Time Frame: 6 months comparison between intervention and control groups] [Designated as safety issue: No]
- Number of Emergency Department visits [Time Frame: 6 month comparison between intervention and control groups] [Designated as safety issue: No]
- All cause mortality [Time Frame: 6 month comparison between intervention and control groups] [Designated as safety issue: No]
- Number of Heart Failure Clinic visits [Time Frame: 6 month comparison between intervention and control groups] [Designated as safety issue: No]

Estimated Enrollment:	100
Study Start Date:	March 2009
Study Completion Date:	September 2010
Primary Completion Date:	September 2010 (Final data collection date for primary outcome measure)

Other sources of bias

- Funding from sources with a conflict of interest
- Carry over effects in cross-over trials
- Significant baseline imbalances

Do NOT include:

- imprecision (e.g. small sample size)
- diversity (e.g. inadequate dose, unusual population)
- other measures of quality (e.g. ethics approval)

Risk of bias assessment in systematic reviews

- All systematic reviews should have a RoB assessment with analytic results for each study
- At least two assessors – content and methods experts
- Pilot on 3-6 studies to check consistency of assessment
- Looking for missing information
  - Study protocol
  - Contact authors

"Risk of Bias" tables

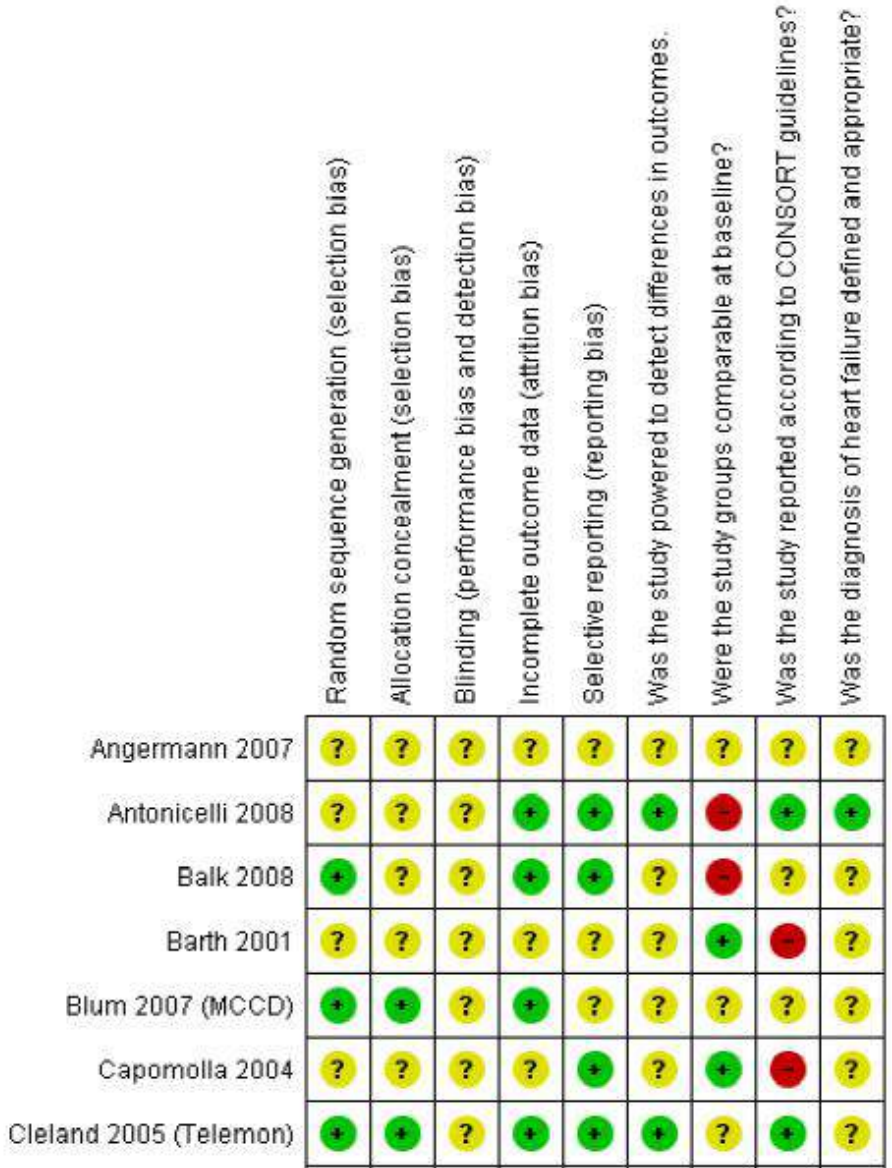
- One for each included study
- Your judgement for each domain
  -  Low risk
  -  High risk
  -  Unclear risk – not enough information to make a clear judgment
- Support for judgment
  - direct quotes from the paper or study author where possible
  - additional comments
  - rationale for any assumptions (e.g. "probably done")
  - state explicitly if no information available

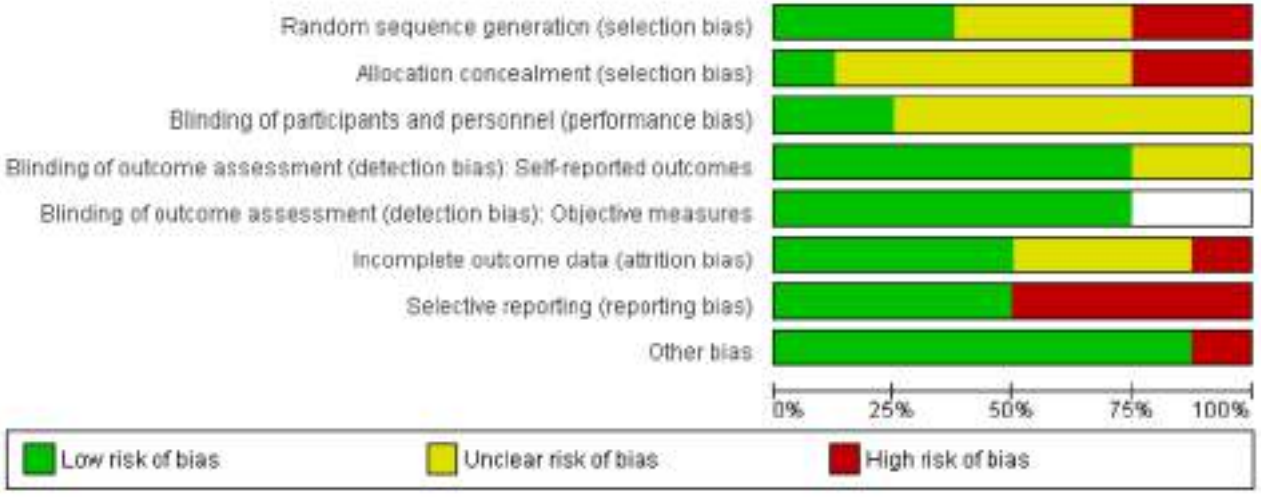
Transparency

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Before initiation of the study, we reviewed the adherence rate for asthma clinic appointments scheduled during a PED visit and found similar rates regardless of the day and time the patient presented to the PED. After oral consent was obtained, eligible children were randomized by day to group 1 (no skin test) or group 2 (skin test) using a random number table. Randomization by day was chosen because at Jacobi Medical Center, all children with asthma exacerbations are treated in the same area. Offering only some children skin tests would not have been acceptable to some parents and may have contaminated the ability to test the hypothesis of the study."
Allocation concealment (selection bias)	High risk	"A single investigator (C.A.S.) previously trained to administer the skin tests enrolled all eligible children during the times she was present in the PED." Comment: The allocation sequence could not have been adequately concealed. The allocation sequence is revealed after recruitment of the first patient for any given day. The main investigator who enrolled all eligible children was also the one who administered the intervention (skin test). Therefore, the possibility of selective enrolment cannot be excluded.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel not blinded
Blinding of outcome assessment (detection bias)	Low risk	Quote "Adherence to follow-up was evaluated by computer confirmation of the patient's asthma clinic visit." Comment: Although no details were provided with respect to blinding of outcome assessors, review authors do not believe this will introduce bias.
Incomplete outcome data (attrition bias)	Low risk	No evidence of incomplete outome data
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other bias

Risk of bias summary and graph - examples





Take home messages

- Biased studies may lead to misleading reviews and decision making
- Use appropriate caution when interpreting the results of the study
- Seven domains of bias to be assessed
- RoB requires critical thinking and judgement
- If you are doing a systematic review you have to assess RoB in the included studies and use the results appropriately in the interpretation of results and formulation of conclusions

References

- Higgins JPT, Altman DG, Sterne JAC (editors). **Chapter 8: Assessing risk of bias in included studies**. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Higgins, J.P., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savović, J., Schulz, K.F., Weeks, L. and Sterne, J.A., 2011. **The Cochrane Collaboration's tool for assessing risk of bias in randomised trials**.*BMJ*, *343*, p.d5928.

Thank you for your attention!

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