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Cochrane
Bias Methods Group
(BMG)

Using the RoB tool to assess risk of bias of included studies

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Bias Method Group
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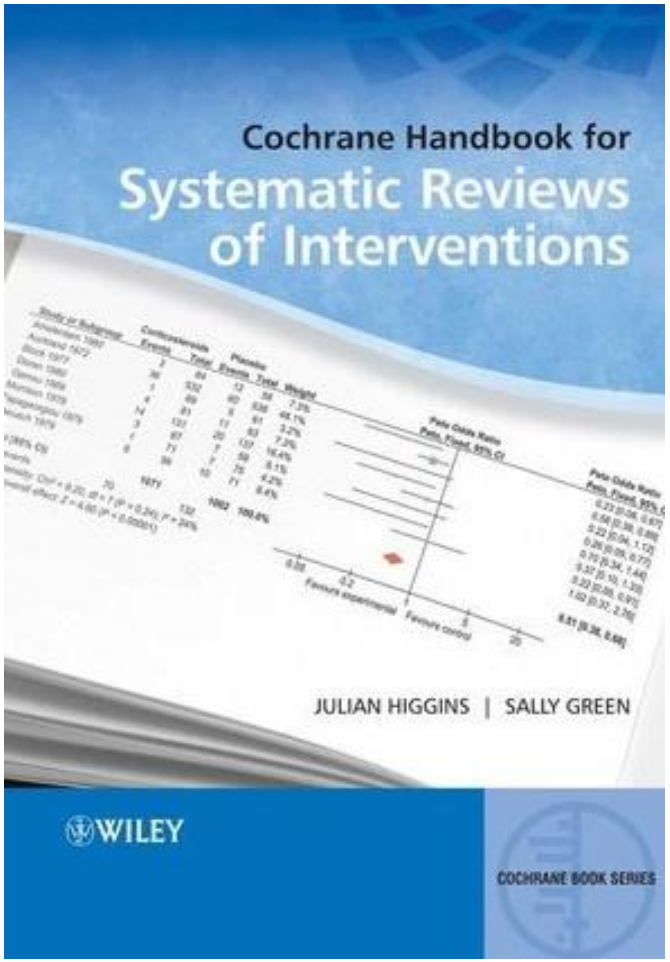
Outlines

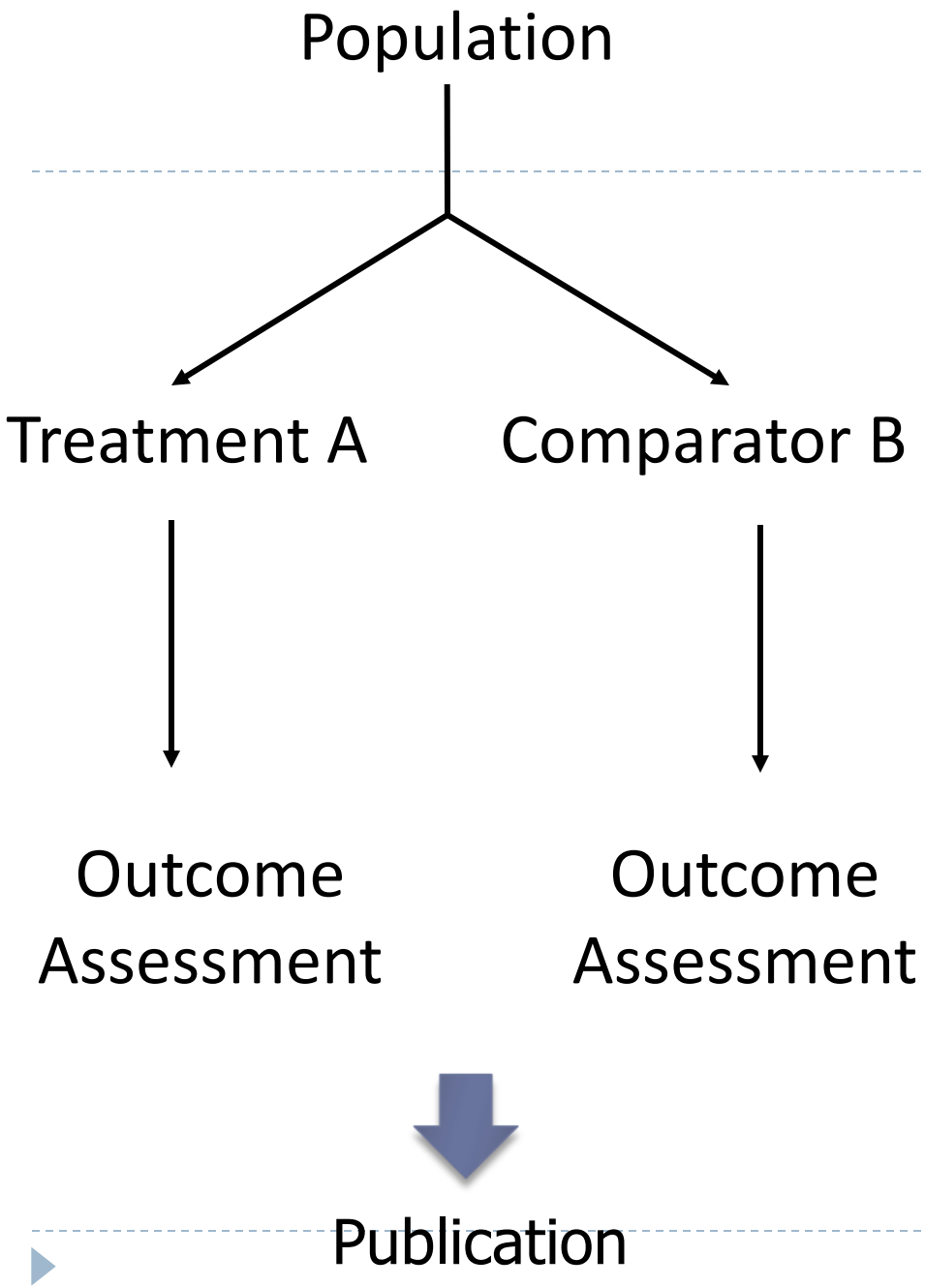
- General principles of the RoB tool
- Selection bias
  - Definition / Examples
- Performance bias
  - Definition / Examples
- Detection bias
  - Definition / Examples
- Attrition bias
  - Definition / Examples
- Risk of bias summary

The Risk of Bias Tool



http://www.cochrane-handbook.org/

Chapter 8



Bias

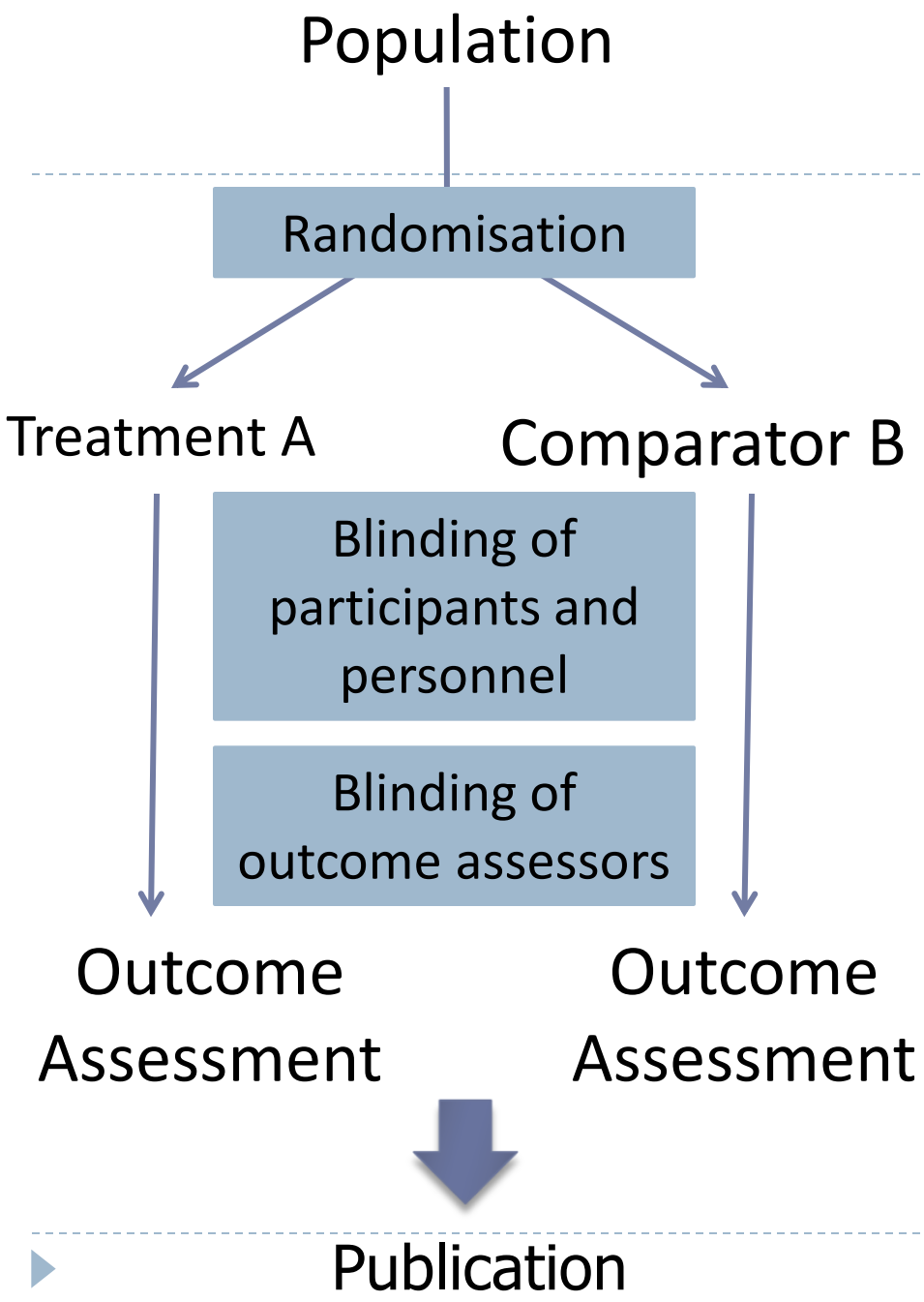
Selection bias

Performance bias

Detection bias

Attrition bias

Reporting bias



Bias

Selection bias

Performance bias

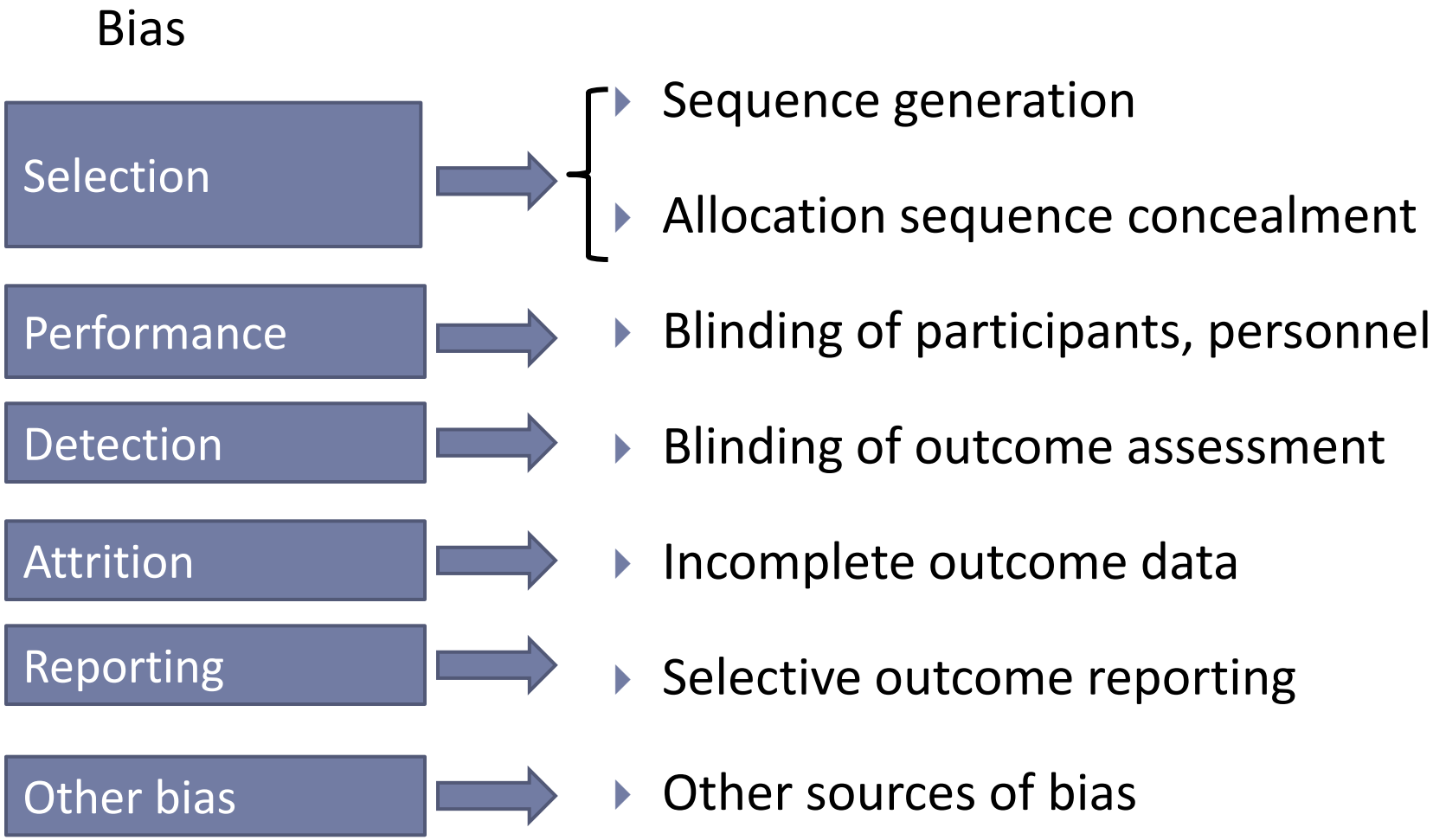
Detection bias

Attrition bias

Reporting bias

The "Risk of Bias" tool

The 7 items



The Cochrane “Risk of Bias” tool

- Sequence generation
- Allocation sequence concealment
- Blinding participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data

Separate assessment for each outcome

- Selective outcome reporting
- Other sources of bias

The “Risk of Bias tool” (RoB)

General principles

- **2 steps**
  - What was **reported**
    - Extraction of what was reported in the published report / protocol/ contact with authors
    - Comment
  - **Judgment** relating to the risk of bias
    - Low risk of bias
    - High risk of bias
    - Unclear (judgment is impossible)

The "Risk of Bias tool" (RoB)

General principles. What was reported?

Sequence generation.	Low	Quote: "patients were randomly allocated". Comment: Probably done, since earlier reports from the same investigators clearly describe use of random sequences (Cartwright 1980).
Blinding of participants and personnel (performance bias)	Low	Quote: "double blind, double dummy"; "High and low dose tablets or capsules were indistinguishable in all aspects of their outward appearance. For each drug an identically matched placebo was available". Comment: Probably done
Blinding of outcome assessment (detection bias) (Mortality)	Low.	Quote: "Obtained from medical records" Comment: review authors do not believe this will introduce bias.

The “Risk of Bias tool” (RoB)

General principles. Judgment

- High risk of bias
  - Bias of sufficient magnitude to have a notable impact on the results
- Unclear risk of bias
  - Insufficient details reported
  - Appropriate reporting, but the risk of bias is unknown

BMJ

RESEARCH

Risk of bias versus quality assessment of randomised controlled trials: cross sectional study

Lisa Hartling, assistant professor Maria Ospina, project manager Yuanyuan Liang, research scientist and biostatistician Donna M Dryden, assistant professor Nicola Hooton, project coordinator Jennifer Krebs Seida, project coordinator Terry P Klassen, professor

Table 1 | Inter-rater agreement using risk of bias tool

	Risk of bias assessments			
Domain	High	Unclear	Low	Weighted κ (95% CI)
Sequence generation	4	107	52	0.74 (0.64 to 0.85)
Allocation concealment	5	105	53	0.50 (0.36 to 0.63)
Blinding	16	49	98	0.35 (0.22 to 0.47)
Incomplete data	25	52	86	0.32 (0.19 to 0.45)
Selective reporting	16	19	128	0.13 (−0.05 to 0.31)
Other sources of bias	15	85	63	0.31 (0.17 to 0.44)
Overall risk of bias	61	96	6	0.27 (0.13 to 0.41)

Hartling L, BMJ, 2009

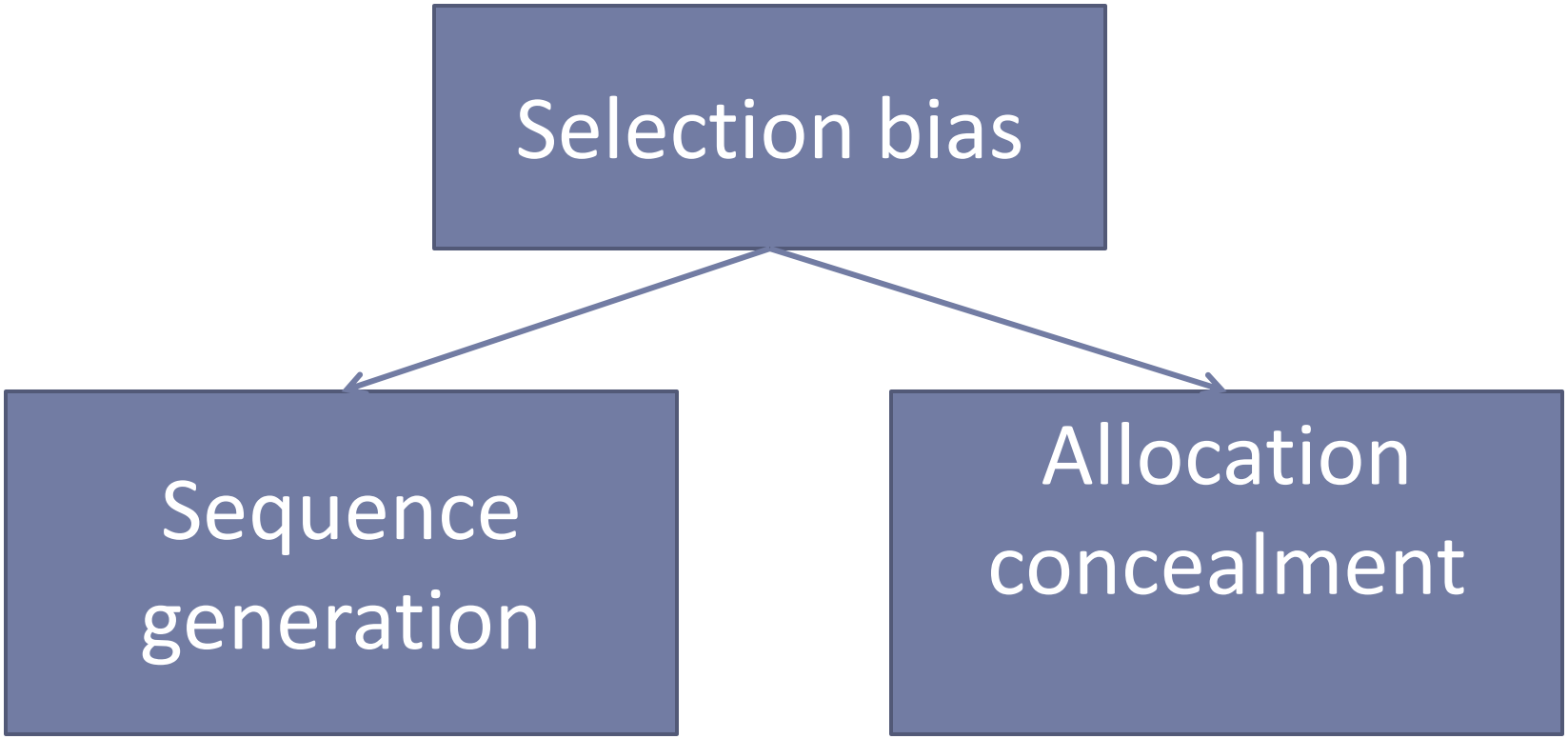
The “Risk of Bias tool” (RoB)

General principles

- Reviewers specifically trained
- Independent duplicate assessment with consensus
- Decisions need to be pre-specified in the protocol
  - Classification of outcomes (subjective / objective)
  - Blinding: successful blinding procedure
  - Missing data
  - Other risk of bias
- Contact authors for missing information

The “Risk of Bias tool” (RoB)

Selection bias



Sequence generation

‘Low risk’ of bias

Row #	A	B	C	D	E	F
1	197	41	286	346	18	259
2	210	350	290	252	258	357
3	318	12	50	274	77	101
4	266	281	280	64	360	103
5	110	349	246	305	305	343
6	264	57	193	313	245	49
7	281	318	287	40	125	231
8	76	175	66	338	96	322
9	266	327	23	85	323	8
10	95	300	239	138	3	71
11	303	119	93	310	64	175
12	134	229	207	84	147	127

Minimization

Sequence generation

‘High risk’ of bias

- A non-random component in the sequence generation process
  - odd or even date of birth
  - some rule based on date (or day) of admission
  - some rule based on hospital or clinic record number…
- Approaches involving judgment
  - Allocation by judgment of the clinician
  - Allocation by preference of the participant
  - Allocation based on a laboratory test or a series of tests
  - Allocation by availability of the intervention…

Sequence generation

‘Unclear risk’ of bias

- No description of the process
- Incomplete description of the process
  - Blocked randomization reported
  - No reporting of the process of selecting the blocks
    - Random number table
    - Computer random number generator

Allocation concealment

'Low risk of Bias'

- Participants and investigators enrolling participants could not foresee assignment
  - Central allocation (including telephone, web-based and pharmacy-controlled randomization)
  - Sequentially numbered drug containers of identical appearance
  - Sequentially numbered, opaque, sealed envelopes

Allocation concealment

‘High risk of Bias’

- Participants or investigators enrolling participants could possibly foresee assignments
  - Using an open random allocation schedule
  - Assignment envelopes were used without appropriate safeguards
  - Alternation or rotation
  - Date of birth
  - Case record number

- Any other explicitly unconcealed procedure

Example


Research

Open Access

High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]

- *"Randomization was by a sequentially numbered computerized randomization algorithm. The allocation to treatment was concealed until study entry."*

Bollen, Critical Care, 2005

Example


Research

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Sequence generation: low risk of bias
Allocation concealment: unclear risk of bias

Bollen, Critical Care, 2005

Combined Intraarterial/Intravenous Thrombolysis for Acute Ischemic Stroke

AJNR Am J Neuroradiol 22:352–358, February 2001

ical Disorders and Stroke (NINDS) study (1). Pretreatment examination revealed 45 eligible patients who presented with a severe but stable hemispheric syndrome who were then randomized to either the thrombolysis or control group, one after another, according to the order of admission. After informed consent requirements were completed, only 12 patients remained in the thrombolysis group whereas 33 patients were included in the conventional treatment, or control, group. Base-

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Sequence generation: high risk of bias
Allocation concealment: high risk of bias

ORIGINAL ARTICLE

Randomised controlled comparison of continuous positive airways pressure, bilevel non-invasive ventilation, and standard treatment in emergency department patients with acute cardiogenic pulmonary oedema

S D Crane, M W Elliott, P Gilligan, K Richards, A J Gray

Emerg Med J 2004;**21**:155–161. doi: 10.1136/emj.2003.005413

Twenty patients each were randomly assigned to standard face mask oxygen, CPAP, or bilevel ventilation. The randomisation sequence was generated using random numbers produced by Microsoft Excel. Assignments were concealed in an opaque envelope, which was then further concealed within another. Once enrolled within the study it was impossible to mask treatment allocation. We aimed to enrol 60 consecutive eligible patients.

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Published as: *Lancet*. 2011 June 30; 378(9785): 49–55.

Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial

Caroline Free[a,*], Rosemary Knight[a], Steven Robertson[a], Robyn Whittaker[b], Phil Edwards[a], Weiwei Zhou[a], Anthony Rodgers[c], John Cairns[a], Michael G Kenward[a], and Ian Roberts[a]

Randomisation and masking

We randomised participants using an independent telephone randomisation system that included a minimisation algorithm balancing for sex (male, female), age (16–18 years, 19–34 years, and >34 years), educational level (to age ≤16 years, >16 years), and Fagerstrom score for nicotine addiction (≤5, >5). The system automatically generated intervention or control group texts according to the allocation. Researchers who gathered data and undertook laboratory analyses were masked to treatment allocation.

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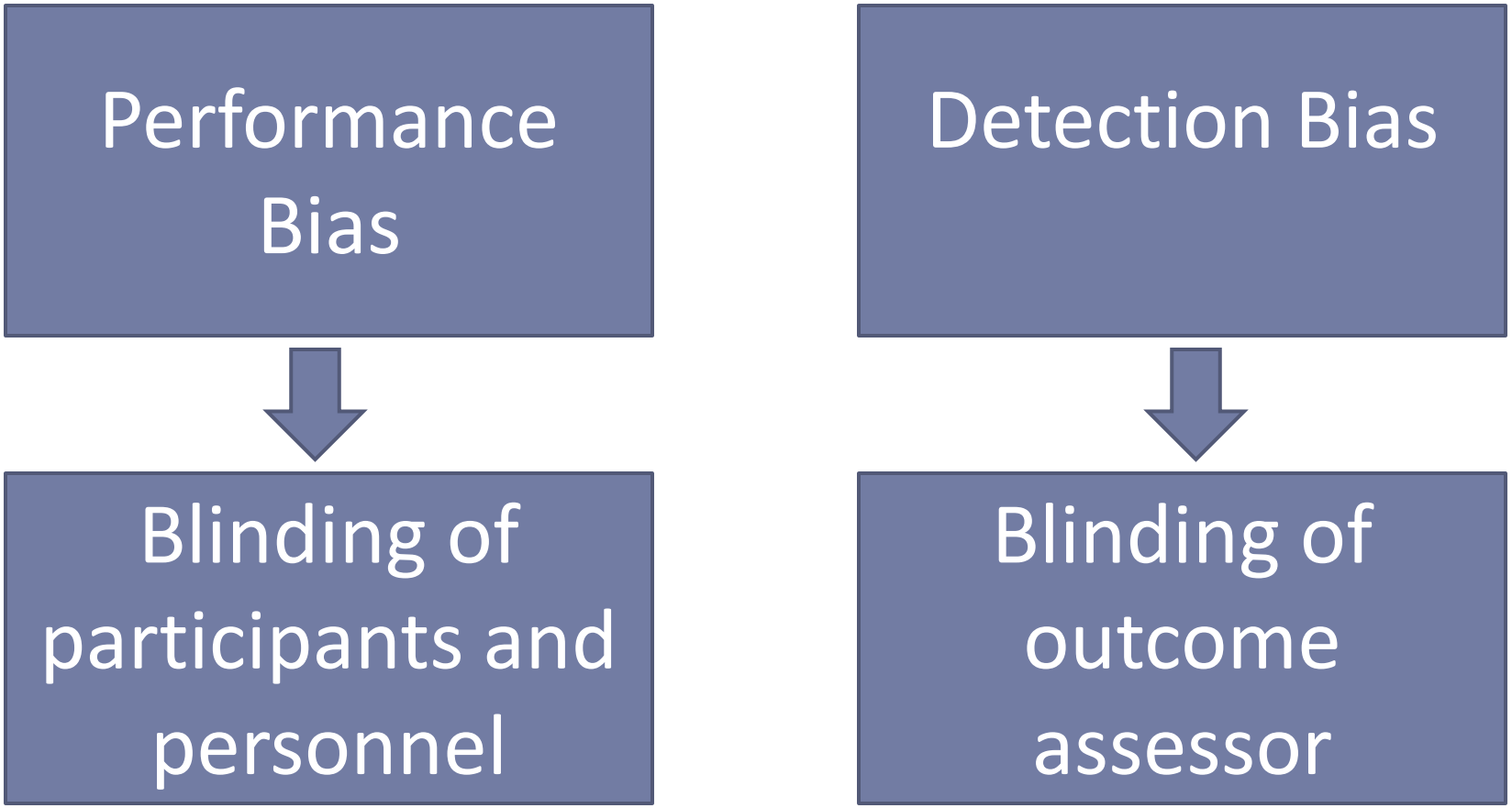
Sequence generation: low risk of bias
Allocation concealment: low risk of bias

The “Risk of Bias tool” (RoB)

Performance and detection bias



The "Risk of Bias tool" (RoB)

Who is blinded?

ELSEVIER

Journal of Clinical Epidemiology 65 (2012) 262–267

Journal of Clinical Epidemiology

ORIGINAL ARTICLES

Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid

Elie A. Akl[a,b,c,*], Xin Sun[c,d], Jason W. Busse[c,e], Bradley C. Johnston[c], Matthias Briel[c,f], Sohail Mulla[c], John J. You[c,g], Dirk Bassler[h], Francois Lamontagne[i], Claudio Vera[j], Mohamad Alshurafa[c], Christina M. Katsios[g], Diane Heels-Ansdell[c], Qi Zhou[c], Ed Mills[c], Gordon H. Guyatt[c,g]

The “Risk of Bias tool” (RoB)

Who is blinded?

No explicit statement about blinding status of patients, heathcare providers, data collectors and outcome adjudicator

- **Probably blinded**
  - Placebo controlled drug trial
  - Active control drug trial with mention « double dummy » or identical
- **Probably not blinded**
  - Active control drug trial no with mention « double dummy » …
  - Non drug trial

The “Risk of Bias tool” (RoB)

Who is blinded?

Reporting as “single”, “double”, “triple” blind

- Single blind
  - Use the best judgment to assign « **probably blinded »** to 1 group et « **probably not blinded** » to the other
- Double blind or triple blind
  - Probably blinded for patients, care providers, data collectors, outcome assessor.

The “Risk of Bias tool” (RoB)

Who is blinded?

Agreement between the consensus using the specific coding scheme and contact of authors

	Agreement
Patients	98.2%
Care Providers	100%
Data collectors	96.3%
Outcome adjudicator/assessor	93.6%

The "Risk of Bias tool" (RoB)

What is the blinding procedure?

- Assessment of zinc treatment for common cold[1,2]
  - Specific taste and aftertaste of zinc
  - Hunches: « anything tasting as bad as zinc and with as much aftertaste as zinc must be a good medicine »
  - Success of blinding was questionnable
- Beta Blocker Heart Attack Study trial[3]
  - Comparison of propanolol and placebo
  - Heart rate change was a major cause of treatment identification

1) Desbiens et al, Annals of Internal Medicine, 2000
2) Fair, J et al.. Chronic Dis., 1987
3) Byington et al., JAMA, 1985

Performance bias

Low risk of bias

- **Blinding** of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

- No blinding or incomplete blinding, but the review authors judge that the outcome **is not likely** to be influenced by lack of blinding

Performance bias

High risk of bias

- No blinding or incomplete blinding, and the outcome **is likely** to be influenced by lack of blinding

- Blinding of key study participants and personnel attempted, but **likely that the blinding could have been broken**, and the **outcome is likely to be influenced** by lack of blinding.

Example

Research

Open Access

High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]

- Outcome: cumulative survival without mechanical ventilation or oxygen dependency at 30 days
- No mention on blinding and blinding of patients and care providers not feasible
- "Patients were crossed over to the alternative ventilator in case of therapy failure"
  - **Seven patients (19%) treated with HFOV crossed over to CV**
  - **in the CV group four patients (17%) were switched to HFOV.**
  - **Of the four patients that crossed over in the CV group, two patients died and one patient was on supplemental oxygen therapy at 30 days. In the HFOV group, five patients that crossed over died and two patients were still on ventilator or needed extra oxygen.**

Bollen, Critical Care, 2005

Example

Research

Open Access

High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]

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Blinding of participant and personnel: High risk of bias

Bollen, Critical Care, 2005

Detection bias
Assessment

- Who is assessing the outcome?
  - Patients
  - Care providers
  - Other
- Is the outcome assessment blinded?
- Is the blinding procedure efficient?
- Is the outcome subjective/objective?

Detection bias

Low risk of bias

- **Blinding of outcome assessment** ensured, and unlikely that the blinding could have been broken

- **No blinding** of outcome assessment, but the review authors judge that the outcome measurement is **not likely** to be influenced by lack of blinding

Detection bias

High risk of bias

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- **Blinding** of outcome assessment, but likely that the blinding could have been **broken**, and the outcome measurement is **likely to be influenced** by lack of blinding

Photochemotherapy for severe psoriasis without or in combination with acitretin: A randomized, double-blind comparison study

A. Tanew, MD,[a] A. Guggenbichler, MD,[b] H. Hönigsmann, MD,[a] J. M. Geiger, MD,[c] and P. Fritsch, MD[b] *Vienna and Innsbruck, Austria, and Basle, Switzerland*

Acitretin (1 mg/kg body weight/day) or placebo was given for 5 days as a monotherapy. Beginning on day 6, photochemotherapy (four PUVA exposures per week) was added to the drug treatment. The combined treat-

[...]

for a maximum of 11 weeks. All patients were seen twice weekly by the same investigator for assessment of treatment response and UVA dose adjustments.

PO: clearing of psoriasis

Tanew, J Am Acad Dermatol. 1991

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- Double blind procedure: not credible because of high frequency of cheilitis
- Outcome: subjective outcome
- **High risk of bias**

Tanew, J Am Acad Dermatol. 1991

Example

Research

Open Access

High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]

- *Assessment of the principal outcomes and repeated measurements **was not blinded**.*

- *Outcomes consisted of:*
  - *Therapy failure*
  - *Mortality*

Bollen, Critical Care, 2005

Example

Research

Open Access

High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]

- *Assessment of the principal outcomes and repeated measurements* ***was not blinded****.*

- *Outcomes consisted of:*
  - *Therapy failure;*
  - *Mortality*

Blinding of outcome assessment

Mortality: low risk of bias

Therapy failure: high risk of bias

Bollen, Critical Care, 2005

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Outcomes

Self-reporting continuous abstinence at 6 months

Biochemically verified continuous abstinence at 6 months

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Blinding of outcome assessment

- **Self-reporting continuous abstinence at 6 months : high risk**
- **Biochemically verified continuous abstinence at 6 months : low risk**

Rheumatology 2003;42:1545–1549
doi:10.1093/rheumatology/keg394, available online at www.rheumatology.oupjournals.org
Advance Access publication 16 June 2003

Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone

A. Marchesoni, N. Battafarano, M. Arreghini, B. Panni, M. Gallazzi[1] and S. Tosi

Study design

This was a 12-month, controlled, randomized single-blind (the clinical investigator was blinded to the treatment) trial designed to compare the efficacy of CsA plus MTX with that of MTX alone in terms of radiographic progression.

Concomitant medication

Corticosteroids were allowed but their dose could not exceed 10 mg/day of prednisone or equivalent. Local corticosteroid injections were not allowed in the joints of the hands or feet used to score the radiographic changes.

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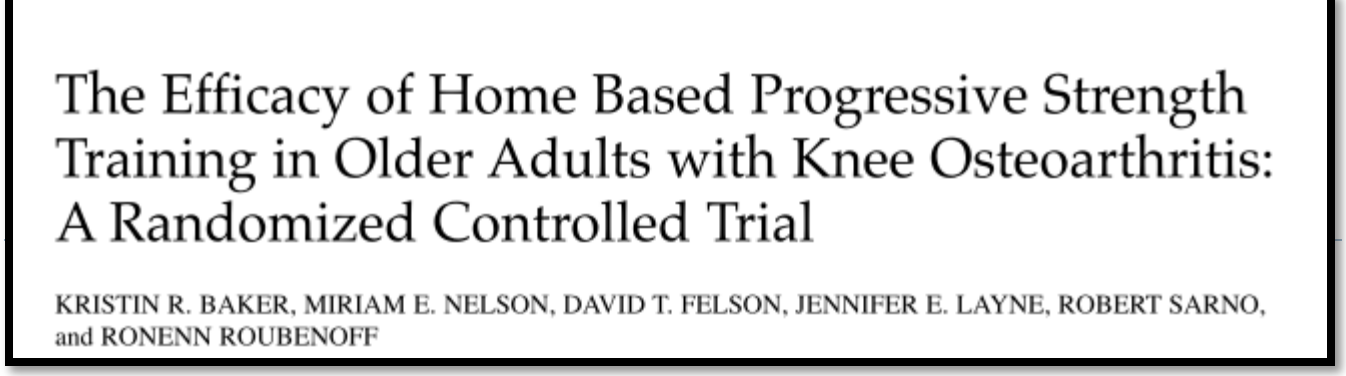
Primary outcome: radiographic damage score assessed by blinded outcome assessors

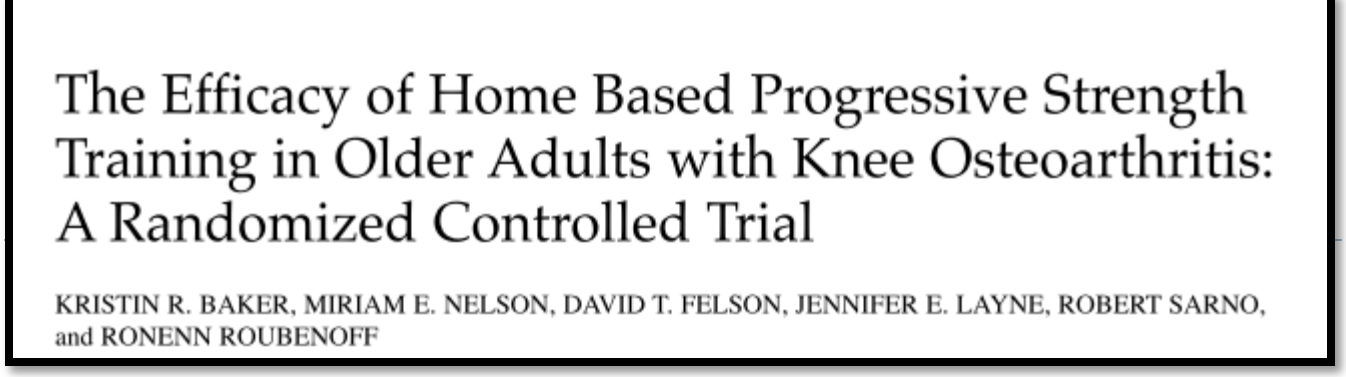
Blinding of patients and personnel: low risk of bias
Blinding of outcome assessment: low risk of bias



The Efficacy of Home Based Progressive Strength Training in Older Adults with Knee Osteoarthritis: A Randomized Controlled Trial

KRISTIN R. BAKER, MIRIAM E. NELSON, DAVID T. FELSON, JENNIFER E. LAYNE, ROBERT SARNO, and RONENN ROUBENOFF

- Experimental treatment: Home-based exercise
- Comparator: attention control intervention on Nutrition
  - Believable treatment
  - Behavior change similar to exercise.
  - Booklet
  - Home visits
  - Food logs
- Patients blinded to the active treatment
  - Information: comparison of the effects of both exercise and nutrition.



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- Outcome: WOMAC (patient reported outcome measuring pain and function)
- Adherence
  - Exercise group: Mean (SD) = 84+/-27%
  - Nutrition group: Mean (SD) = 65+/-32%

Performance bias??
Detection bias??

The “Risk of Bias tool” (RoB)

Attrition bias

- How much data is missing from each group?
- Why are data missing in each group?
- How were data analysed?
  - Handling of incomplete outcome data

Attrition bias

Low risk of bias

- No missing outcome data
- Reasons for missing data not related to outcome
- Missing data balanced across groups, with similar reasons
- Missing data not enough to have a clinically relevant impact on the intervention effect estimate
- Missing data have been imputed using appropriate methods.

Attrition bias

High risk of bias

- Reason for missing data related to outcome, with either imbalance in numbers or reasons
- Missing data enough to induce clinically relevant bias in intervention effect estimate
- ‘As-treated’ analysis with substantial departure of the intervention received from that assigned at randomization
- Inappropriate use of imputation

Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial

*Michael Rud Lassen, Gary E Raskob, Alexander Gallus, Graham Pineo, Dalei Chen, Philip Hornick, and the ADVANCE-2 investigators**

Outcome measures

The primary outcome measure of efficacy was the composite of adjudicated asymptomatic or symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause death (all venous thromboembolism and all-cause death), with onset during the intended treatment period of 12 days (within 2 days) or within 2 days of last dose of study drug, whichever was longer. The main secondary outcome measure (major venous thromboembolism) was the composite of

and venous thromboembolism-related death during this period. The presence or absence of asymptomatic deep vein thrombosis at the end of the intended treatment period was assessed with bilateral venography[11] done between day 10 and day 14 (day 1 was the day of surgery). Clinically suspected deep vein

surgery.

Primary efficacy analysis included data for all patients randomly allocated to treatment who had an assessable efficacy outcome (patients who, during the intended treatment period, had a venogram adjudicated as assessable, who developed confirmed deep vein thrombosis or pulmonary embolism, or who died from any cause); patients who had important protocol violations were excluded from the per-protocol analysis.

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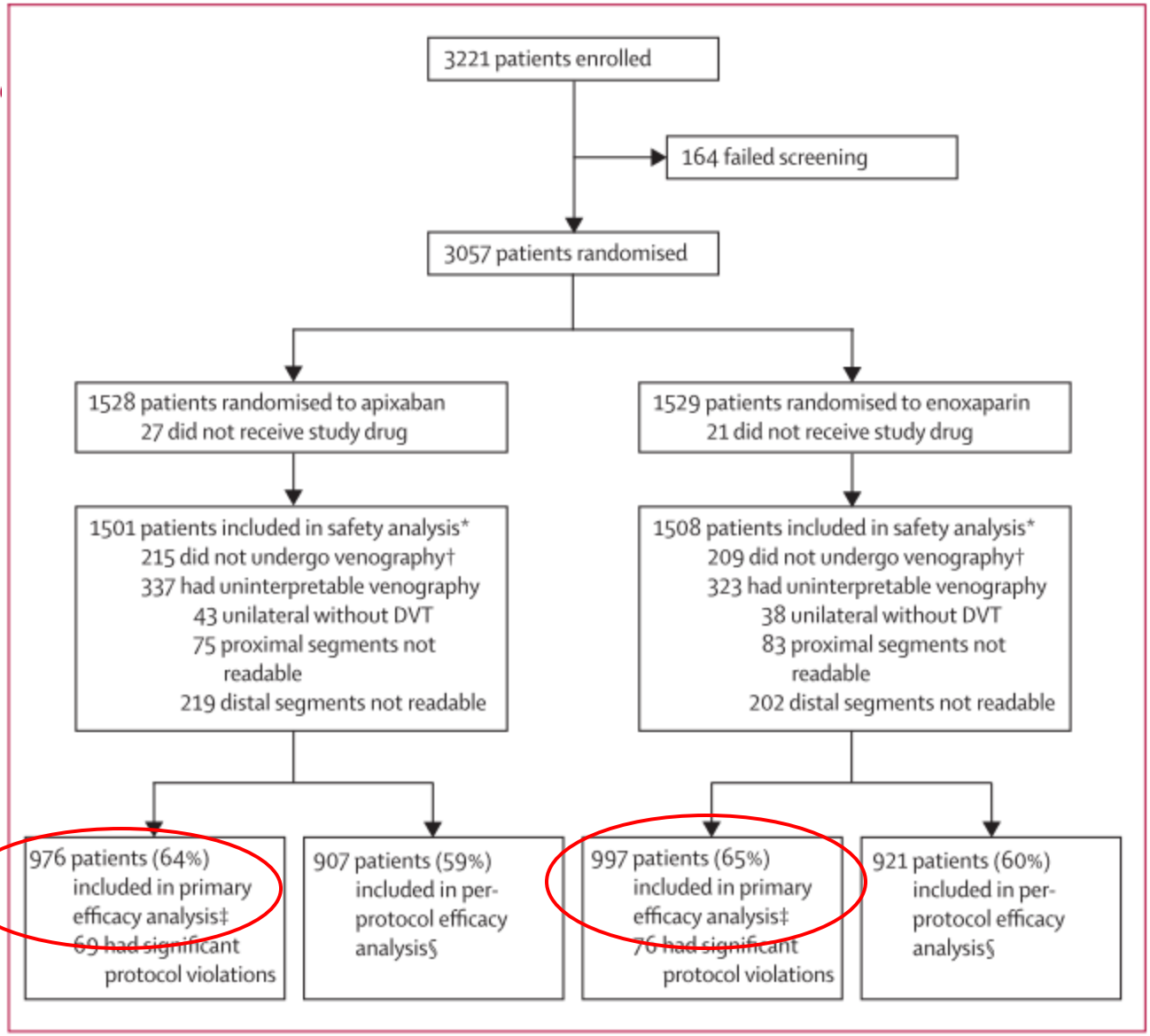
Michael Rud Lassen, Gary E Raskob, Alexander Gallus,



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Incomplete outcome data

PO: High risk of bias: Missing outcome: 35%

The Gerontologist
Vol. 44, No. 2, 217–228

Impact of the Fit and Strong Intervention on Older Adults With Osteoarthritis

Susan L. Hughes, DSW,[1] Rachel B. Seymour, MS,[1] Richard Campbell, PhD,[1] Naomi Pollak, MS, PT,[1] Gail Huber, MHPE, PT,[2] and Leena Sharma, MD[3]

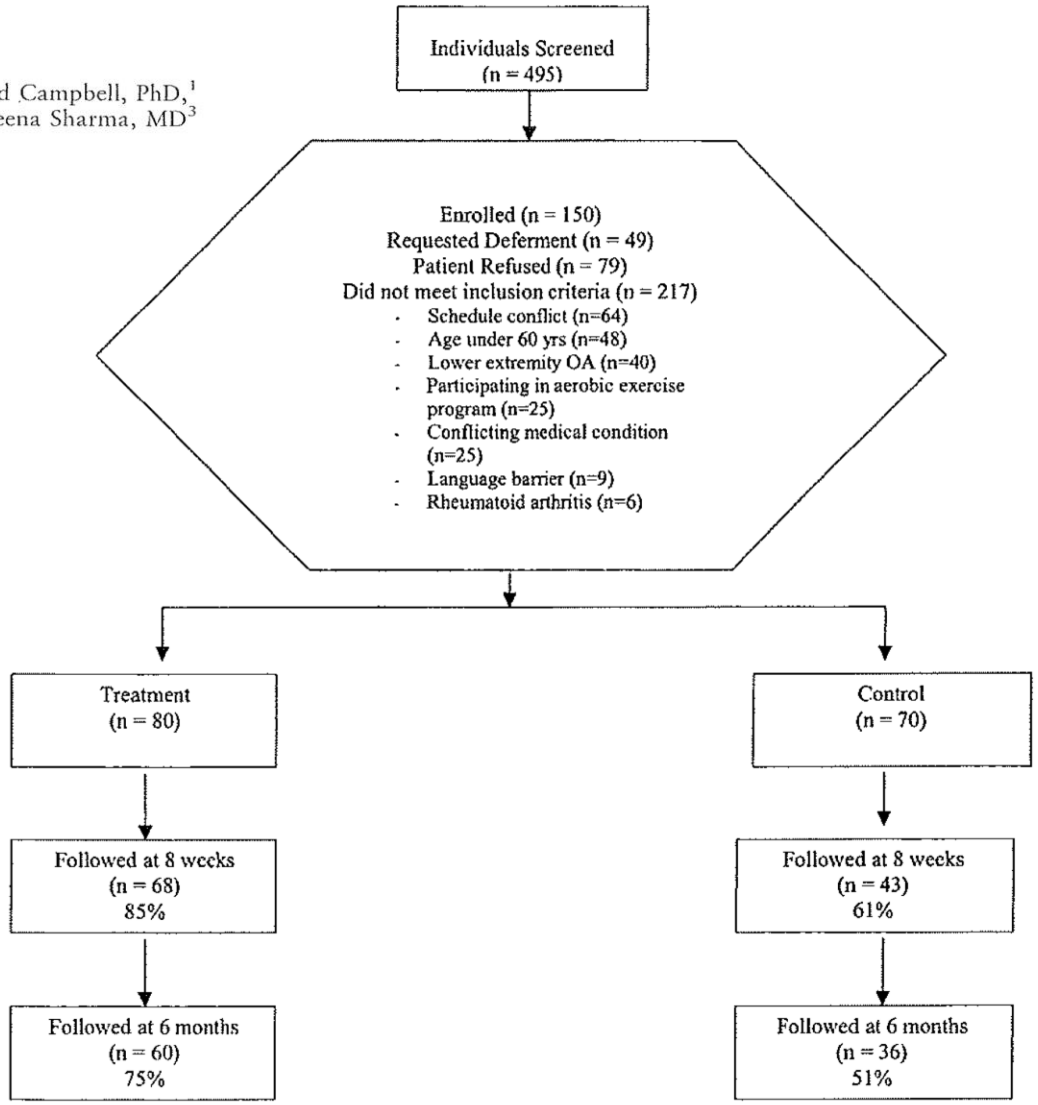
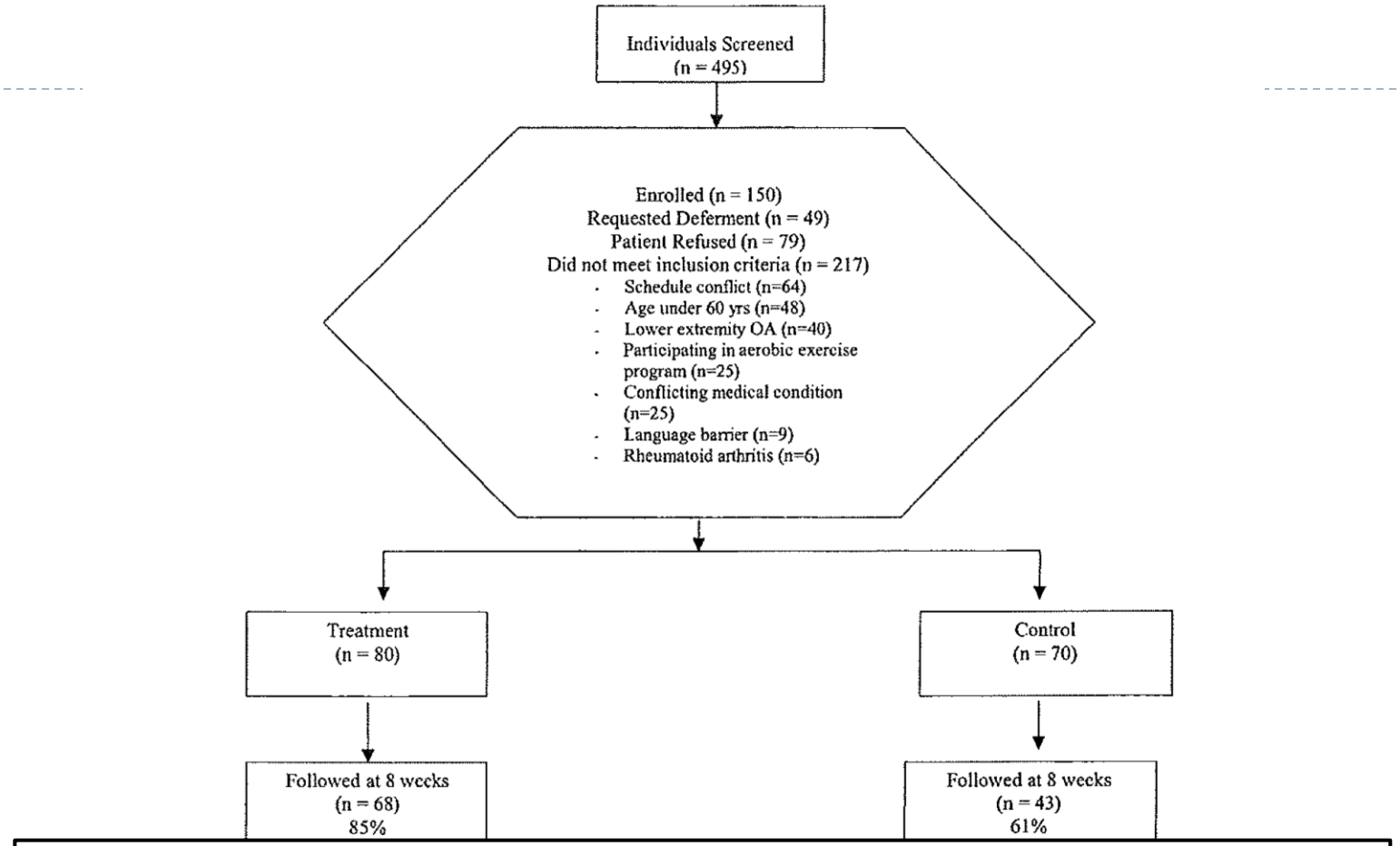


Figure 1. Flow diagram: Iterations 1–7 (OA = osteoarthritis).



Incomplete outcome data

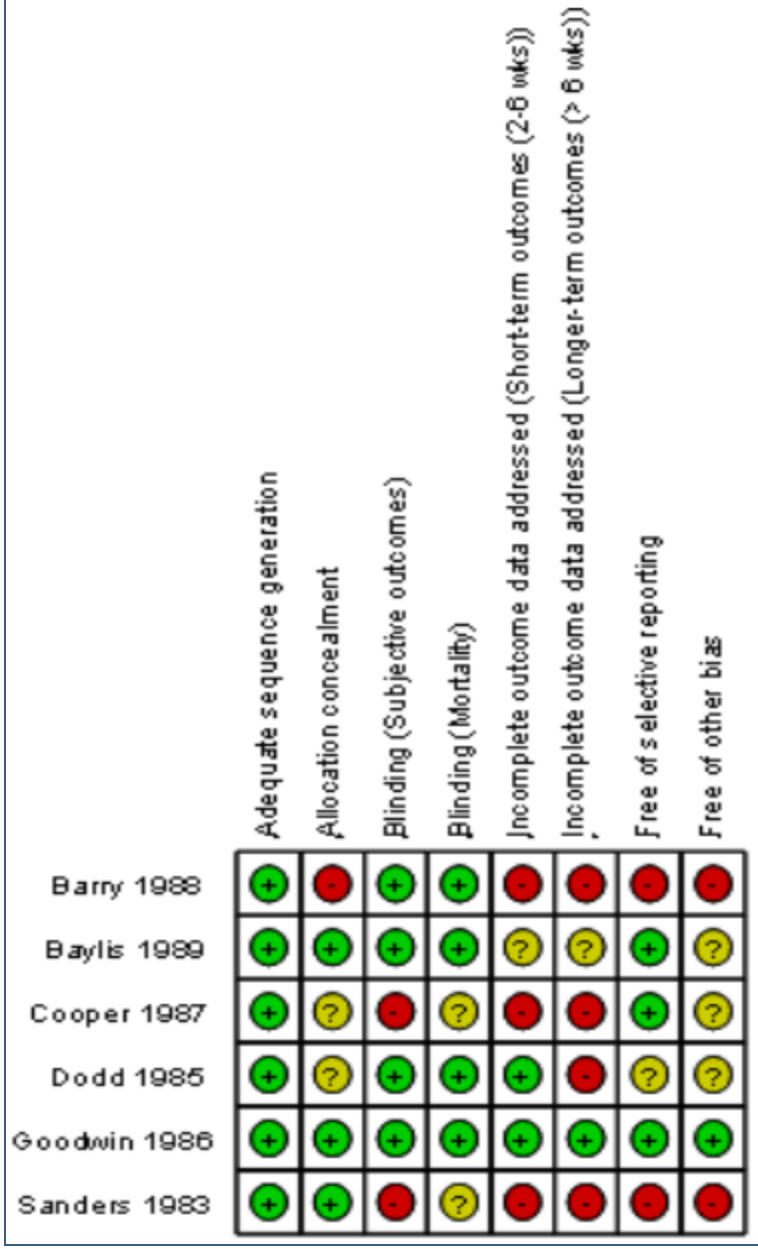
High risk of bias

Figure 1. Flow diagram: Iterations 1–7 (OA = osteoarthritis).

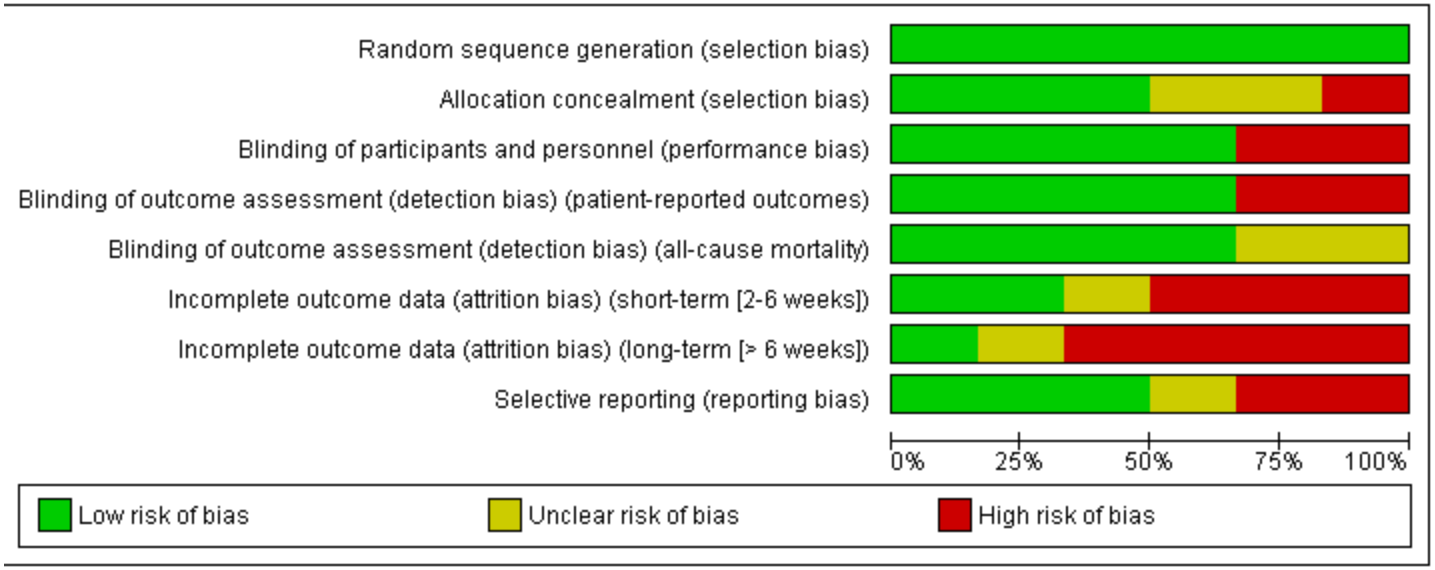
Risk of bias summary

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "...participants born on even days were assigned to the experimental group and participants born on odd days were assigned to the control group."
Allocation concealment (selection bias)	High risk	Comment: allocation by date of birth would allow prediction of the allocation sequence.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "Caffeinated and decaffeinated coffee... was identical in appearance, colour and taste." Comment: it is likely that participants were blinded. Blinding of study personnel was not described.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Comment: Blinding of outcome assessors was not described.
Blinding of outcome assessment (detection bias) Reaction time	Low risk	Comment: Blinding of outcome assessors was not described, but is unlikely to affect measurement of this outcome.
Incomplete outcome data (attrition bias)	High risk	Comment: outcome data for adverse events were only reported for 53 of 58 participants in the caffeine group. Reasons for loss to follow-up were not described.
Selective reporting (reporting bias)	High risk	Comment: alertness was the primary outcome of the study, but data were not reported. Study protocol was not available to identify any other unreported outcomes. Outcome data were presented for drowsiness although this was not listed as an outcome of interest in the study methods.
Other bias	Low risk	Comment: none were identified.

Figure 8.6.c: Example of a 'Risk of bias summary' figure



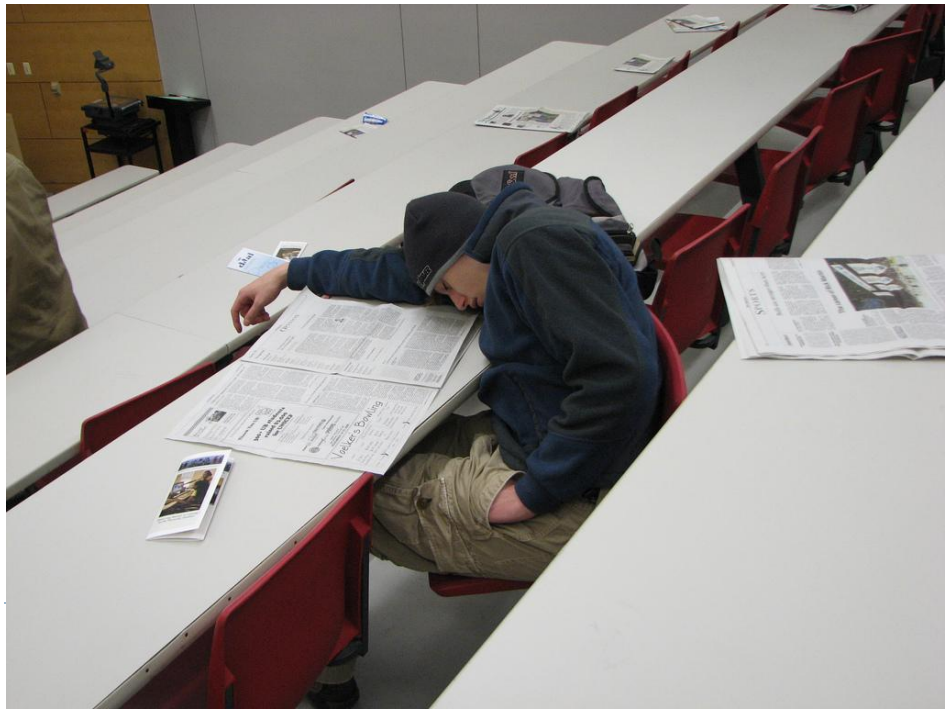
Risk of bias summary



Assessing risk of bias in included studies

CHOC-ATT Trial

Does **CHOC**olate improve **ATT**ention during workshops and reduce sleepiness?



Conclusions

- Assessing the risk of bias is an essential step for an appropriate interpretation of systematic reviews and meta-analysis
- 7 items to be evaluated
- Training and use of the handbook recommendations
- Need for transparency