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LECTURE 2: SEARCHING, SCREENING THE LITERATURE; DATA EXTRACTION; QUALITY ASSESSMENT

Joel J. Gagnier MSc, PhD

Overview

- Searching for studies
- Screening studies
- Data Extraction
- Evaluating the quality of studies

Locate studies: the search

- Most important part of a SR
- Must collect all possible relevant studies relative to your inclusion/exclusion criteria
- Can be done in duplicate
  - But more important to just be comprehensive

Identifying studies

- Involve a library and information scientist
  - Consult your institutions library
- Take a course on searching
  - Keywords
  - Boolean operators
  - Truncation
  - MeSH Headings
  - Related links etc
- Take tutorials for different databases

Database Searching

- Look at what other people did in their SRs on the same/similar topic
- Must search all of the relevant databases
  - Even if you know the topic
  - May be obscure but relevant databases
  - Medline only is not sufficient

Databases

- MedLine
- EMBASE
- CINAHL: Cumulative Index to Nursing and Allied Health Literature
- Cochrane Library, Controlled trials register
- ToxNet: Databases on toxicology, hazardous chemicals, environmental health, and toxic releases
- UK National Research Register
- Clinical trials.gov
- Google Scholar
- Etc…are many and are discipline specific
  - Consult your library and information scientist

Database searching

- Keep a track of
  - Search terms used for electronic searches
  - Dates searched
- Other people will want to check on this
  - Replicate your work
  - So be transparent

Searching

- Examine the references of articles of relevance
  - Included studies and relevant reviews
- Contact authors
- Snowballing (esp for complex questions or interventions)
- Contact companies, organizations, societies etc
- Hand search important journals
- Search for ongoing studies (prelim data)
  - Clinicaltrials.gov ; controlled-trials.com (ISRCTN)
- Citation tracking

Grey literature

- Various definitions
  - Everything that is not peer-reviewed and published
- E.g., dissertations (DAI), conference proceedings (ERIC), government reports, unpublished manuscripts, company research, magazines etc

Electronic Searching

- Take you research question (P.I.C.O.T.)
  - Extract terms
  - Find synonyms
  - Medical Subject Headings (MeSH)
  - Consult an expert
- Combine with terms for the type of articles you are looking for
  - randomized controlled trials
  - observational studies
  - etc

Electronic Search Strategy example

PubMed

- (knee AND injury) AND (anterior cruciate ligament OR ACL OR soft tissue injuries OR sprain OR athletic injuries OR knee injuries) AND (prevention OR preventive) AND (education OR strengthening OR conditioning OR proprioceptive OR proprioception OR varied training OR comprehensive training OR plyometrics OR neuromuscular training) AND ((Humans[Mesh])

Electronic Search Strategies

- Controlled Trials search for PubMed
  - (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* {tw})) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] or volunteer* [tw]) NOT (animal [mh] NOT human [mh]

Robinson KA & Dickerson K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epid. 2002;(31:150-153

Electronic Search Strategies

- Observational studies
  - "Cohort studies" [MESH] OR "Risk" [MESH] OR ("Odds" [WORD] AND "ratio*" [WORD]) OR ("Relative" [WORD] AND "risk" [WORD]) OR "Case" control*" [WORD] OR Case-control studies [MESH]

Wilczynski NL et al. Developing optimal search strategies for detecting clinically sound causation studies in Medline. AMIA. 2003:719-723.

Selection of Eligible Studies

Select studies

Eligibility checked by two individuals

- Separately and independently
- Get a sample of studies
- Apply inclusion/exclusion criteria
  - First to abstract and title
  - If unknown on any, get full text and review

Inclusion/Exclusion Spreadsheet

Study ID: record number, first author last name, journal, year, volume	One of: 1. Primary Outcome: the occurrence of a new non-contact ACL injury, and outcome rates expressed per unit of at-risk exposure (e.g., per hour of playing time or per number of active events such as practices or competitions) or, per number of subjects; 2. Secondary intermediate outcomes: (measured prior to ACL injuries) include biomechanical parameters or performance measures that are expected to increase the risk of future ACL injury (e.g., muscular strength, skill level, and neuromuscular control or) or degree of injury; Y/N/?	Study Design: randomized or quasi-randomized or observational; Y/N/?	Participants: male or female; 13 yoa or > ;Y/N/?	Interventions: One or more of: educational or instructional programs, isolated strengthening, isolated conditioning, isolated proprioceptive training, or neuromuscular training (e.g., technique, proprioception and strengthening, varied training, comprehensive training); Y/N/?	Control Group: Does the study have one or more of: (1) participants in other real or sham interventions; 2) untrained individuals or athletes not participating in any type of training program; or 3) the experimental participants themselves before being exposed to the intervention under study; Y/N/?	Initial Inclusion reading title and abstract?(Y/N/?)
Pilot 1: pasanen, bmj, 2008, 337	y	y	y	y	y	y
Pilot 2: gilchrist	y	y	y	y	y	y
Pilot 3: myklebust	y	y	y	y	y	y
Pilot 4: pfeiffer	y	y	y	y	y	y
1. hupperets	n	y	?	y	y	n
2. Lehance	y	y	y	? Pre-season muscle strength	y	y
3. Renstrom	y	n	y	y	n	n
4. hupperets	n	y	?	y	y	n
5. Brushoj	n	y	y	y	y	?
6. van tiggelen	n	n	?	n sleeve	n	n
7. Buist	n	y	y	y	y	?
8. Abernethy	y	n	y	y	n	n
9. silvers	y	n	?	y	?	?
10, myer	y	y	?	y	y	?
11, Soderman	n	y	y	y	y	n
12. Myklebust	y	y	?	y	y	y

Inclusion/Exclusion

Strategy to resolve disagreement

- The two meet to discuss disagreements on inclusion and try to resolve them
  - E.g. sit down and discuss papers individually
- If can't resolve 3rd party
- Calculate agreement

Measures of Agreement

- Raw percentage agreement
  - # inclusion criteria agreed on divided by the total number of criteria
- Kappa Coefficient
  - Chance corrected agreement
  - The percentage agreement between assessors when chance agreement has been eliminated
  - But is not accurate for a small (<50%) or large (>80%) raw agreement
- Generally people like to see these

Select Studies

Track everything

- # title and abstracts were read from the searches
- # full texts retrieved and read
- # you chose to exclude and why
- Include a flow chart and a table with reasons for excluded studies (Cochrane asks for this)
- Flow chart
  - See PRISMA statement

PRISMA flowchart

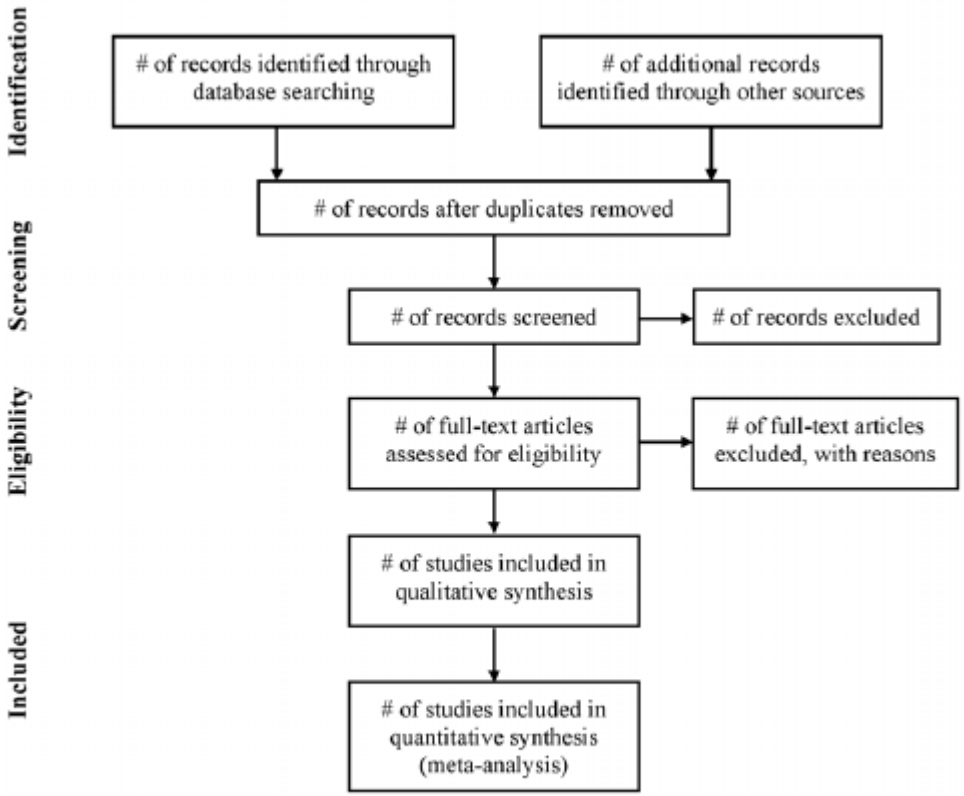


Figure 1. Flow of information through the different phases of a systematic review.
doi:10.1371/journal.pmed.1000097.g001

 http://www.prisma-statement.org/

Organizing your studies

- Use a reference/database tool of some kind
  - Reference Manager http://www.refman.com/
  - Endnote http://www.endnote.com/
  - Very useful to organize and format reference lists

Assess Study Risk of Bias (ROB) / Methodological Quality

- Independently by two reviewers
- Separately for different trial designs
- May include:
  - Discrete criteria for each
    - e.g., generation of randomization sequence
  - An open criterion
    - other potential threats to validity
    - e.g., baseline differences

Bias

- Consider the role of the following biases in the relevant studies
  - Selection bias
    - Systematic differences in the initial composition of groups
  - Performance bias
    - Systematic differences in the care provided to groups apart from the interventions under investigation
  - Attrition bias
    - Systematic differences in dropouts and withdrawals that alter initial group composition
  - Detection bias
    - Systematic differences in the outcome assessment

ROB Assessment

- Scoring
  - 1, 0
  - Y, N, DK
  - Should assess whether reported at all
  - Must go beyond scoring and look at individual aspects of these studies

ROB assessment

- Make an assessment (for each study; & across studies for each outcome):
  - Magnitude of bias
    - Try to make an assessment of how this methodological flaw might bias the summary treatment effect for that study and for the pooled effect estimate
    - Explore with statistical techniques
      - Do meta-regression for methodological aspects and influence on summary effect
      - Subgroup/sensitivity analyses with and without low quality studies
  - Likely direction of bias
    - Look at empirical literature
      - Cochrane Library, Methodological studies database
      - CONSORT database http://www.consort-statement.org/database/evidence-underpinning-consort/

Cochrane Risk of Bias Tool

- Cochrane Handbook 2009
  - Download with RevMan software
  - Very useful resource
- Moved away from study quality to risk of bias
- Applicable to randomized controlled trials only

‘Quality’ or ‘Risk of bias’?

Quality ≈ “did they do the best they could?”

Bias ≈ “should I believe the result?”

- We never know biases, but there is rationale for considering **risk of bias**
  1. Key consideration in Cochrane reviews is *believability*; risk of bias targets this question squarely
  2. ‘High quality’ research methods can still leave a study at important risk of bias. (e.g. when blinding is impossible, baseline imbalances)
  3. Some markers of quality in medical research are unlikely to have direct implications for risk of bias (e.g. ethical approval)
  4. Overcomes ambiguity between quality of *reporting* and the quality of the underlying *research*

The new tool: principles

- Provides a framework for assessing the whole trial
- Explicitly judgemental – but separates the facts from the judgements
- Transparent and so repeatable

The new tool: Domains to address

Sequence generation (randomization)

Allocation concealment

Blinding of participants, personnel and outcomes

Incomplete outcome data (attrition and exclusions)

Selective outcome reporting

Other (including topic-specific, design-specific)

The new tool: how to assess them

Two components

1. Description of what happened
   - possibly including 'done', 'probably done', 'probably not done' or 'not done' for some items
2. Review authors' judgement
   - whether bias unlikely to be introduced through this item (Yes, No, Unclear)
     - Yes = Low risk of bias
     - No = High risk of bias
     - Unclear = Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias

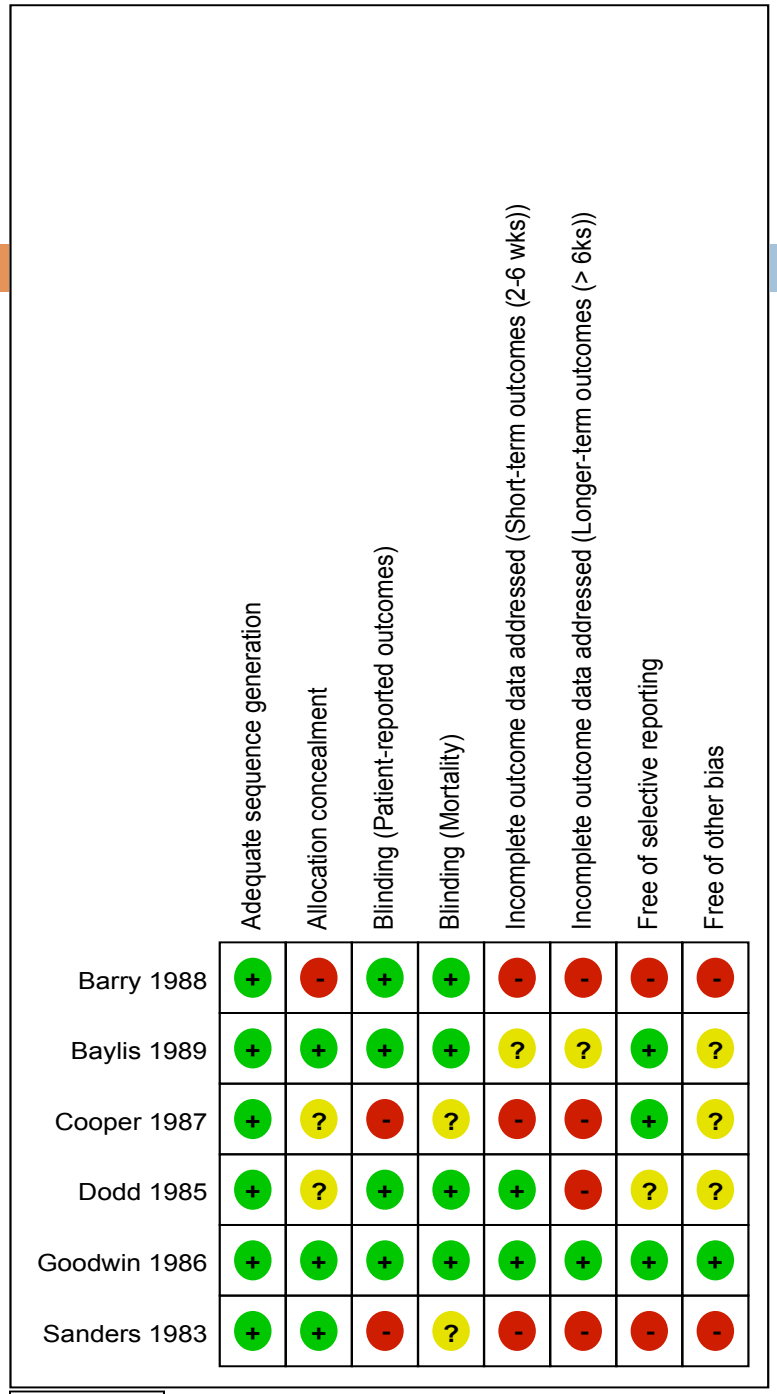
'Blinding' and 'Incomplete outcome data' may need separate assessments for different outcomes

‘Risk of bias’ assessment in Cochrane reviews: Summary Table

⊟ **Risk of bias table**

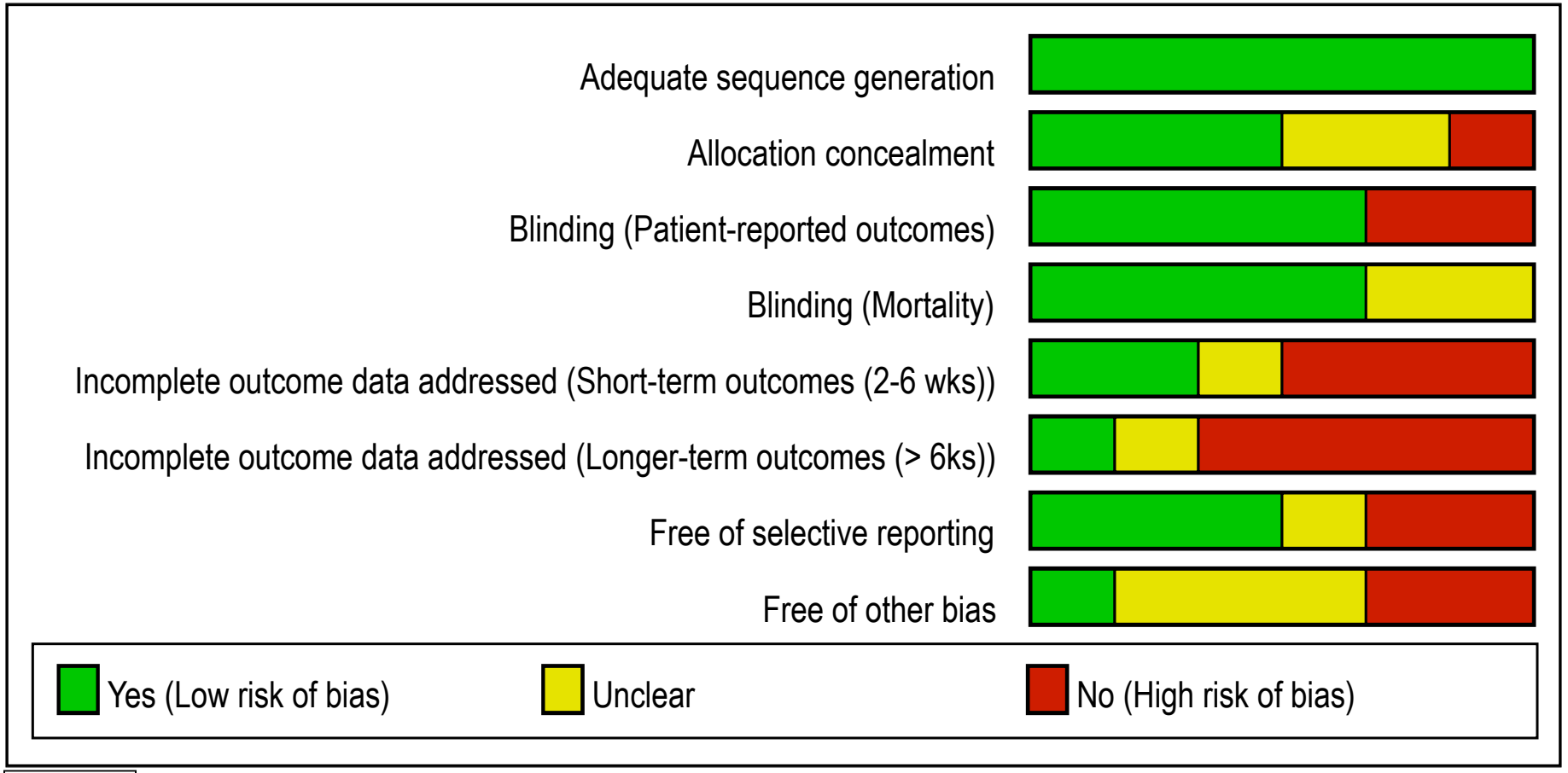
Item	Authors' judgment	Description
Adequate sequence generation?	Unclear	"Patients were randomly allocated"
Allocation concealment?	Unclear	No information.
Blinding?	Yes	"double blind design". "Millet... resembles lecithin in appearance... When ground, each substance could be distinguished from the other by hue and taste but staff were not informed as too which was which."
Incomplete outcome data addressed?	No	Data unavailable for meta-analysis. Randomised: lecithin = Not stated, placebo = Not stated, Total = 33.Missing: lecithin = 7 (non-cooperation or diarrhoea = 2; moved to nursing home = 4, death = 2), placebo = 5 (non-cooperation or diarrhoea = 3, death = 2), total missing = 36%.
Free of selective reporting?	No	No quantitative results reported due to lack of effect.It is apparently clear which outcomes were measured.
Free of other bias?	Yes	No problems apparent

Risk of bias summary



- Here 'Blinding' and 'Incomplete outcomes data' have been assessed for two sets of outcomes

Risk of bias graph



Summary Assessments of ROB

- Empirical evidence of bias:
  - See Cochrane handbook for all categories
  - For "other" risk of biases seek-out empirical data or have strong rational argument
- Likely direction of bias
  - Usually over estimates of effect when high likelihood of bias
- Likely magnitude of bias
  - Varies; look at evidence base
  - Consider it relative to the estimated magnitude of effect
  - Statistical testing

Summary assessment by outcome

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key items	Most information is from studies at low risk of bias
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key items	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key items	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results

Assessing Risk of Bias for Observational Studies

ROB Item	Rating	Description
1. Is the outcome absent at the start of the study?	Y/N/DK	
2. Was clustering at the group level accounted for the in analyses?	Y/N/DK	
3. a. Were the outcome assessors (for the primary outcome) blind to the intervention? Describe how the outcome was measured (be sure there is no detection bias) b. Was the outcome measurement performed in the same manner with similar intensity in the groups being compared?	a.Y/N/DK b.Y/N/DK	a. b.
4. Was a similarly trained individual administering the intervention across groups? Describe who this was and their training if available.	Y/N/DK	
5. Was the outcome measurement performed in the same manner with similar intensity in the groups being compared?	Y/N/DK	
6. Were the groups similar at baseline? Describe any differences (values and significance tests)	Y/N/DK	
7. Did the authors perform analyses adjusting for known confounders? Describe the variables and analyses.	Y/N/DK	
8. Were all the withdrawals described? Describe the numbers and reasons for withdrawals in each group.	Y/N/DK	
9. Other possible sources of bias: Describe each	Y/N/DK	
10. Other possible sources of bias: Describe each	Y/N/DK	

Assessing Risk of Bias for RCTs

ROB Item	Rating	Description
1. Was the randomization method appropriate? Also, describe the unit of randomization.	Y/N/DK	
2. Was the allocation sequence concealed from those assigning patients to groups?	Y/N/DK	
3. Were the participants blind to the intervention?	Y/N/DK	
4. a. Were the outcome assessors (for the primary outcome) blind to the intervention? Describe how the outcome was measured (be sure there is no detection bias)	Y/N/DK	a.
4. b. Was the outcome measurement performed in the same manner with similar intensity in the groups being compared? (describe who measured outcomes and how… was it valid?)	Y/N/DK	b.
5. Were similarly trained individuals administering the intervention across groups? Describe who this was and their training if available.	Y/N/DK	
6. Were all the withdrawals described? Describe the numbers and reasons for withdrawals in each group.	Y/N/DK	
7. Were all originally randomized participants analyzed in the groups they were assigned to (i.e. An intention to treat analysis)?	Y/N/DK	
8. Was clustering at the group level accounted for the in analyses?	Y/N/DK	
9. Were the groups similar at baseline? Describe any differences (values and significance tests)	Y/N/DK	
10. Other possible sources of bias avoided: Describe each	Y/N/DK	
11. Other possible sources of bias avoided: Describe each	Y/N/DK	

Data Extraction

Design and pilot **extraction /asbtraction** form

- Be sure to pilot and revise this
- Spreadsheet to extract information and data from each trial
  - study design
  - sample size
  - patient characteristics
  - outcome measures
  - statistical analysis
  - results (data)
  - author conclusions
  - methodological drawbacks

Data Extraction

- Consider dual extraction
  - Train them (good tips in Littell)
  - Independent, two individuals
  - Meet to discuss any problems
- Coding may make things easier
  - E.g., for study design, types of outcomes, age grouping etc
- Note missing information/data (dk)
  - Will have to contact them
  - Under reporting is a big problem in the literature

Analyze and present results

Report and tabulate individual study results

- Summary of findings table (detailed trial designs, methods, results, important methodological notes)
  - Improves readability of the review
- Allows examination of possible differences between the studies that may
  - Preclude a meta-analysis
  - Direct explorations of heterogeneity

Example Summary Table

TABLE 1
Estimation of Injury Incidence per 1000 Exposures

Study	Sport	Age, y	Group	Exposure: Game and Practice	ACL Knee Injuries, incidence/1000 exposures	Noncontact ACL, incidence/1000 exposures
Hewett et al[17]	Basketball, soccer, volleyball	14-18	Trained (n = 366)	17 222	0.12[a]	0.00[a]
			Untrained (n = 463)	23 138	0.22[a]	0.22[a]
Heidt et al[18]	Soccer	14-18	Trained (n = 42)	3948[b]	0.25	
			Untrained (n = 258)	24 252[b]	0.33	
Soderman et al[43]	Soccer	20.4 ± 4.6	Trained (n = 62)	4123[c]	0.73	
		20.5 ± 5.4	Untrained (n = 78)	4631[c]	0.22	
Myklebust et al[34]	Team handball	16-35	Trained (n = 263)[d]	38 085[c]	0.08	
			Untrained (n = 645)[d]	55 318[c]	0.25	
			Trained (n = 850)[e]	93 403[c]	0.18	0.08[a]
			Untrained (n = 942)[f]	104 468[c]	0.28	0.17[a]
Mandelbaum et al[31]	Soccer	14-18	Trained (n = 1885)	67 860		0.09[a]
			Untrained (n = 3818)	137 448		0.49[a]
Petersen et al[40]	Team handball	Adult	Untrained (n = 134)	—[c]	0.08	
			Untrained (n = 142)	—[c]	0.42	

[a]Significant decrease in injuries through training intervention.
[b]Injury exposures estimated from Hewett et al[17] soccer exposures times 2 seasons.
[c]Injury exposures estimated as 2 hours = 1 practice or game exposure.
[d]Screening year 2000-2001, completed intervention versus dropped out.
[e]Screening year 2000-2001, intervention, all athletes.
[f]Screening year 1998-1999, no intervention.

 Hewett TE et al. Am J Sports Med. 2006;34(3).

Work on your protocols!!

Protocol Work Sheet 2: Inclusion/Exclusion, Search, Review Methods

Criteria for selecting studies for this review

- Types of studies
- Types of participants
- Types of interventions
- Types of outcome measures

Methods for identification of studies

- Databases,
- Search strategies,
- Screening,
- Personnel, etc

Methods of the review

- Risk of bias assessment
- Data Extraction Methods

Thank-you!!!