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Cochrane Learning live webinar: June 23rd 2020

RoB 2 Domain 1: Bias arising from the randomization process

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With special thanks to Julian Higgins, Jonathan Sterne, Matthew Page, Roy Elbers, Barney Reeves, Asbjørn Hróbjartsson, Isabelle Boutron, Luke McGuinness, Vincent Cheng and all RoB 2 collaborators

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RoB 2: contributors

Core group:

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Session outline

- An overview of how bias can arise during the randomization process
  - Random allocation sequence generation
  - Allocation sequence concealment
- Evidence of problems during randomization from baseline imbalances
- Assessing risk of bias from the randomization process in RoB 2
- An example
- Resources available
- Questions

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Poll

Did you attend the Cochrane learning live webinar “Introduction to RoB 2”?

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Poll

Have you used the original (2008 or 2011) version of the Cochrane risk of bias tool?

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Poll

Have you used RoB 2 before?

Risk of bias in randomized trials

Bias arising from the randomization process

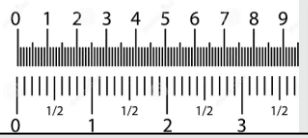
Bias due to deviations from intended intervention

Bias due to missing outcome data

Bias in measurement of the outcome

Experimental

Comparator



Outcome

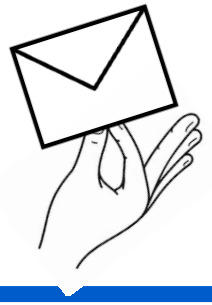
Outcome

1.02 3.87
2.20 4.32
1.38 5.44

Bias in selection of the reported result

Risk of bias in randomized trials

Bias arising from the randomization process



Bias due to deviations from intended intervention

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Comparator

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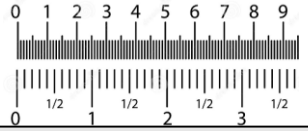

Outcome

Outcome

1.02	3.87
2.20	4.32
1.38	5.44

Bias in selection of the reported result

Bias arising from the randomization process

Biased allocation to groups: *factors that predict the outcome influence group allocation*

Biased enrolment into study: *factors that predict the outcome influence whether a participant is enrolled into the study depending on predicted intervention assignment*

Adequate randomization and allocation concealment prevents both types of bias

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Randomization: a two-step process

- Generate an unbiased, unpredictable allocation sequence
- Conceal the allocation sequence

Random allocation sequence

- allocation of participants to interventions occurs at the start of a trial
  - based on random assignment of participants into experimental or comparator intervention groups
  - avoids systematic differences in known or unknown prognostic factors between groups

Random allocation sequence

Adequate - unpredictable sequence

- these days, almost always computer-generated
- low tech - coin toss, shuffling cards or envelopes, throwing dice, drawing lots, random number tables
- minimization

Inadequate – predictable sequence

- 'quasi-random': alternate allocation, date of birth, day of visit, ID or record number
- non-random: choice of clinician or participant, test results, availability

Allocation sequence concealment

- occurs at the point of allocating participants to interventions
  - it is essential that when a person is recruited to the study, no-one can predict which group they will be allocated to
- ensures that the random sequence is implemented by preventing knowledge of the next allocation from:
  - changing the order of enrolment
  - affecting selection of who to enrol

Allocation sequence concealment

Adequate – cannot foresee

- central allocation (phone, web, pharmacy)
- sequentially numbered, sealed, opaque envelopes
- sequentially numbered, identical drug containers

Inadequate – can foresee

- random sequence known to staff in advance
- envelopes or packaging without all safeguards
- deducing last allocation(s) in fixed size blocks
- any non-random, predictable sequence

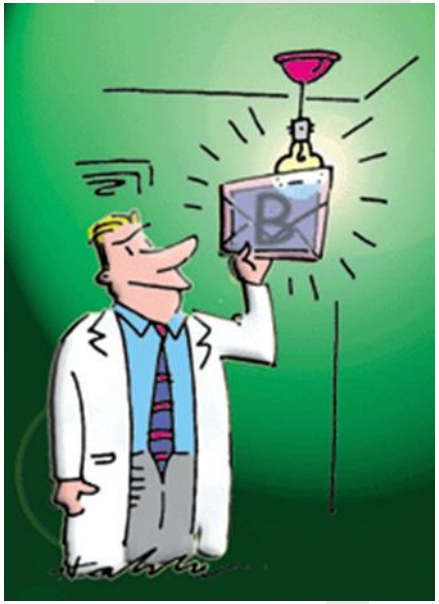
Subverting randomization

Examples from Schultz JAMA 1995;274(18):1456-8.

- Taking advantage of posting of the allocation sequence on a bulletin board.
- Opening unsealed envelopes, holding translucent envelopes up to a light, feeling the differential weight of envelopes, opening unnumbered envelopes until a desired treatment found.
- From appearance of tablets or labels

Reasons?

"They perhaps "know" the more effective treatment, so they may want certain patients to benefit or may want the results of a study to reveal what they believe to be valid."



Evidence from baseline imbalance

- *Occasionally*, baseline imbalance provides evidence that randomization was not performed adequately
  - e.g. substantial differences between **intervention group sizes** (compared with intended allocation ratio)
  - e.g. **substantial excess in statistically significant differences** in baseline characteristics, clearly beyond that expected by chance
    - a few instances of "P <0.05" is not considered a substantial excess

Imbalances in baseline variables that have arisen due to chance do not lead to bias

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Poll

If 20 variables are measured at baseline, would you expect at least one variable to have an imbalance leading to a $p<0.05$?

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Answer

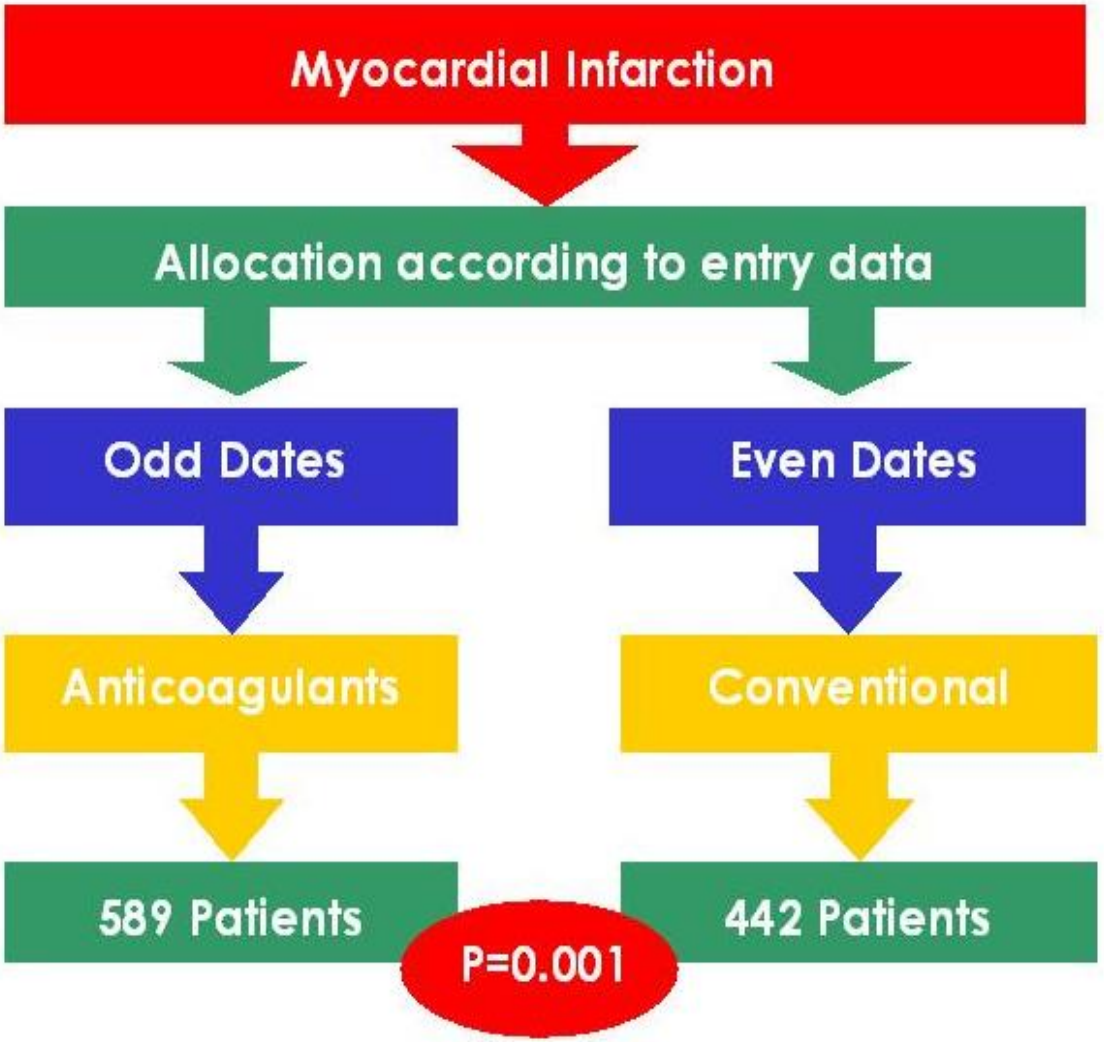
If 20 variables are measured at baseline, would you expect at least one variable to have an imbalance leading to a $p<0.05$?

Yes!

If we assume that the variables measured are uncorrelated (do not affect each other), we would expect 1 in 20 tests to have a $p<0.05$.

More may occur by chance if factors are correlated (for e.g. a chance imbalance in age may lead to imbalance in other factors that are associated with age).

Example: Anticoagulation for myocardial infarction



Wright 1948, Pocock 1991

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Poll

What is the likely reason for unbalanced numbers allocated to the two groups in the anticoagulation for myocardial infarction trial?

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Answer

What is the likely reason for unbalanced numbers allocated to the two groups in the anticoagulation for myocardial infarction trial?

We don’t know for sure but…

there is the suspicion that investigators manipulated the allocation so that more patients were recruited on odd dates, when they would receive the new anticoagulant.

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Baseline imbalance despite solid methods described

International Journal of Epidemiology, 2016, 223–231
doi: 10.1093/ije/dyv292
Advance Access Publication Date: 3 November 2015
Original article

IEA

Miscellaneous

The effect of u
incidence of di
scuba diving: a

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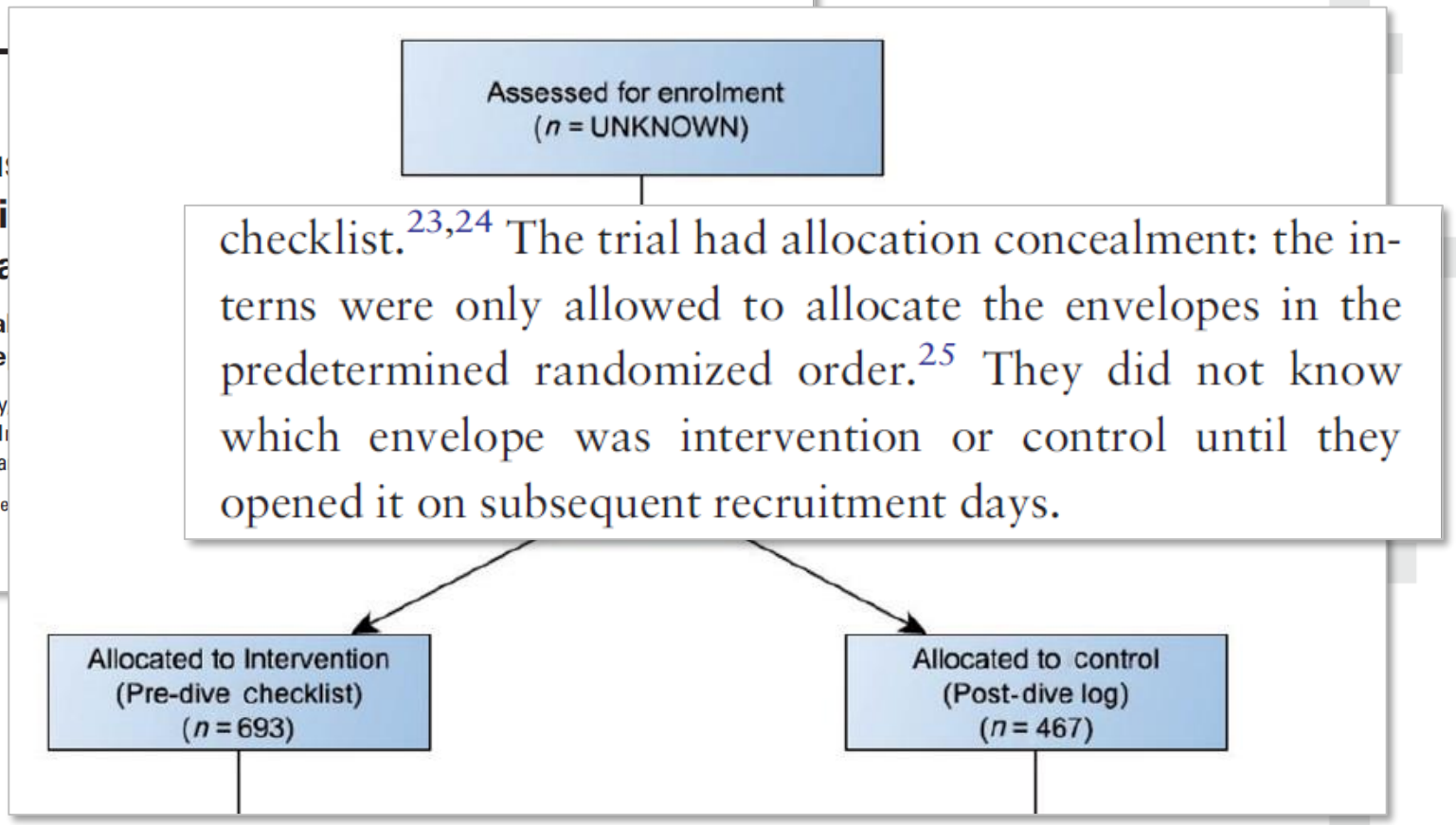

checklist.[23,24] The trial had allocation concealment: the interns were only allowed to allocate the envelopes in the predetermined randomized order.[25] They did not know which envelope was intervention or control until they opened it on subsequent recruitment days.

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Assessing bias arising from the randomization process in RoB 2

Risk of RoB 2 vs. 2011 Cochrane RoB tool

2011 tool included sequence generation and allocation concealment as separate domains

- (both under "*selection bias*"- not an appropriate term)
- Failure to implement either process adequately creates opportunities for either the enrolment into the study or the allocation of enrolled participants into groups to be influenced by prognostic factors

The end result is the same – unbalanced (biased) distribution of patients between groups

- It made sense to combine allocation sequence *generation* and allocation sequence *concealment* into a single domain

Risk of RoB 2 vs. 2011 Cochrane RoB tool

Additional signalling question about baseline imbalances.

Signalling questions and judgements

- **signalling questions** increase transparency
  - 'Yes', 'Probably yes', 'Probably no', 'No', 'No information'
  - support each one with evidence/quotes/explanation
- algorithms map answers to signalling questions onto **risk of bias judgements**
  - '**Low risk of bias**', '**Some concerns**', '**High risk of bias**'
  - "Probably yes" = "Yes", and "Probably no" = "No"
  - algorithms can be overridden
- a 'High risk of bias' judgement in any one domain puts the result at high risk of bias

Domain 1
Signalling Questions

Bias arising from the randomization process

- 1.1 Was the allocation sequence random?
  - Yes / Probably yes / Probably no / No / No information
- 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
  - Yes / Probably yes / Probably no / No / No information
- 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?
  - Yes / Probably yes / Probably no / No / No information

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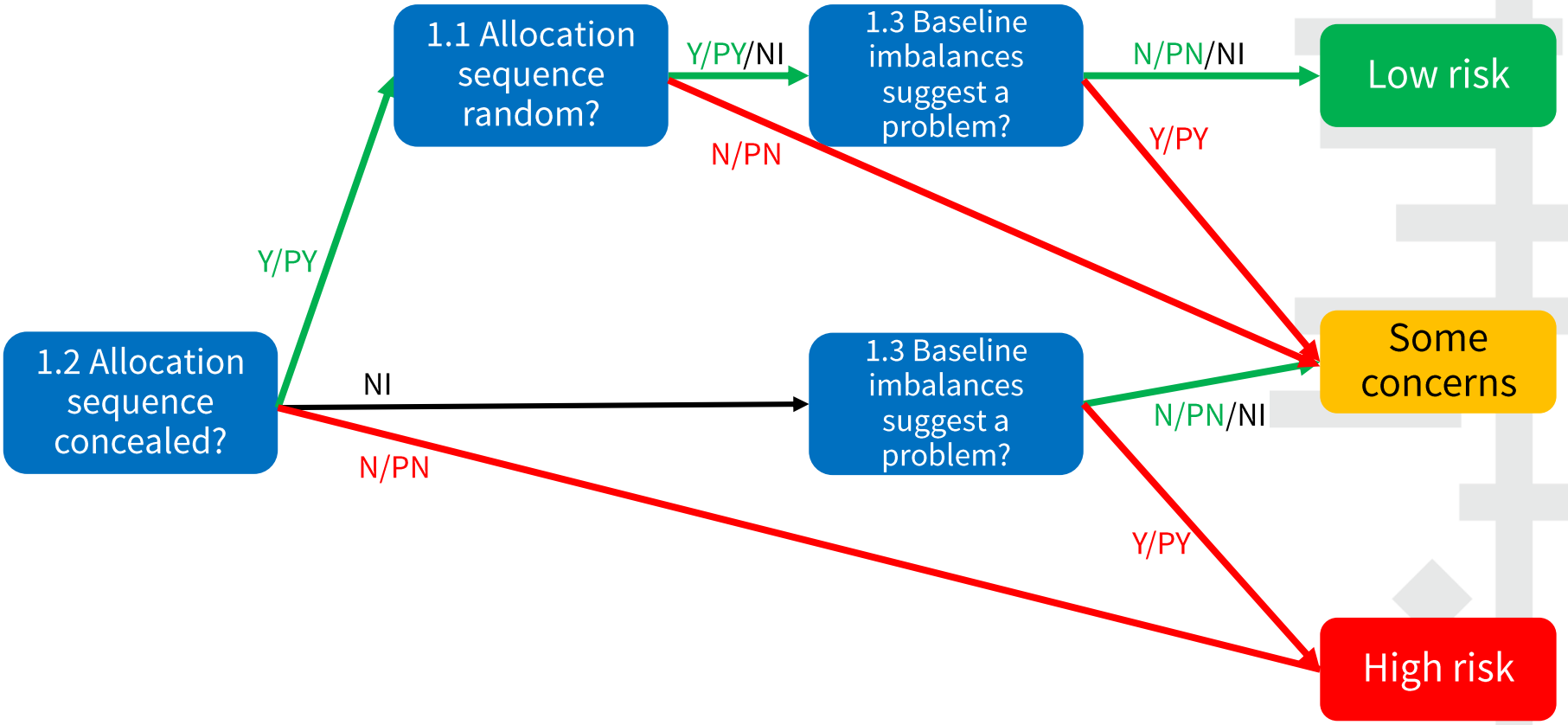
Domain 1: Algorithm



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An example

The DEMO Trial

A Randomized, Parallel-Group, Observer-Blinded Clinical Trial of Strength Versus Aerobic Versus Relaxation Training for Patients With Mild to Moderate Depression

P: Patients with mild to moderate depression

I: Aerobic OR strength training (2x p.w. for 4 months)

C: Relaxation training (2x p.w. for 4 months)

O: Depressive symptoms, Absence from work, Cognitive function, Physical outcomes

Krogh et al. (2009) doi: 10.4088/jcp.08m04241

Trial design

"This randomized, parallel-group, observer-blinded, superiority trial was carried out at a single location at Copenhagen University Hospital in Denmark. If the patients were considered eligible for inclusion, they were referred to randomization and exercise testing. Patients were randomly assigned to strength, aerobic, or relaxation training. Randomization was centralized and stratified according to medicine status: (1) not receiving antidepressant medication, (2) having received antidepressant medication for less than 6 weeks, or (3) having received antidepressant medication for more than 6 weeks. DEMO trial staff contacted the Copenhagen Trial Unit (CTU) by phone. Randomization was carried out by the CTU using computerized restricted randomization with a block size of 6. The block size and thus the allocation sequence were unknown to the DEMO trial staff."

Page 791, doi: 10.4088/jcp.08m04241

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Poll

Was the allocation sequence random?

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Poll

Was the allocation sequence concealed until participants were enrolled and assigned to interventions?

Suggested answers

Was the allocation sequence random: **Yes**

Was the allocation sequence concealed until participants were enrolled and assigned to intervention: **Yes**

Quote we chose:

"Randomization was centralized and stratified according to medicine status...DEMO trial staff contacted the Copenhagen Trial Unit (CTU) by phone. Randomization was carried out by the CTU using computerized restricted randomization with a block size of 6. The block size and thus the allocation sequence were unknown to the DEMO trial staff."

Extract of baseline characteristics table

	Strength (N = 55)	Aerobic (N = 55)	Relaxation (N = 55)
Female, N (%)	45 (81.8)	43 (78.2)	34 (61.8)
Age, mean (SD), y	41.9 (8.7)	38.1 (9.0)	36.7 (8.7)
Ethnicity, N (%)			
Caucasian	50 (90.9)	51 (92.7)	50 (90.9)
Other	5 (9.9)	4 (7.3)	5 (9.1)
Referred from, N (%)			
General practitioner	35 (63.6)	32 (58.2)	31 (56.4)
Private practice psychiatrist	15 (27.3)	11 (20.0)	16 (29.1)
Outpatient department	5 (9.1)	12 (21.8)	8 (14.5)
Depression			
17-Item Hamilton Rating Scale for Depression, mean (SD)	18.2 (3.6)	18.2 (3.8)	16.7 (3.8)
Montgomery-Asberg Depression Rating Scale, mean (SD)	22.0 (5.6)	22.9 (5.5)	21.6 (4.7)
DSM-IV criteria for major depressive disorder, N (%)	39 (70.9)	38 (69.1)	35 (63.6)
Beck Depression Inventory,[42] mean (SD)	30.6 (8.8)	30.5 (6.9)	31.8 (8.3)
14-Item Hamilton Rating Scale for Anxiety, mean (SD)	15.1 (5.7)	15.1 (5.6)	14.7 (5.1)
WHO-5,[43] quality of life, mean (SD)	20 (12.3)	20 (10.1)	23 (11.5)
Using antidepressant medication, N (%)	39 (70.9)	37 (67.3)	38 (69.1)
Having used antidepressant medication > 6 wk, N (%)	35 (63.6)	35 (63.6)	32 (58.2)
Receiving psychotherapy, N (%)	24 (43.6)	28 (50.9)	25 (45.5)
Previous episodes of depression, mean (SD)	1.3 (2.0)	1.3 (1.9)	1.0 (1.7)
Time since diagnosis of current depression, mean (SD), mo	13.2 (21.7)	20 (37.4)	20.8 (30.2)
Work			
Unemployed, N (%)	23 (41.8)	30 (54.5)	20 (36.4)
Working full-time ~37 h/wk, N (%)	22 (40.0)	18 (32.7)	23 (41.8)
Working part-time ~20 h/wk, N (%)	8 (14.5)	6 (10.9)	10 (18.2)
Working < 20 h/wk, N (%)	2 (3.6)	1 (1.8)	2 (3.6)
Sick leave, N (%)	29 (52.7)	23 (41.8)	24 (43.6)
Percentage of days absent from work in last 10 d, mean (SD)	17.8 (31.5)	30 (34.7)	26.6 (35.3)
Cognitive skills, mean (SD)			
Verbal intelligence			
Danish Adult Reading Test	33.4 (9.2)	34.2 (8.7)	32.9 (8.1)

From Table 1

Page 794

doi: 10.4088/jcp.08m04241

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Poll

Did baseline differences between intervention groups suggest a problem with the randomization process?

Suggested answers

Did baseline differences between intervention groups suggest a problem with the randomization process: **Probably No**

Rationale:

- HAM-D17 score was lower in the relaxation group, which also had a higher proportion of male participants
- Although there are slight differences between the groups, these seem compatible with chance given that there are only 55 participants in each group and many variables were measured.

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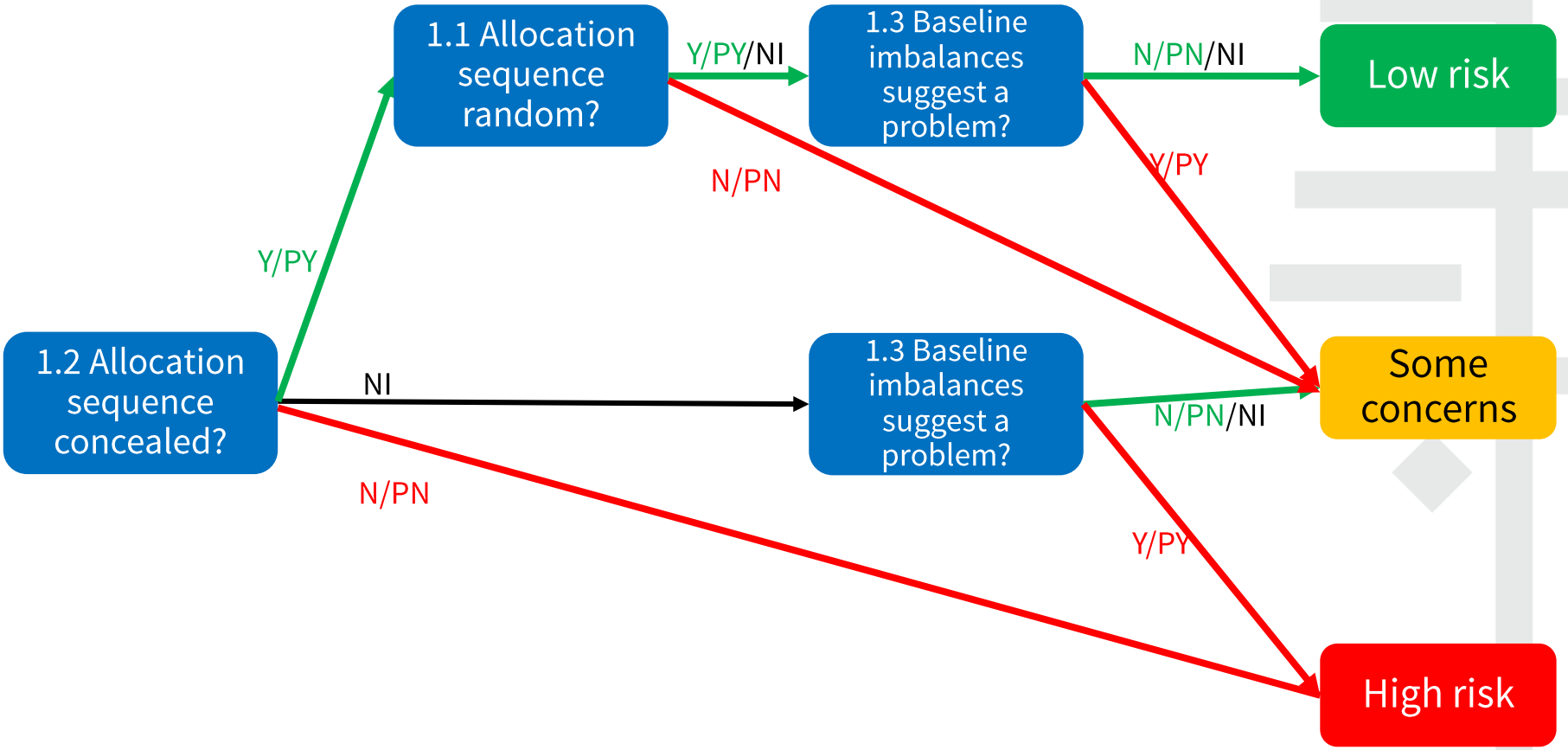
Poll

Risk of bias arising from the randomization process?



Suggested answers

Low

Rationale:

- Allocation sequence was adequately generated and concealed, and baseline imbalances appear to be compatible with chance.

- Your risk of bias rating will depend on how you answered the signalling questions.

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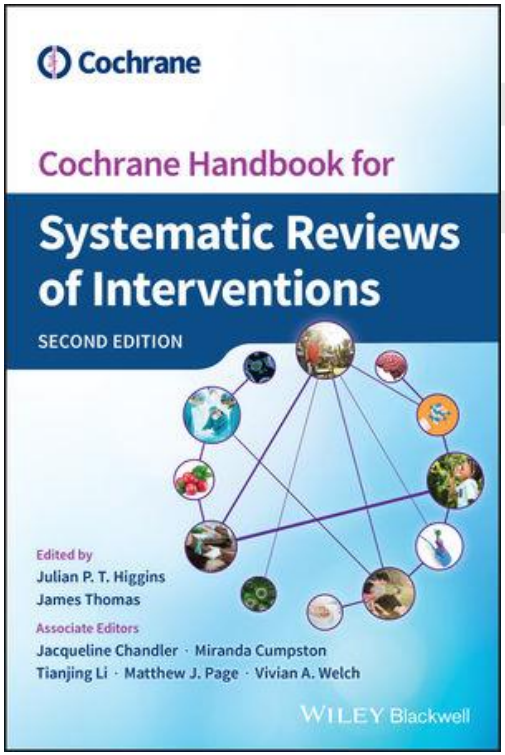
Resources available

Cochrane Handbook (v 6)

- **Chapter 7** explains risk of bias issues in general
- **Chapter 8** provides a brief overview of the RoB 2 tool
- **MECIR** items summarize *Handbook* guidance



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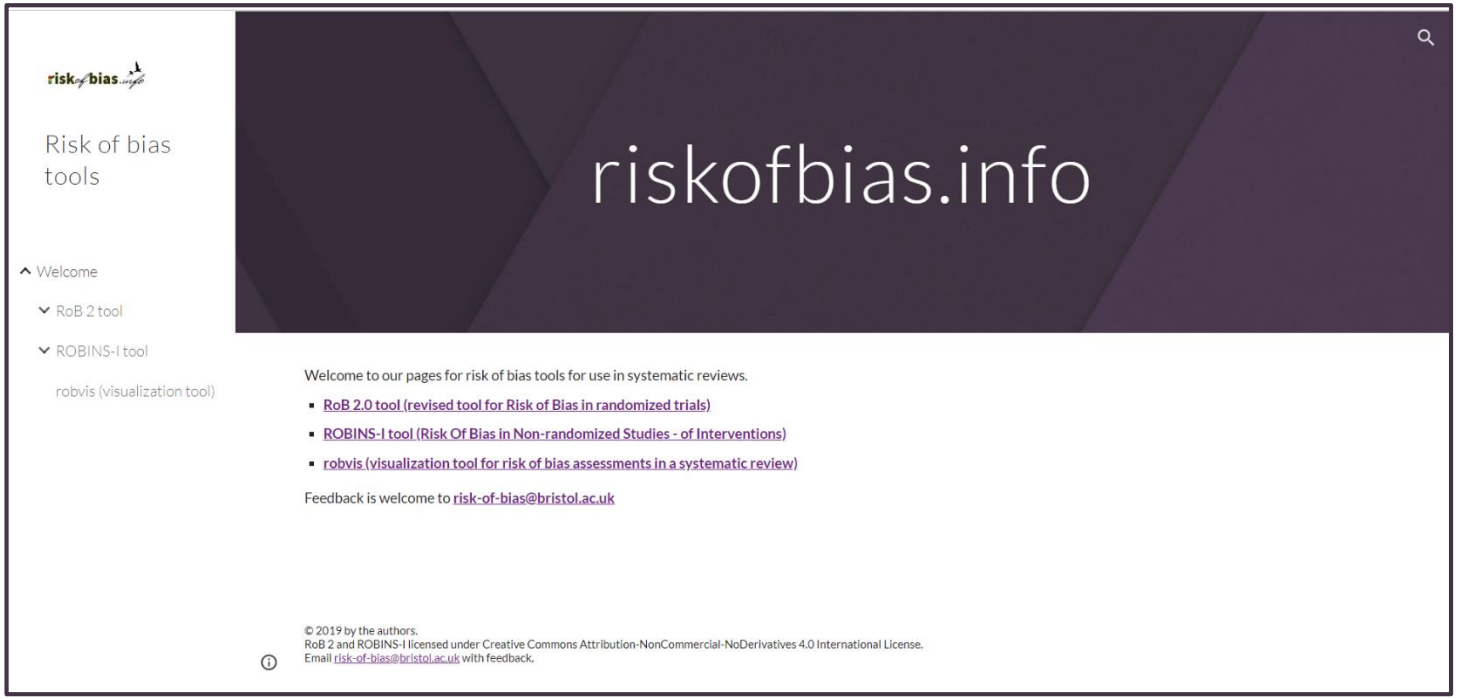
riskofbias.info



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riskofbias.info

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

22 August 2019

Dedicated to Professor Douglas G Altman, whose contributions were of fundamental importance to development of risk of bias assessment in systematic reviews

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Questions

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