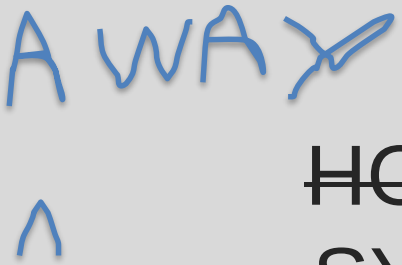
TEACHING EVIDENCED BASED MEDICINE



~~HOW~~ TO TEACH ABOUT SYSTEMATIC REVIEWS

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Departmental Lecturer/Senior Researcher
Centre for Evidence based medicine
University of Oxford

September 2018

MSc in EBHC x 25

PICO, searching, levels of evidence, study design, appraise RCTs, stats

90 min – appraising systematic reviews

Followed by 90 min hour workshop

What would you consider "*the essentials*"?

KNOW YOUR AUDIENCE

Objectives

Show some techniques/tips for critical appraisal of systematic reviews

Help you plan your own 1 ½ hour teaching critical appraisal

Help make teaching critical appraisal of systematic reviews fun(ish)

Mr Smith is 64 years old and recently diagnosed with atrial fibrillation (AF), a condition associated with a high risk of stroke. He wants to know if prescribing warfarin will reduce his risk of stroke?

How will you answer this?

I would…

Conduct a trial?

Search and appraise a relevant RCT?

Conduct a systematic review?

Strip down to your underwear and do a ceremonial dance to the great and mighty evidence gods?!

Search and appraise a relevant SR?

EBM and Systematic Review

EBM (quick & dirty)

Steps

1. **Q**uestion (PICO)?
2. **F**ind the best evidence?
3. **A**ppraise?
4. **S**ynthesised?
5. Apply?

Time: 120 seconds

1 - 20 articles

This patient survives!

Systematic Review

Steps

1. **Q**uestion (PICO)
2. **F**ind the best evidence x 2+
3. **A**ppraise x 2+
4. **S**ynthesize
5. ---

Time: 6 months+, team

≤ 2,000 articles

This patient is dead

Find a systematic review (and appraise it quickly)!

Objectives

By the end of this session you will:

Explain

- what a systematic review is
- the steps involved in producing one

Be able to (rapidly) critically appraise a systematic review using available tools

Have learned something new

Have had (some) fun!

THINK “DO” OBJECTIVES

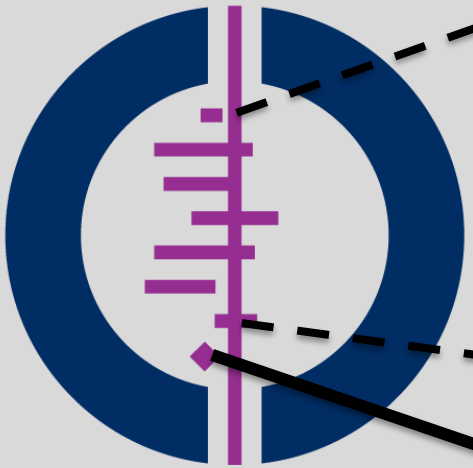
What is a systematic review?

"The application of strategies (*methods*) that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic."

Oxford Centre of Evidence Based Medicine (OCEBM) Levels Table

Why is research synthesis important?

Dangerous



1972 First RCT

1991

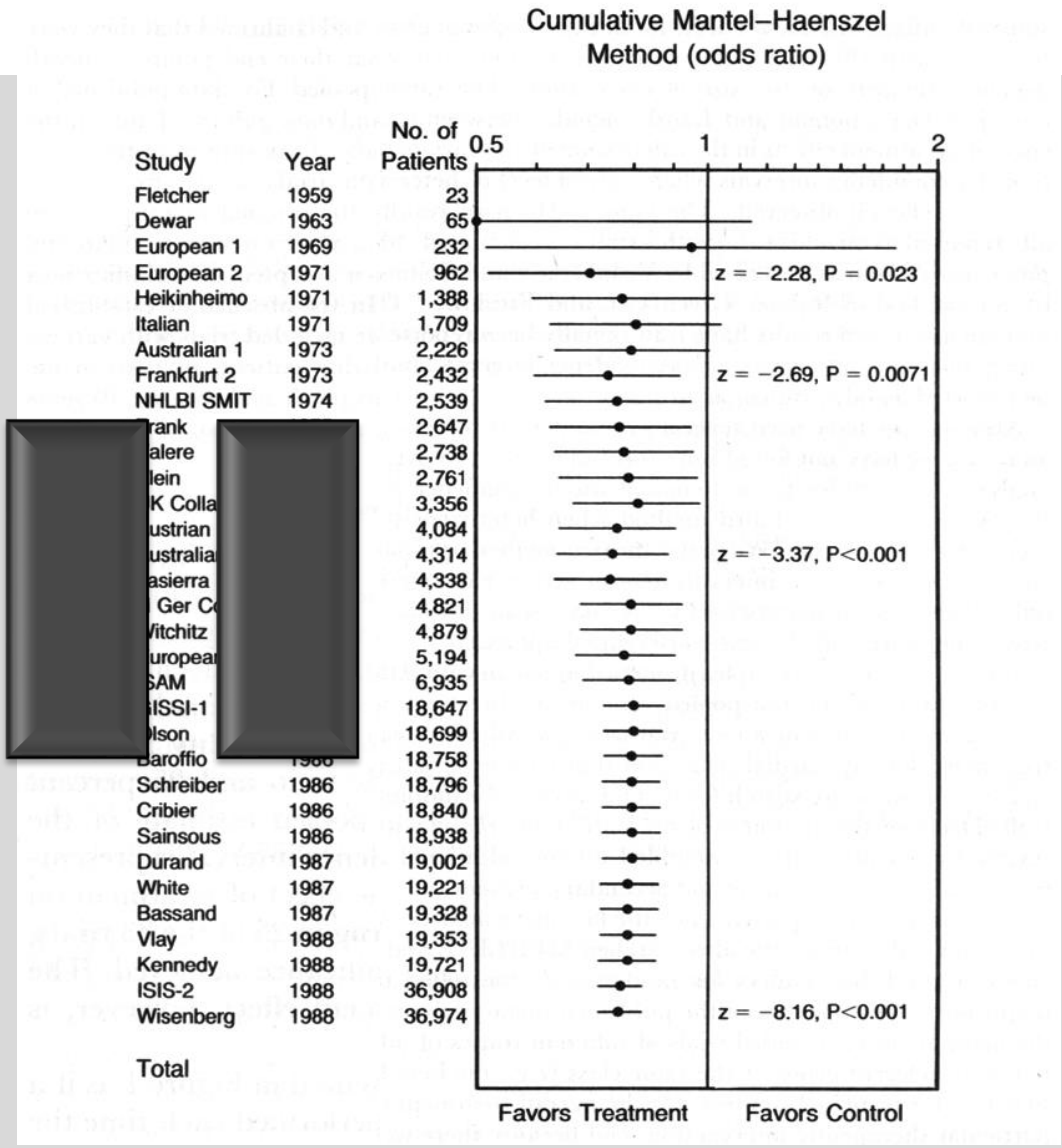
Steroids lower risk of death by 30-50%

Unethical?

a) I can tell which of these trials were potentially unethical to perform

b) If I had more time I could sort of work it out, maybe…

c) Huh?!....



SET EXPECTATIONS

What makes a review “Systematic”?

	Traditional	Systematic
Question	Vague	Focused
Search	Not stated	Stated explicitly
Selection	Unclear	Objective criteria
Assessment	Absent	Standardised
Results	Qualitative	Quantitative if possible

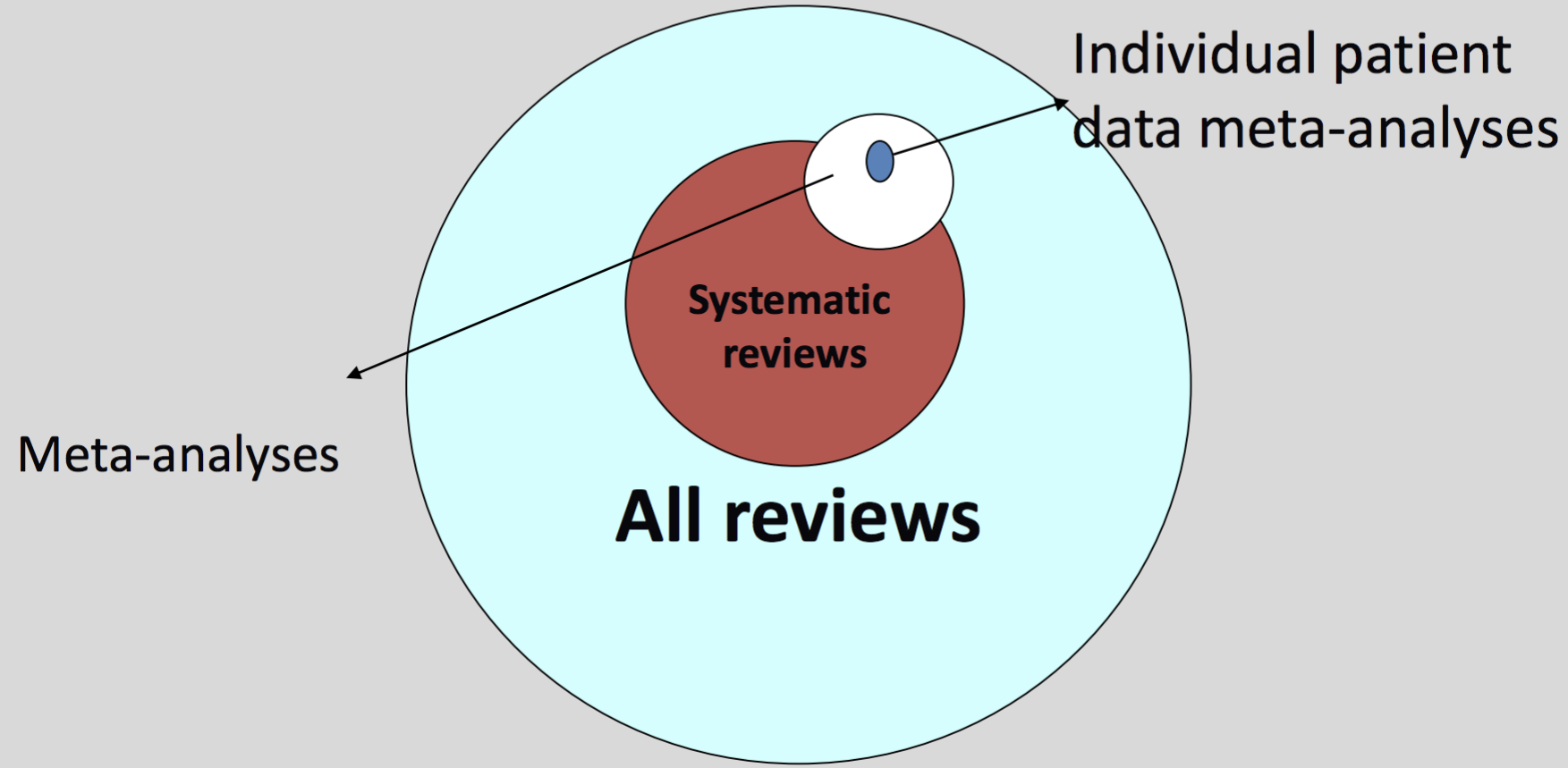
Meta-analysis

= calculated "best guess" of the true effect size

- The statistical combination of the results gives a single, pooled [**weighted**] average of the primary results
- Allows more precise estimate and exploration of subgroups
- Optional part of SR

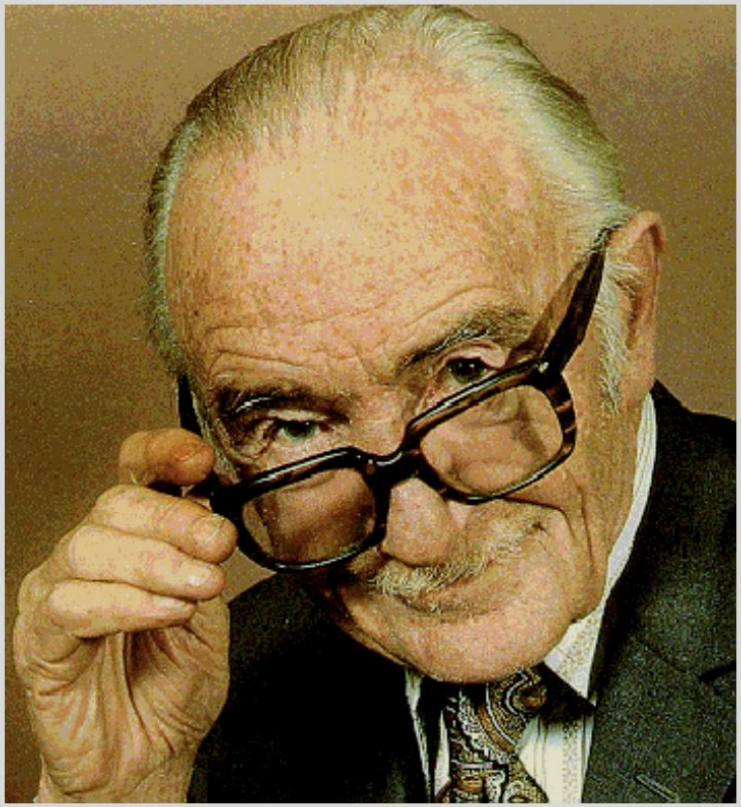
Meta-analyses performed outside a systematic review

Not all meta-analyses are part of systematic reviews



Prof Archibald Cochrane
(1909 - 1988)

"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials" (1979)



Source: http://www.cochrane.org/cochrane/archieco.htm

Cochrane

1980s: international collaboration to develop the Oxford Database of Perinatal Trials

1992: first Cochrane Centre in Oxford, UK

1993: The Cochrane Collaboration

2015: Cochrane

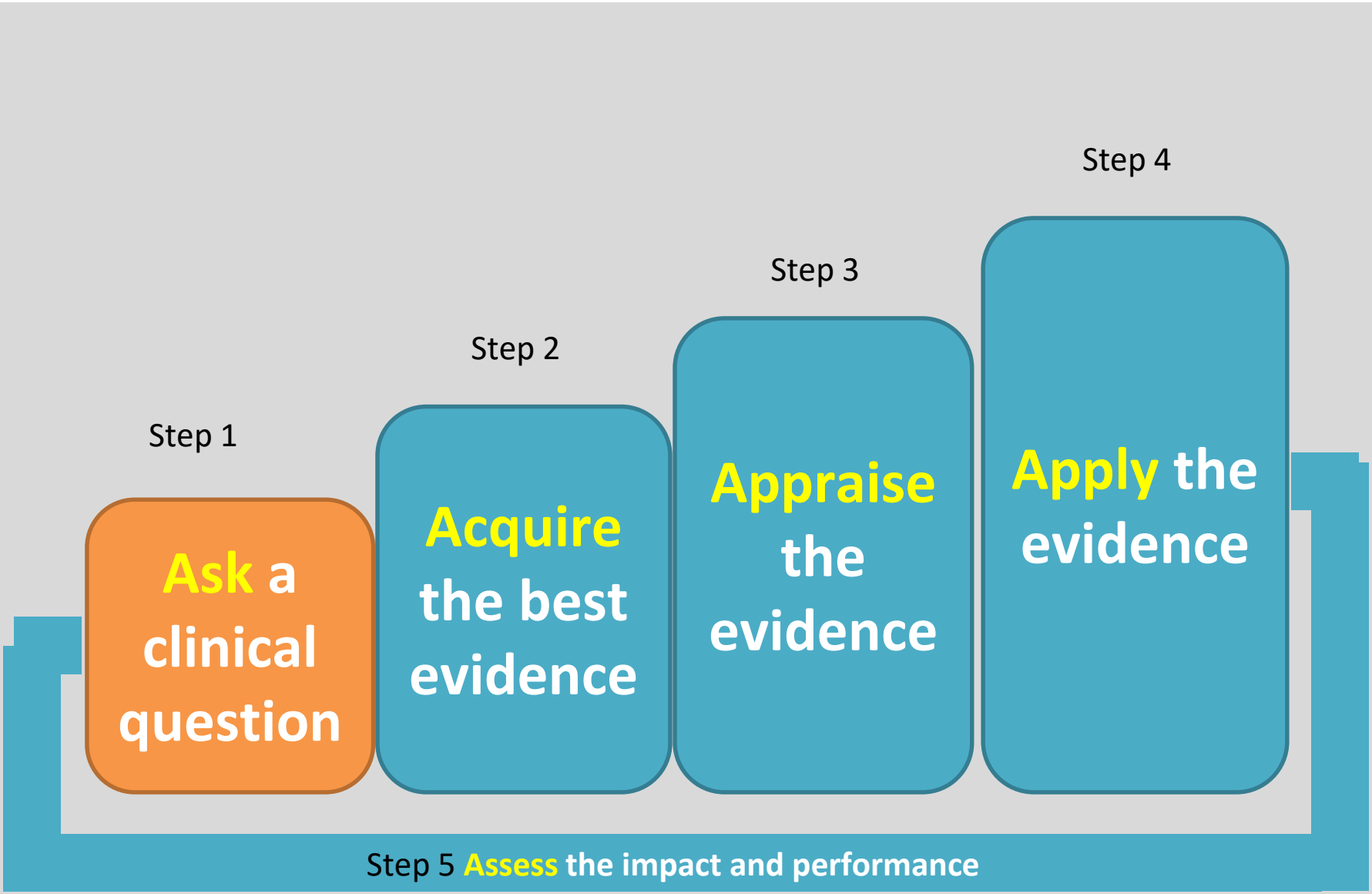
JUST ENOUGH!


CORDÃO DE OU
GUARA
CORDÃO DE OUR
GUARA
CORDÃO DE OU
GUARA

Delay or not delay?

FIND A HOOK

Practising EBM – the 5 A's



Our clinical question?

Population
Amongst adults with acute ACL injuries, does

Intervention
early reconstructive surgery compared with

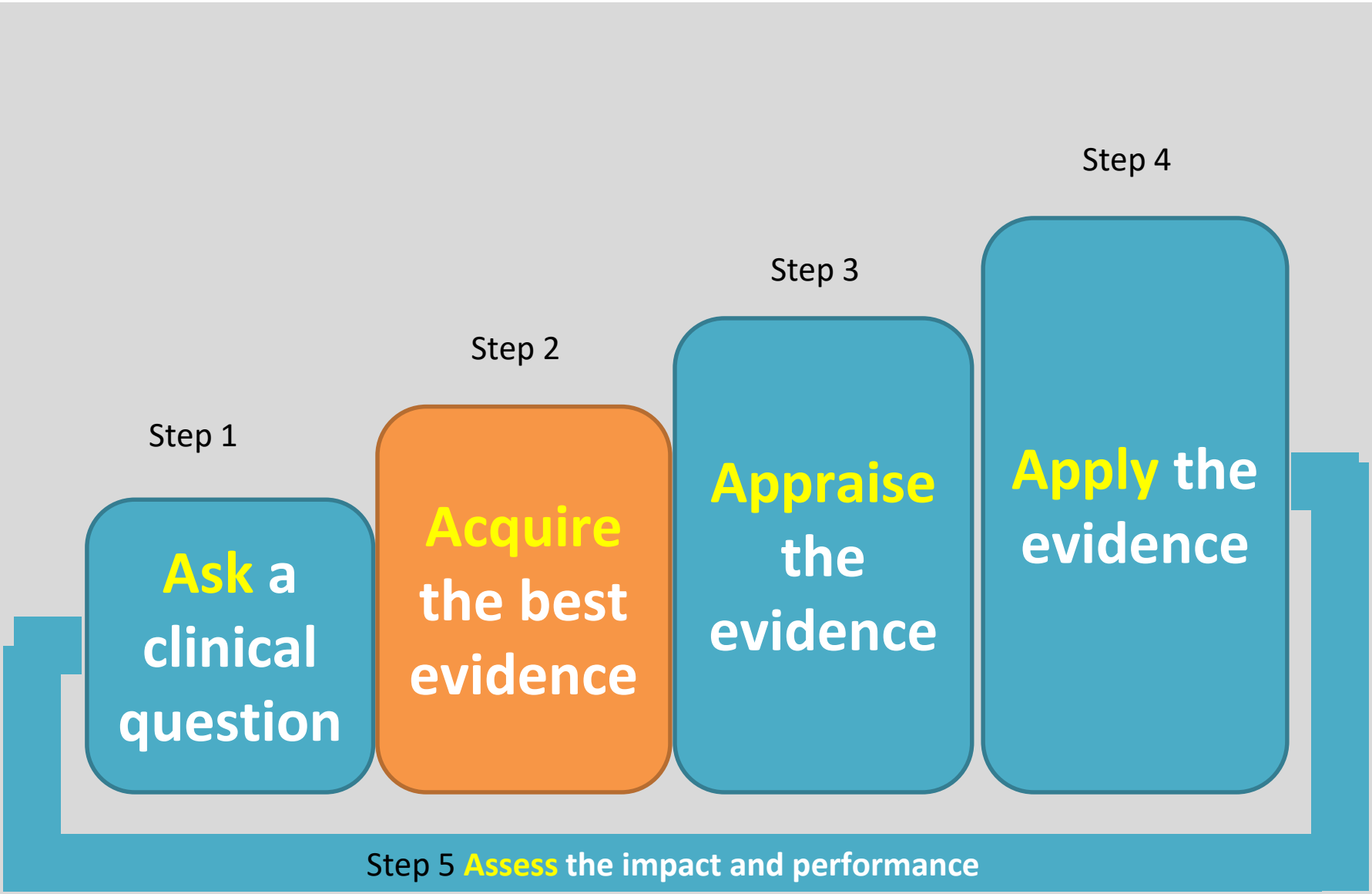
Control
delayed reconstructive surgery lead to

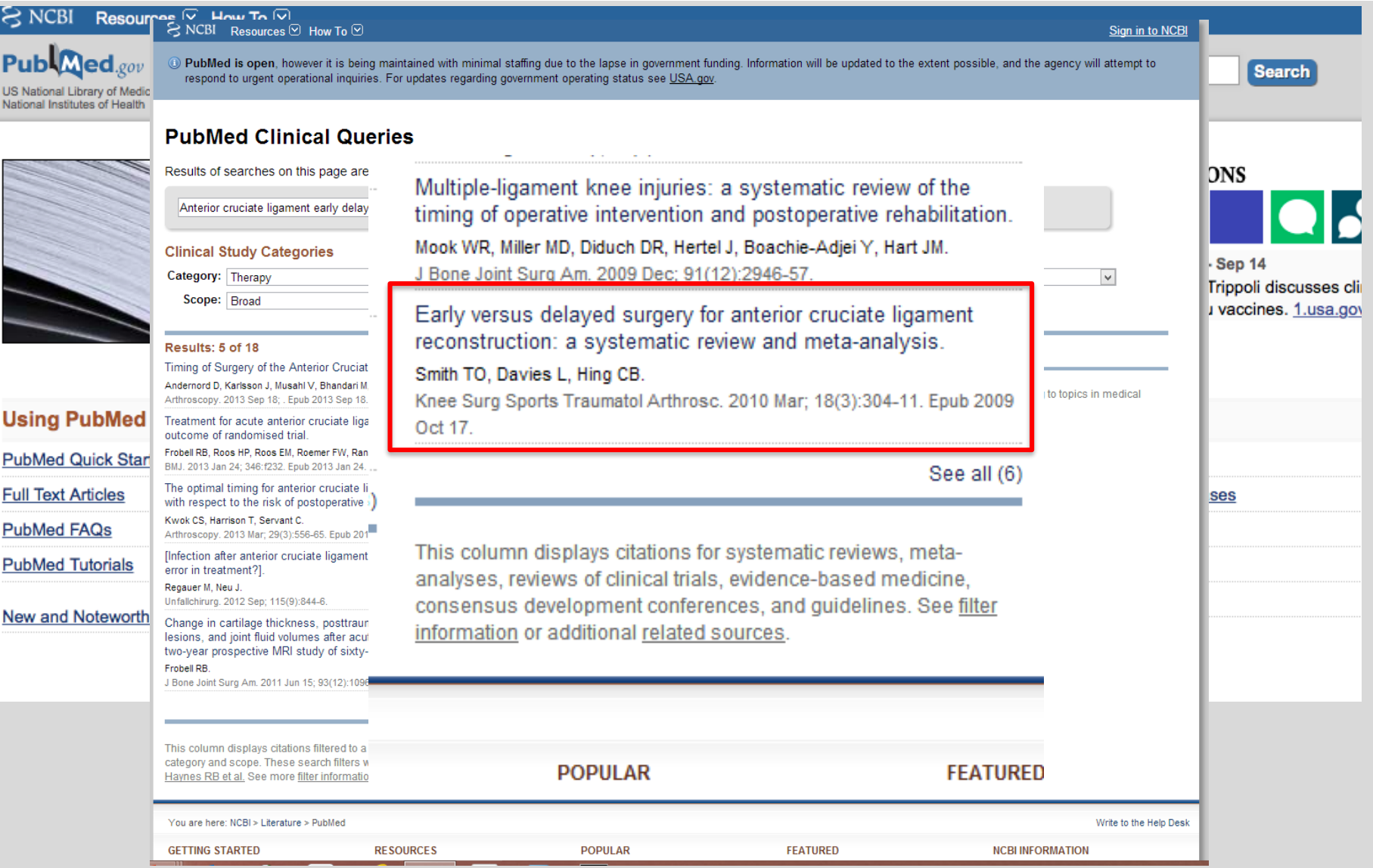
Outcome 1
favourable return to former activity and/or risk of

Outcome 2
recurrent knee injury?

REINFORCE KEY CONCEPTS

Practising EBM – the 5 A's




NCBI Resources How To
Sign in to NCBI
PubMed is open, however it is being maintained with minimal staffing due to the lapse in government funding. Information will be updated to the extent possible, and the agency will attempt to respond to urgent operational inquiries. For updates regarding government operating status see USA.gov.
PubMed Clinical Queries
Results of searches on this page are
Anterior cruciate ligament early delay
Clinical Study Categories
Category: Therapy
Scope: Broad
Results: 5 of 18
Timing of Surgery of the Anterior Cruciat
Andernord D, Karlsson J, Musahl V, Bhandari M
Arthroscopy. 2013 Sep 18; . Epub 2013 Sep 18.
Treatment for acute anterior cruciate liga
outcome of randomised trial.
Frobell RB, Roos HP, Roos EM, Roemer FW, Ran
BMJ. 2013 Jan 24; 346:f232. Epub 2013 Jan 24.
The optimal timing for anterior cruciate li
with respect to the risk of postoperative
Kwok CS, Harrison T, Servant C.
Arthroscopy. 2013 Mar; 29(3):556-65. Epub 201
[Infection after anterior cruciate ligament
error in treatment?].
Regauer M, Neu J.
Unfallchirurg. 2012 Sep; 115(9):844-6.
Change in cartilage thickness, posttraur
lesions, and joint fluid volumes after acu
two-year prospective MRI study of sixty-
Frobell RB.
J Bone Joint Surg Am. 2011 Jun 15; 93(12):1096
This column displays citations filtered to a
category and scope. These search filters w
Haynes RB et al. See more filter informatio
Multiple-ligament knee injuries: a systematic review of the timing of operative intervention and postoperative rehabilitation.
Mook WR, Miller MD, Diduch DR, Hertel J, Boachie-Adjei Y, Hart JM.
J Bone Joint Surg Am. 2009 Dec; 91(12):2946-57.
Early versus delayed surgery for anterior cruciate ligament reconstruction: a systematic review and meta-analysis.
Smith TO, Davies L, Hing CB.
Knee Surg Sports Traumatol Arthrosc. 2010 Mar; 18(3):304-11. Epub 2009 Oct 17.
See all (6)
This column displays citations for systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines. See filter information or additional related sources.
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PubMed Tutorials
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to topics in medical
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Practising EBM – the 4 A's

“Hang on. Systematic reviews collect, appraise and combine evidence!

“So why do we need to appraise them?”

- Quality of included studies
- Quality of SR methodology
- Quality of decisions about research synthesis

It matters…

February 1, 1995, Vol 273, No. 5 >

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ARTICLE | February 1, 1995

Empirical Evidence of Bias

Dimensions of Methodological Qual[redacted]ciat

Estimates of Treatment Effects in Co[redacted]l Tri

Kenneth F. Schulz, PhD, MBA; Iain Chalmers, MBBS, MSc; Rich[redacted]MSc; D[redacted]man

JAMA. 1995;273(5):408-412. doi:10.1001/jama.1995.035202900[redacted]ze: A A A

Article | References

ABSTRACT

- 41% (27% to 52%) for inadequately concealed trials
- 30% (21% to 38%) for unclearly concealed trials

WHY IT MATTERS

Allocation bias

Systematic difference in how participants are assigned to treatment and comparison groups in a clinical trial.

Impact

There is evidence that over 80% trials may have unclear allocation concealment. Trials in which allocation was inadequately concealed reported estimates that were between 7% and 40% larger than effects in trials in which allocation was adequately concealed, although the size and direction of the effect were not predictable. A simulation of trials using realistic conditions for allocation concealment showed that up to about 20% of true null hypotheses could be rejected because of false positive effects.

Appraising a systematic review

Knee Surg Sports Traumatol Arthrosc (2010) 18:304–311
DOI 10.1007/s00167-009-0965-z

KNEE

Early versus delayed surgery for anterior cruciate ligament reconstruction: a systematic review and meta-analysis

Toby O. Smith · Leigh Davies · Caroline B. Hing

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Keywords Anterior cruciate ligament · Reconstruction · Timing of surgery · Meta-analysis

Introduction

The anterior cruciate ligament (ACL) is the most frequently injured ligament of the knee with an incidence of 8 per 100,000 cases per year [6, 28]. Surgery is the typical treatment for younger athletes or those with physically demanding occupational or sporting pursuits since it restores stability and limits the potential for progressive degeneration and long-term instability of the knee [2, 4, 19].

Surgical techniques of ACL reconstruction have evolved over the past three decades with debate regarding timing of reconstruction [37]. In a national survey by Francis et al. [12], of 101 consultant orthopaedic surgeons in the UK, 81% reported that they considered the ideal time span from injury to operation to be between 1 and 6 months, although it was acknowledged that only 35% of ACL reconstructions are performed within this time-frame in National Health Service hospitals.

Proponents of early surgical intervention during the initial weeks post-injury have suggested that restoring tibiofemoral stability may minimise the risk of further meniscal and chondral injury which may be associated with degenerative joint changes [3, 9, 35]. Early surgery may also facilitate return to sporting and occupational pursuits with considerable economic consequences. Delayed ACL reconstruction may be associated with an increase in muscle atrophy and reduced strength which may delay early rehabilitation [10, 29]. Conversely, delaying surgical intervention allows optimisation of pre-operative knee range of motion and recovery of surrounding soft tissues from the initial injury potentially reducing the incidence of

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C. B. Hing
Watford General Hospital, Watford, UK

Tools for critical appraisal

- CASP: Critical Appraisal Skills Programme Checklists
- Critically Appraised Topics (ACP Journal club)
- SIGN: Scottish Intercollegiate Guidelines Network
- GATE frame

Critical Appraisal Worksheets

English

- Systematic Reviews Critical Appraisal Sheet
- Diagnostics Critical Appraisal Sheet
- Prognosis Critical Appraisal Sheet
- Randomised Controlled Trials (RCT) Critical Appraisal Sheet

Chinese – Translated by Chung-Han Yang and Shih-Chieh Shao

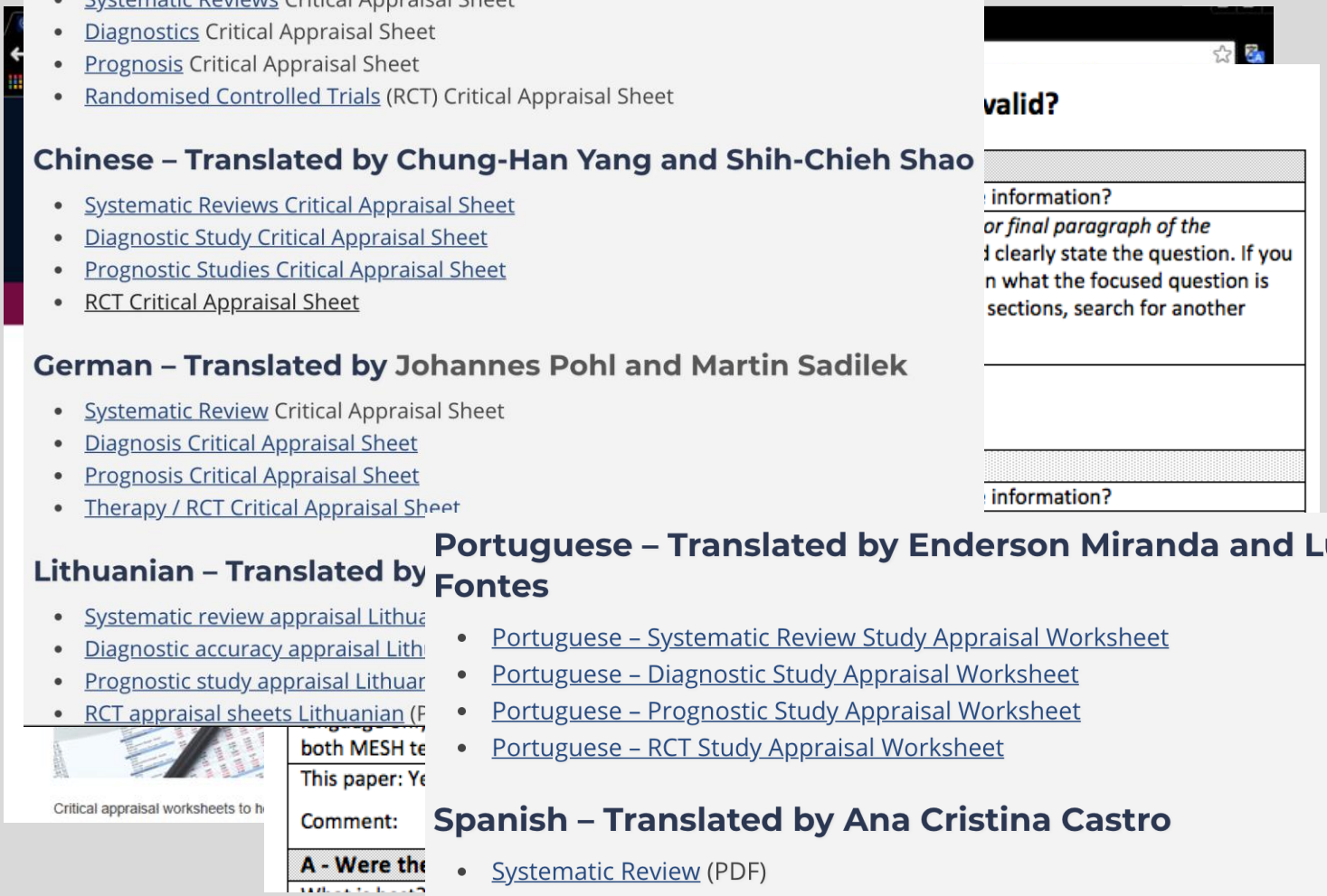
- Systematic Reviews Critical Appraisal Sheet
- Diagnostic Study Critical Appraisal Sheet
- Prognostic Studies Critical Appraisal Sheet
- RCT Critical Appraisal Sheet

German – Translated by Johannes Pohl and Martin Sadilek

- Systematic Review Critical Appraisal Sheet
- Diagnosis Critical Appraisal Sheet
- Prognosis Critical Appraisal Sheet
- Therapy / RCT Critical Appraisal Sheet

Lithuanian – Translated by

- Systematic review appraisal Lithua
- Diagnostic accuracy appraisal Lith
- Prognostic study appraisal Lithuar
- RCT appraisal sheets Lithuanian (F



Portuguese – Translated by Enderson Miranda and Luis Eduardo Fontes

- Portuguese – Systematic Review Study Appraisal Worksheet
- Portuguese – Diagnostic Study Appraisal Worksheet
- Portuguese – Prognostic Study Appraisal Worksheet
- Portuguese – RCT Study Appraisal Worksheet

Spanish – Translated by Ana Cristina Castro

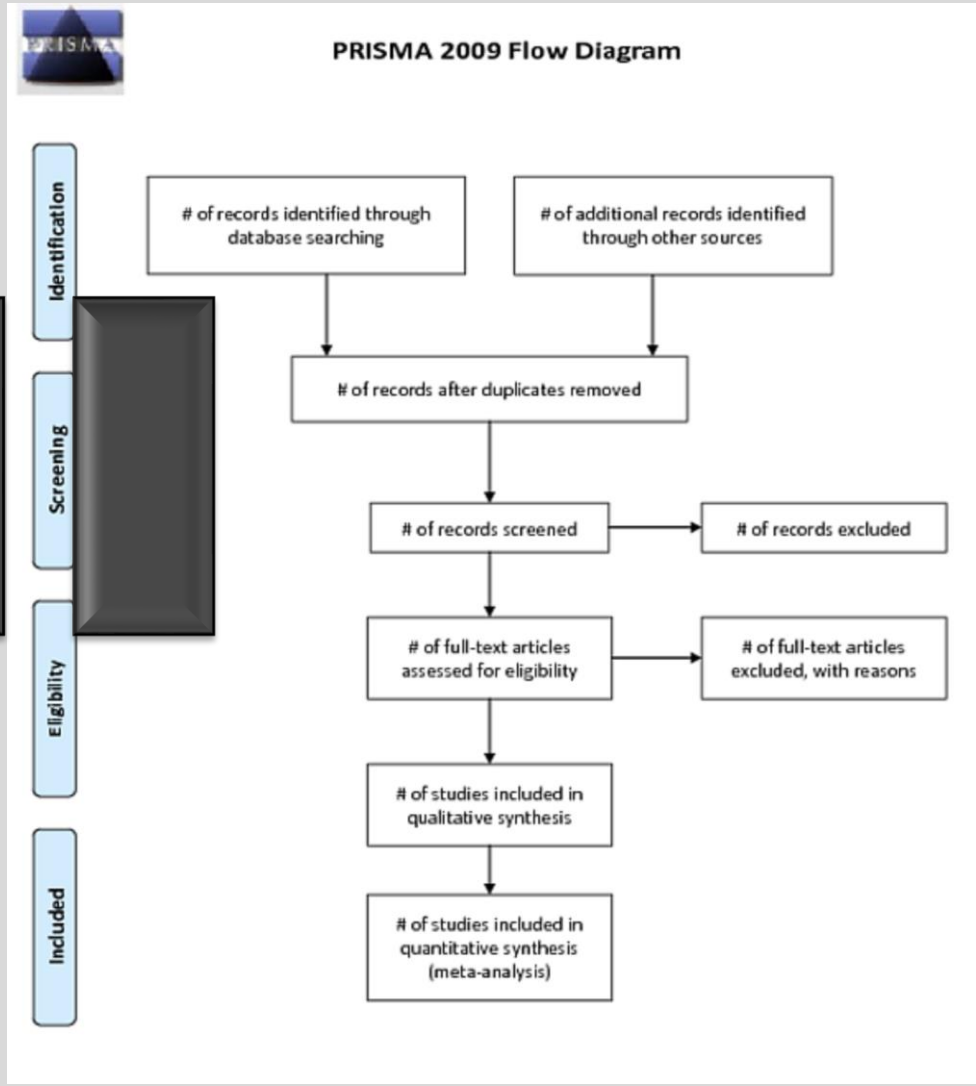
- Systematic Review (PDF)
- Diagnosis (PDF)
- Prognosis Spanish Translation (PDF)
- Therapy / RCT Spanish Translation (PDF)

PRISMA (QUOROM)

***P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-**A**nalyses*

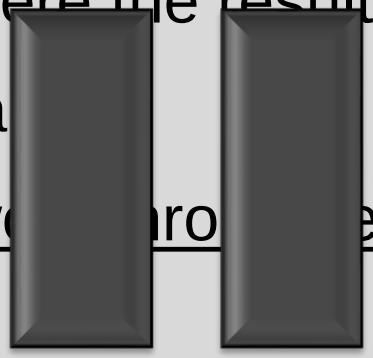
- Consists of a 27-item checklist and four phase flow diagram
- Evidence-based minimum se items for reporting in system reviews and meta-analyses
- Helps critical appraisal but n designed for it

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



TOOLS TO GUIDE **SYSTEMATIC** APPRAISAL

- 2 steps to CEBM systematic review appraisal sheet:
  - Step 1: Are the results of the review valid?
  - Step 2: What were the results?
- 6 questions in tota
- <u>We are going to wo ro each section as a group</u>



TRY TO CREATE A SAFE ENVIRONMENT

Appraising a systematic review

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L. Davies
Physiotherapy Department, Norfolk and Norwich University Hospital, Norwich, UK

C. B. Hing
Watford General Hospital, Watford, UK

3 minutes

Step 1

Are the results of the review valid?

Question – what is the PICO (etc.)

Find(ing) – comprehensive?

Appropriate/**A**ppraise – PICO/good studies?

Synthesize/**S**imilar - numerically/appropriate?

1. What question (PICO) did the systematic review address?

Is question clearly stated early on?

Treatment/exposure described?

Comparator/control described?

Outcome(s) described?

Title, abstract [introduction]

Knee Surg Sports Traumatol Arthrosc (2010) 18:304–311

post-operative arthrofibrosis and wound complications [17, 31, 37, 38].

There is no consensus in the current literature regarding the optimal time of surgical intervention [29]. The purpose of this study was to assess the effects of duration from injury to surgical intervention for patients undergoing ACL reconstruction by comparing the clinical and radiological outcomes of early to delayed ACL reconstruction following initial injury.

P
I
C
O's

Step 1

Are the results of the review valid?

Question – what is the PICO (etc.) ?

Find(ing) – comprehensive? ? X

Appraise – did they select good ones?

Synthesise – numerically/appropriate?

Is it worth continuing?

4. Were the included studies sufficiently valid for the type of question?


TRASH

Criteria for quality assessment defined?

Data extraction and quality assessment

Two investigators (TS, LD), blinded to the source, publication date, authors and affiliations for each paper, used a standardised extraction form. All papers were then evaluated against the eleven-item PEDro scoring system by TS and LD independently. The PEDro appraisal tool has demonstrated reliability and validity in the assessment of

Do your homework!

5. Were the results similar from study to study?

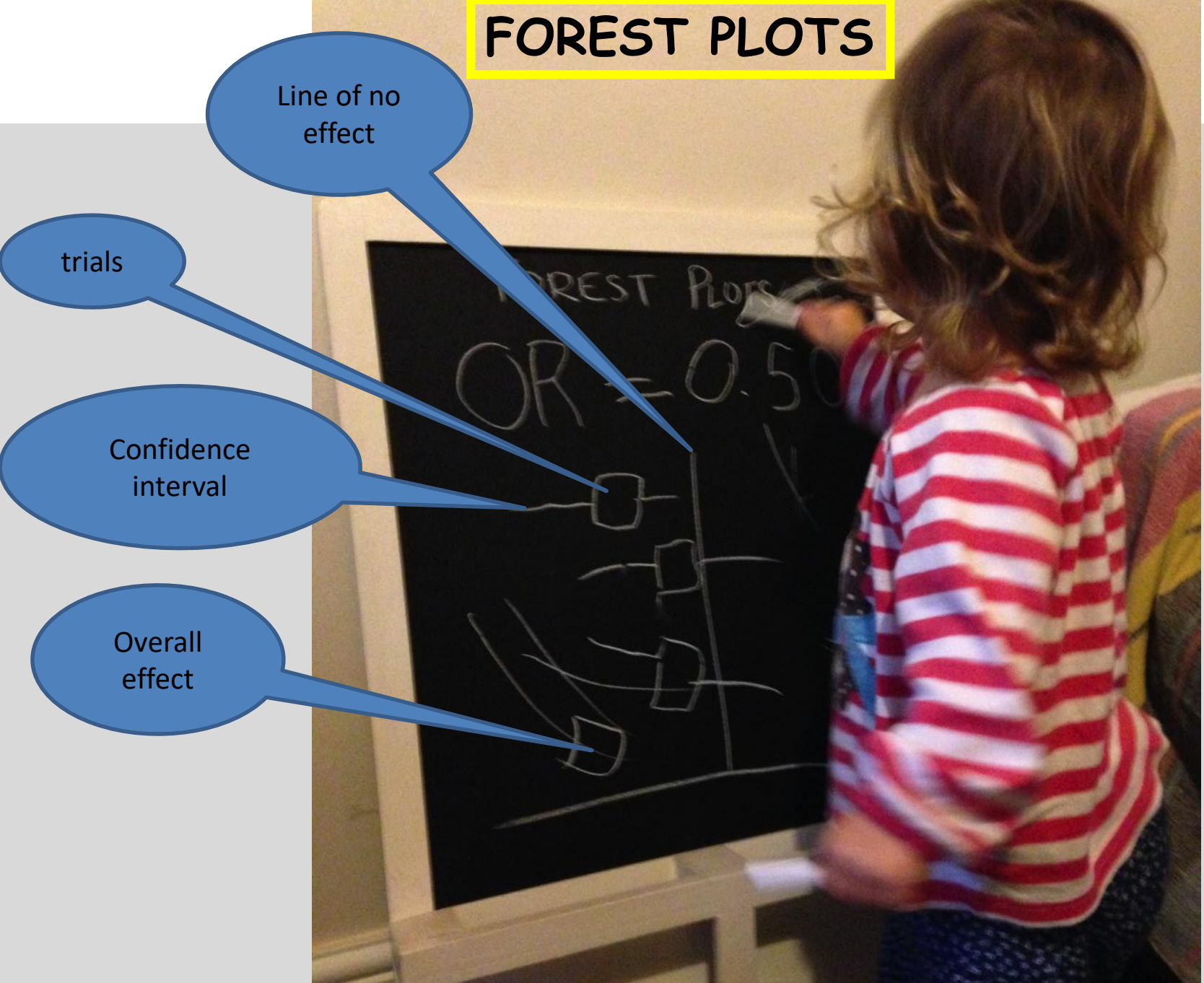
Consider whether

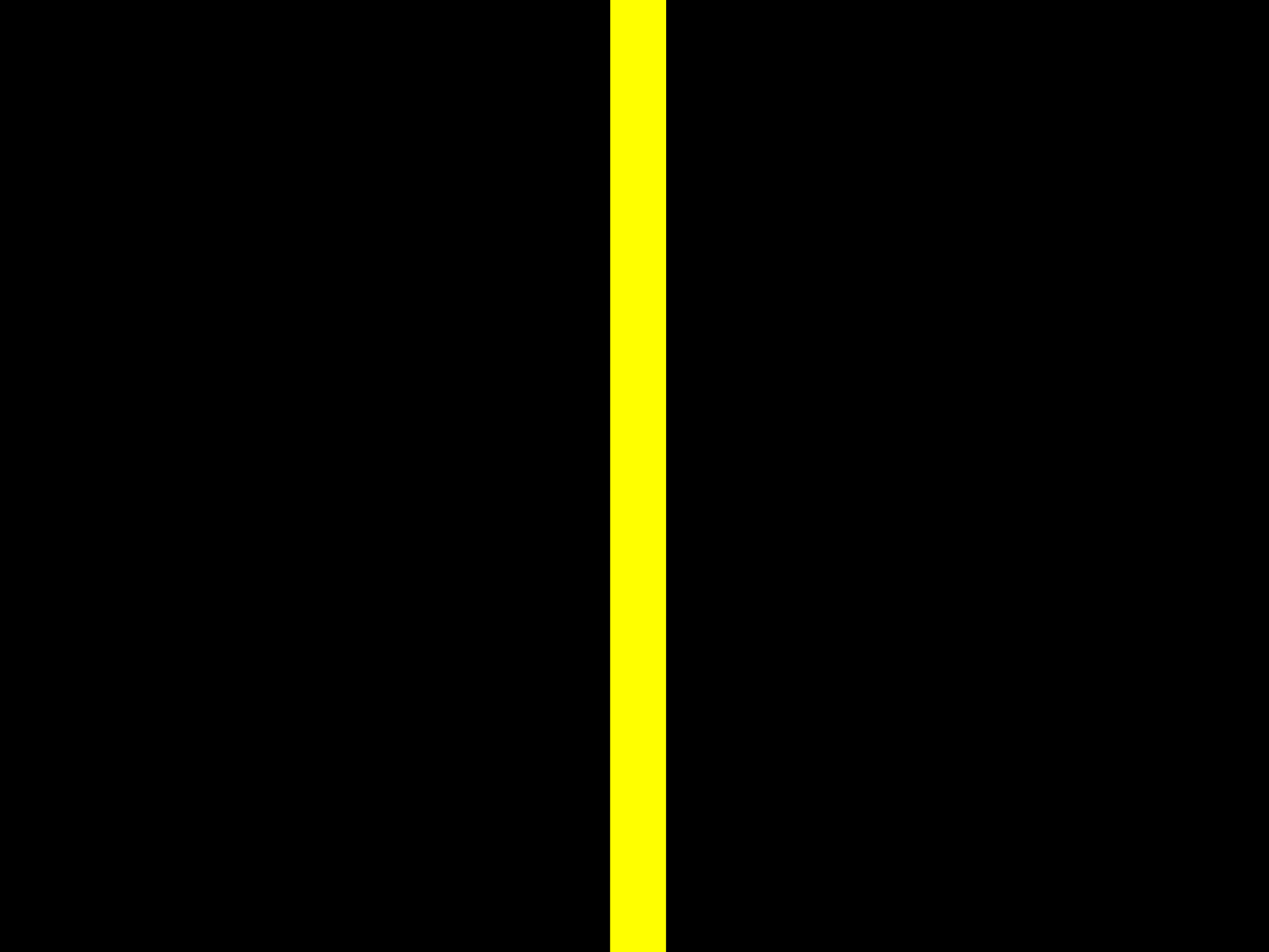
The results of all the included studies are clearly displayed

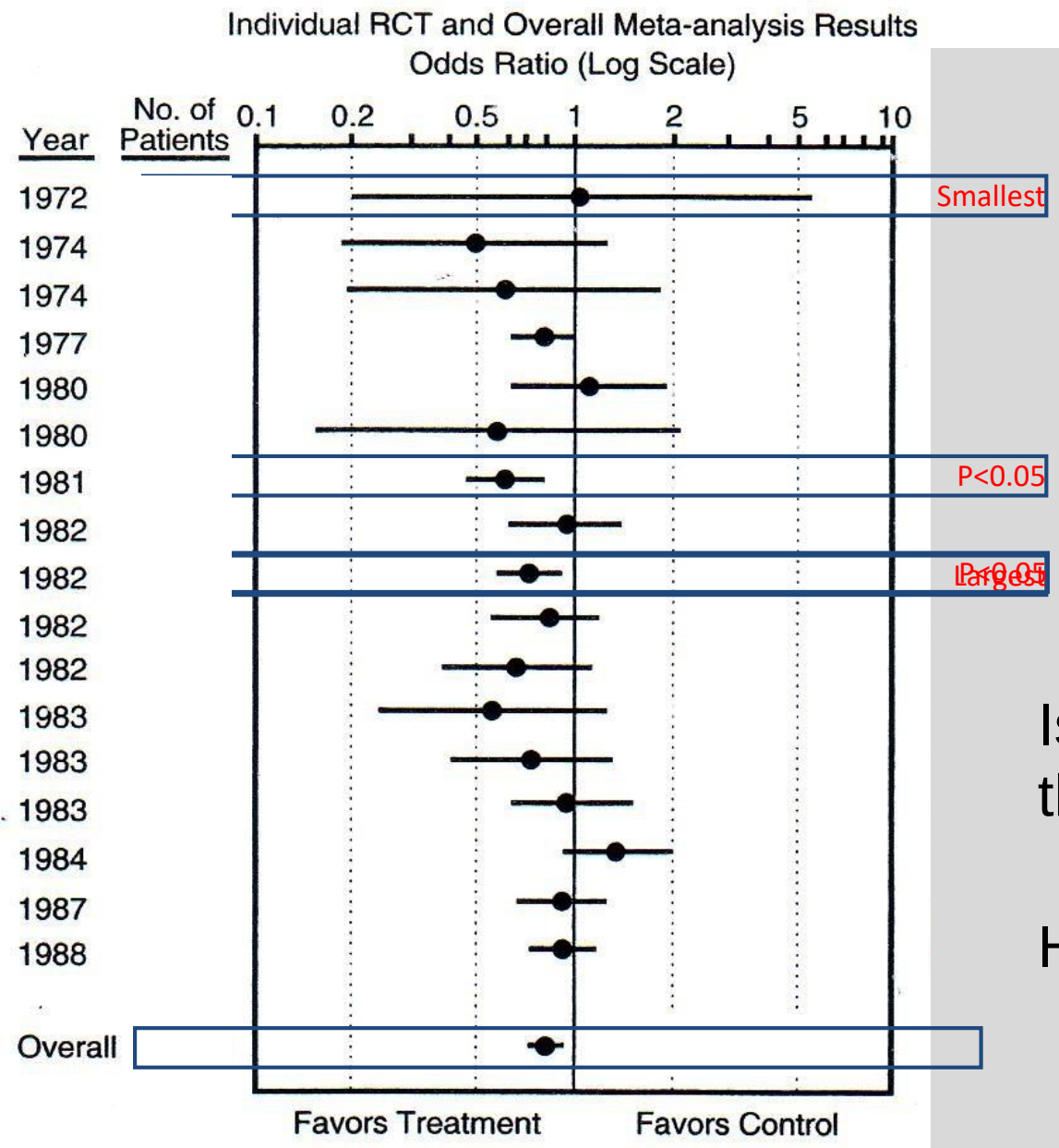
The results are combined (meta-analysis) - *are studies sufficiently similar?*

The reasons for any variations in results are discussed

FOREST PLOTS







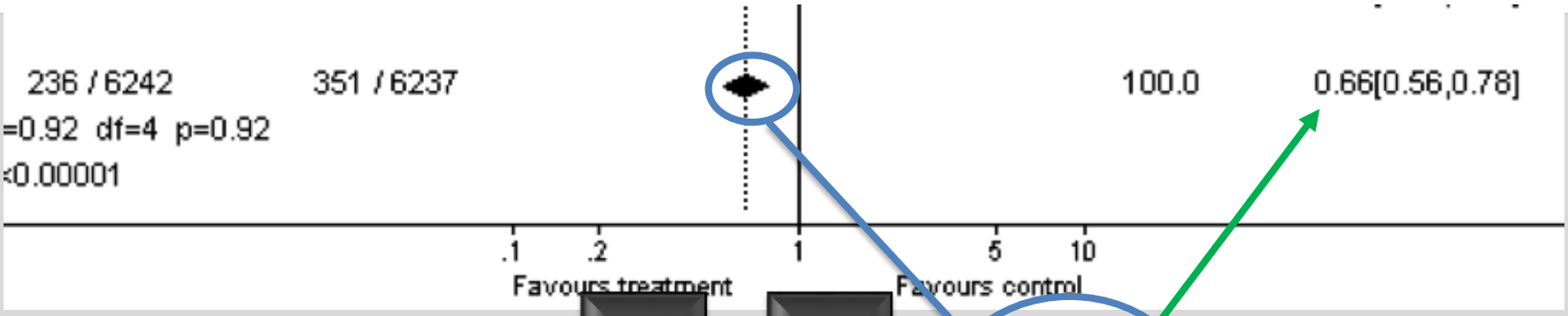
A. Which is the smallest study?

B. Which is the largest study?

C. How many are statistically significant?

Is treatment better than control?

How much better?


236 / 6242
351 / 6237
100.0
0.66[0.56,0.78]
=0.92 df=4 p=0.92
<0.00001
.1
.2
1
5
10
Favours treatment
Favours control

Effect size =

Heterogeneity

"The quality or state of being diverse in character or content"

DIFFERENT

Heterogeneity

Clinical heterogeneity

Differences in the participants, interventions and/or outcomes studied

Methodological heterogeneity

Differences in study deign and risk of bias

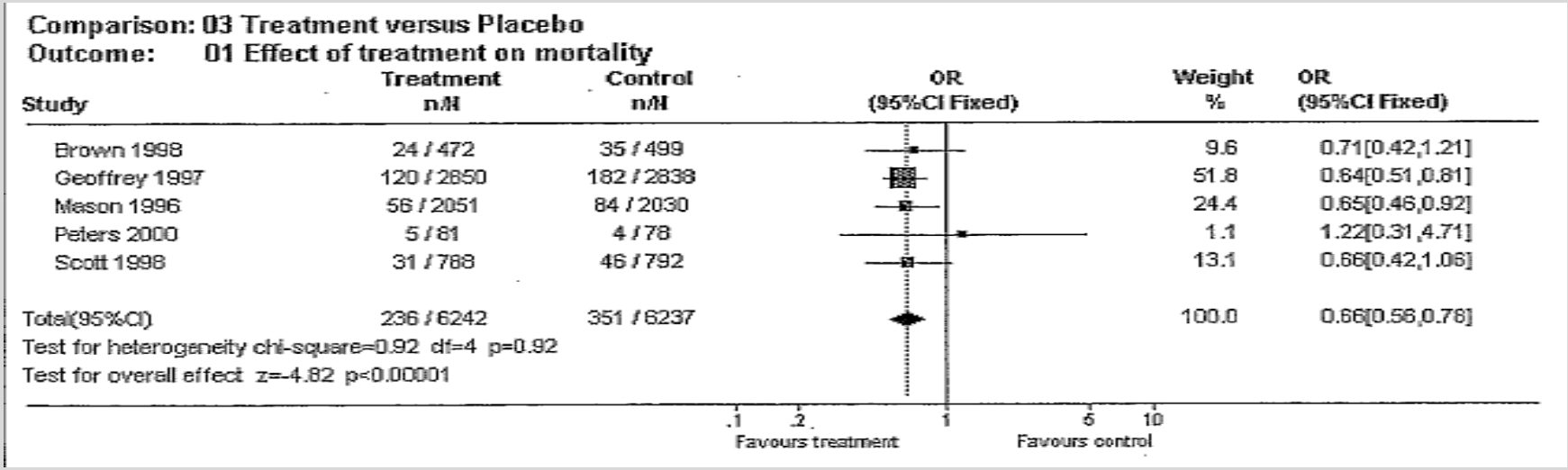
Statistical heterogeneity

The observed intervention effects being more different from each other than we would expect due to random error (chance) alone

High heterogeneity

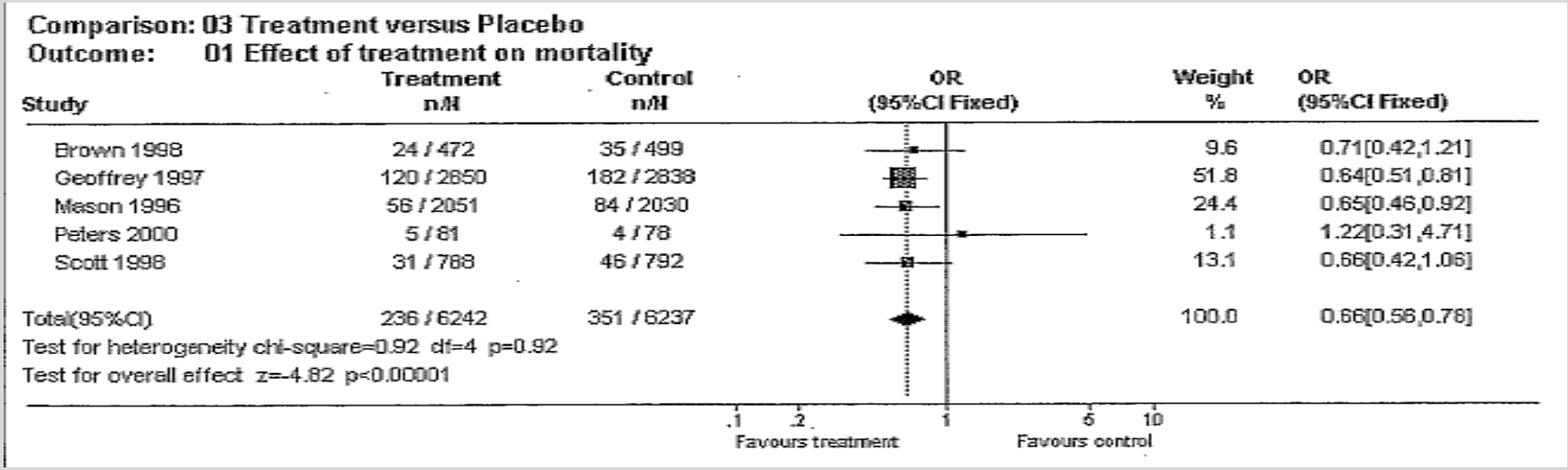
=

appropriate to pool data?



Are the results similar across studies?

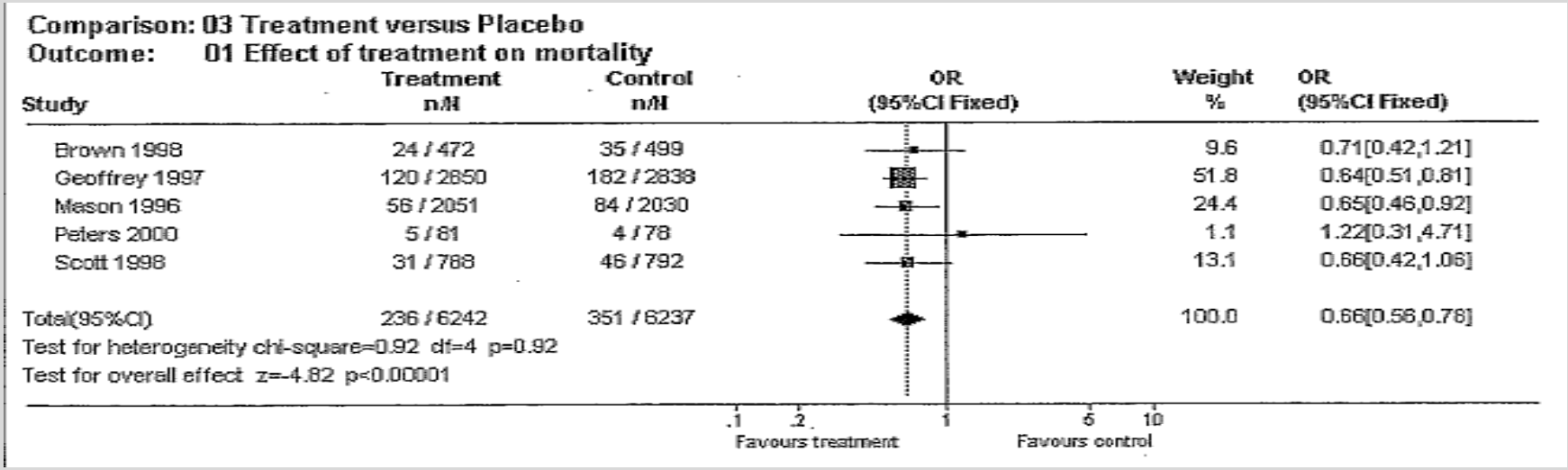
3 TESTS



‘Eyeball’ test

1

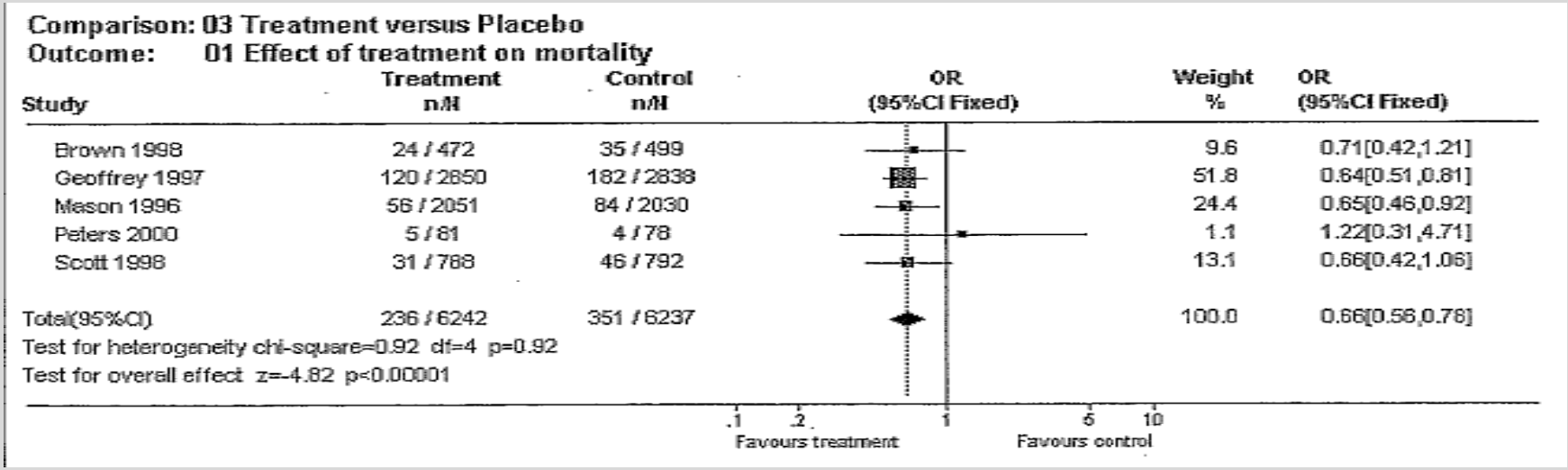
Do they look they same?



Formal (statistical) tests

2

I^2 (i-squared)



Formal tests

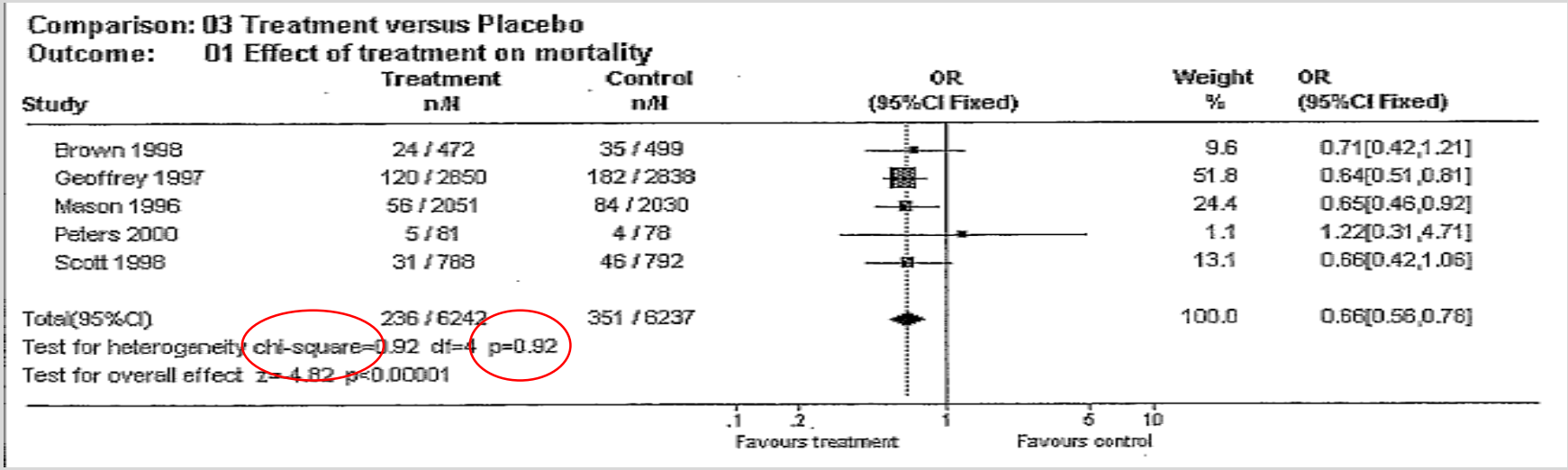
2

0% to 40%: might not be important;

30% to 60%: may represent moderate heterogeneity;

50% to 90%: may represent substantial heterogeneity;

75% to 100%: considerable heterogeneity



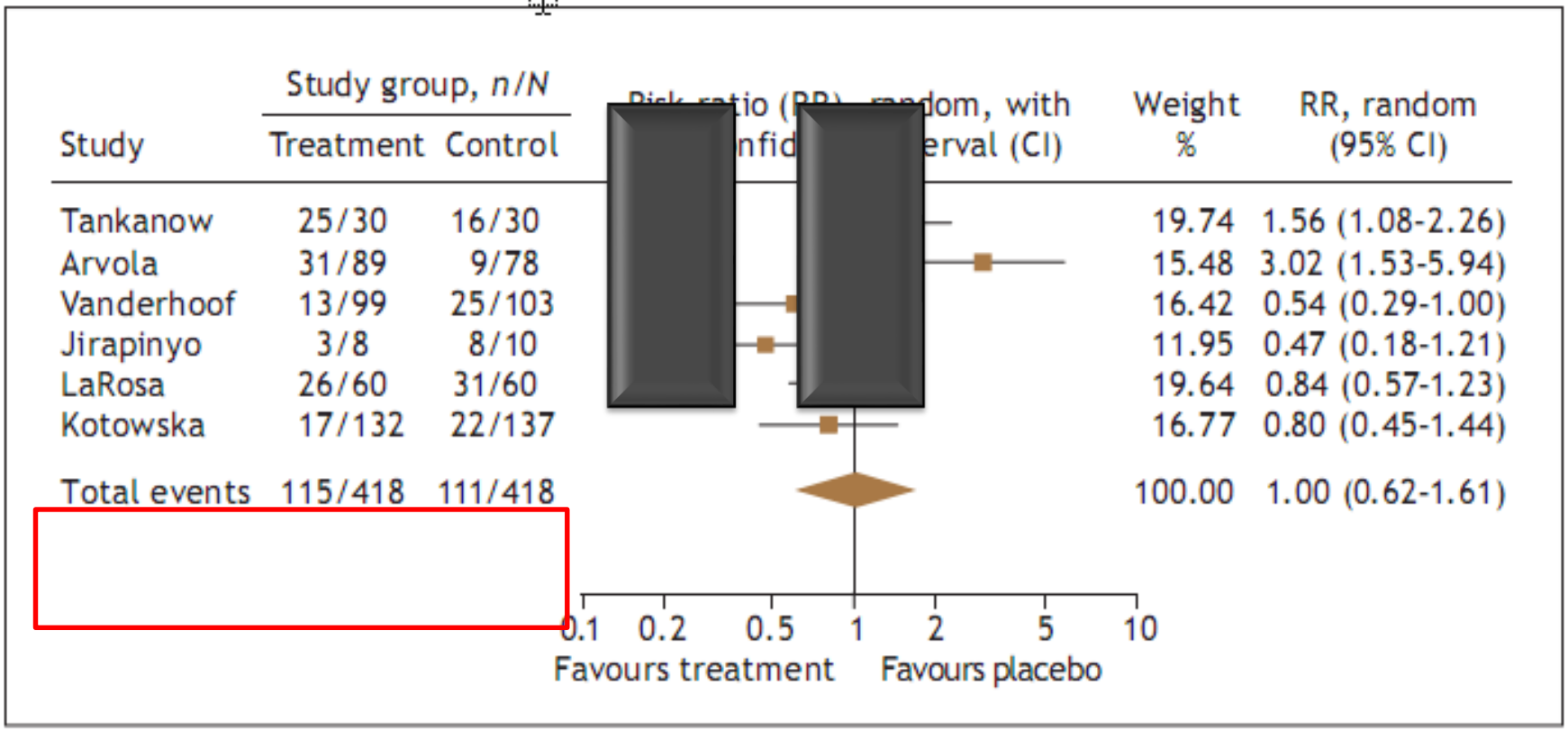
Formal tests

3

Cochrane Chi-square

p<0.10 = heterogeneity

Are these trials different?



(Try to) keep it simple

Step 2

What were the results?

Consider

How were the results presented/expressed (risk ratio, odds ratio, etc.)

What these are (numerically if appropriate)

If you are clear about the review's 'bottom line' results

What are we interested in?

Table 2 Results of meta-analysis

Outcome	Papers	Relative risk (95% CI)	Overall effect (*P* value)	Heterogeneity	
				χ^2	I^2
Lysholm Score	[4, 34, 35]	0.07 (−9.93, 10.08)*	0.99	0.02	81
Lysholm Score (Good/excellent)	[26]				
Tegner Score	[4, 34, 35]	−0.07 (−0.42, 0.29)*	0.71	0.60	0
KT-1000 Arthrometer	[4, 34, 35]	0.05 (−0.52, 0.63)*	0.85	0.19	42
Tibiofemoral Displacement > 3 mm	[25, 35]	0.59 (0.25, 1.43)	0.24	0.19	43
Positive Lachman	[26, 34, 35]	0.64 (0.27, 1.51)	0.31	0.02	73
Positive pivot shift	[26, 34, 35]	0.69 (0.43, 1.11)	0.13	0.52	0
Extension deficit	[4, 35]	−0.90 (−2.39, 0.59)*	0.24	N/E	N/E
Flexion deficit	[4, 35]	−0.50 (−2.55, 1.55)*	0.63	N/E	N/E
Extension deficit > 10°	[4, 26, 34]	0.96 (0.21, 4.37)	0.96	0.21	36
Incidence of arthrofibrosis	[28, 34, 35, 42]	1.83 (0.81, 4.14)	0.15	0.76	0
Incidence of meniscal injury	[4, 26, 28, 34, 42]	0.92 (0.71, 1.19)	0.53	<0.01	74
Incidence of chondral injury	[4, 26, 34, 42]	0.77 (0.44, 1.37)	0.38	0.26	25
Frequency of revision surgery	[26, 28, 34, 35, 42]	0.81 (0.42, 1.58)	0.54	0.30	17
Incidence of patellofemoral pain	[35, 42]	2.05 (0.86, 4.89)	0.11	0.58	0
Incidence of thromboembolic complication	[28, 35]	1.79 (0.21, 27.29)	0.68	0.21	37

* Mean difference (95% confidence intervals), ° degrees, *CI* confidence intervals, *mm* millimetres, N/E not estimated

Our clinical question

Population
Amongst adults with acute ACL injuries, does

Intervention
early reconstructive surgery compared with

Control
delayed reconstructive surgery lead to

Outcome 1
favourable return to former activity and/or risk of

Outcome 2
recurrent knee injury?

Return to former activity (page 306):

There was no statistically significant difference between the early and delayed ACL reconstruction groups for the Lysholm score or Tegner score (Table 2). There was no significant difference between the groups for International Knee Documentation Committee rating score [not significant (n.s.)] [26], IKDC perceived stability rating (n.s.) [26], or the Hospital for Special Surgery score system (n.s.) [35]. There was no reported significant difference in patient satisfaction ($P = 0.19$) [35]. The frequency that patients returned to the same level of sporting participation was assessed in Marcacci et al.'s [26] paper. This reported that there was no statistically significant difference in return rates between the two groups (n.s.) [26].

Risk of recurrent knee injury

Table 2 Results of meta-analysis

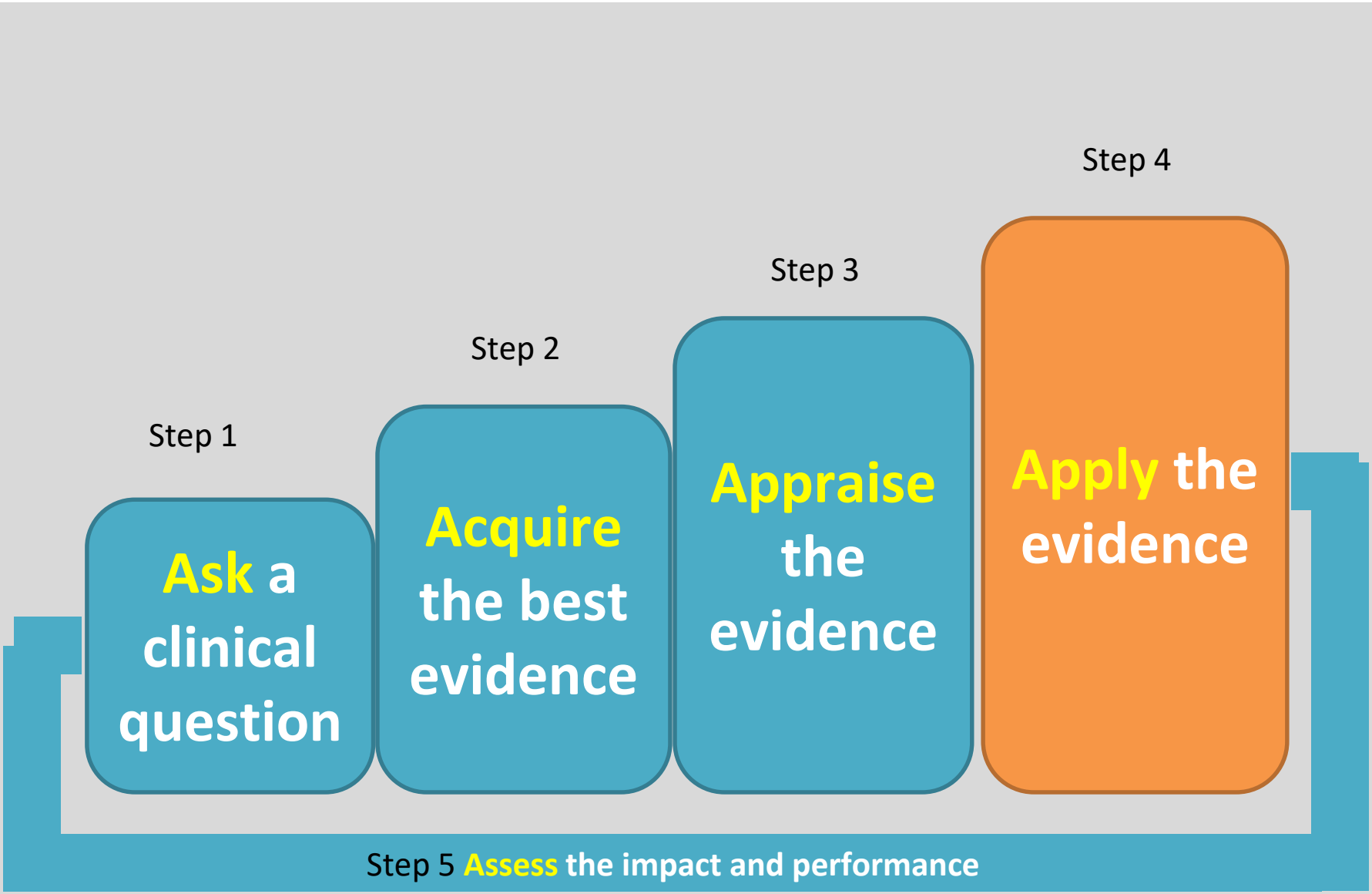
Outcome	Papers	Relative risk (95% CI)	Overall effect (*P* value)	Heterogeneity	
				χ^2	I^2
Incidence of meniscal injury	[4, 26, 28, 34, 42]	0.92 (0.71, 1.19)	0.53	<0.01	74
Incidence of chondral injury	[4, 26, 34, 42]	0.77 (0.44, 1.37)	0.38	0.26	25

What's the 'bottom line' of the review?

Conclusions

The findings of this study suggested that there was no statistically significant difference in outcomes between those patients who underwent earlier compared to delayed ACL reconstruction. The present evidence-base presented with substantial methodological limitations. A sufficiently powerful, well-design randomised controlled trial is required to determine whether of duration from injury to surgical intervention is an important prognostic indicator for patients who undergo an ACL reconstruction.

Practising EBM – the 5 A's



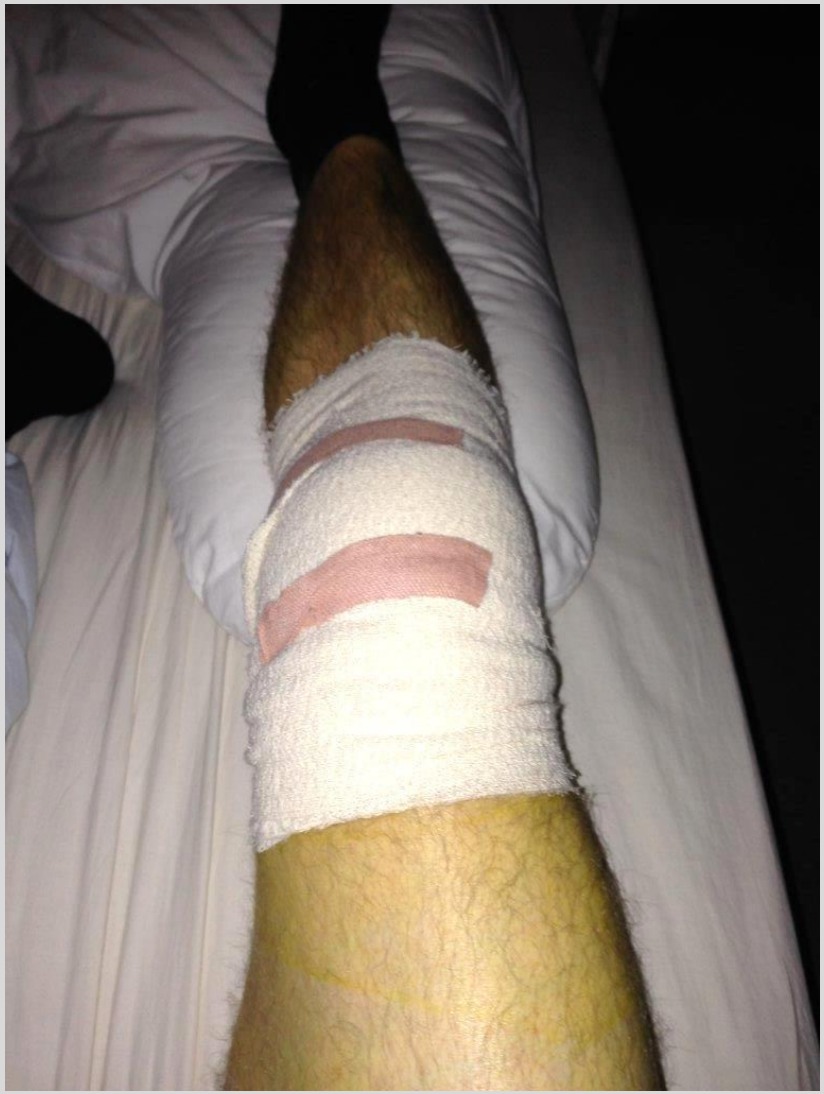
Can I apply these results to my case?

Is my patient so different to those in the study that the results cannot apply?

early were compared to 209 delayed procedures. The mean age was 25.6 years in the early group [Standard deviation (SD) = 2.3] compared to 26.2 years (SD = 1.1) in the delayed group (Table 1).

Delay or not delay?

October 27th 2014



‘Appraisal pearls’

QFAS

“Is it worth continuing?”

I^2 >50%

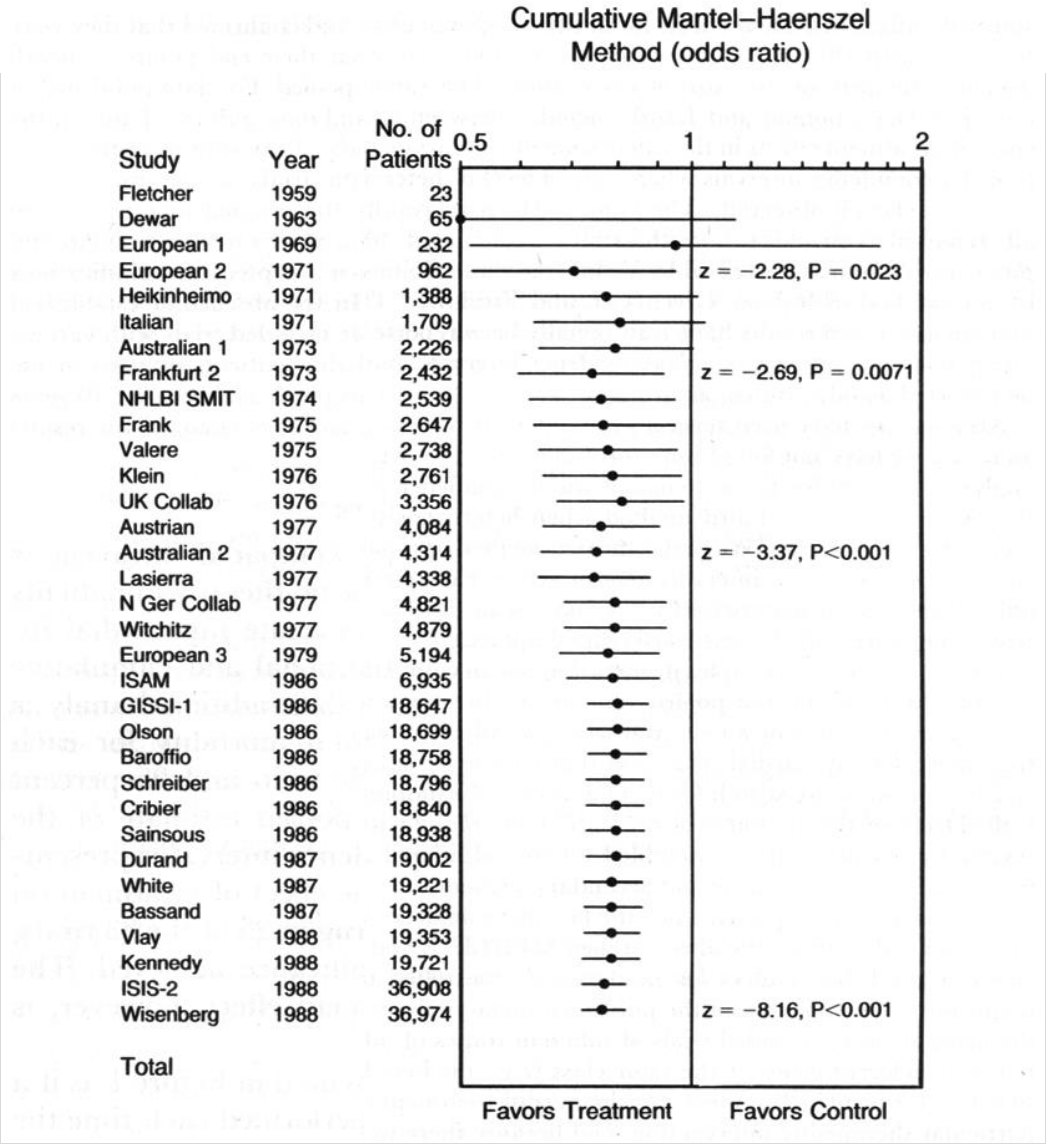
Would your patient get into the trials/studies

Look for ‘key’ references = Cochrane Risk of Bias, GRADE, PRISMA (QUOROM)

a) I can tell which of these trials were potentially dangerous/unethical to perform

b) If I had more time I could sort of work it out, maybe…

c) Huh?!....



Session objectives

By the end of this session you will:

Understand what a systematic review is and the steps involved in producing one

Be able to (rapidly) cr lly raise a systematic review using available ls

Have learned something new

Have had (some) fun!

NEED A COFFEE…

CLOSE THE LOOP

Tips for teaching systematic reviews

Know & engage your audience (have a hook)

Try to create a safe environment

Reinforce relevant concepts (e.g. PICO)

Use a tool to guide critical appraisal

“Is it worth continuing?”

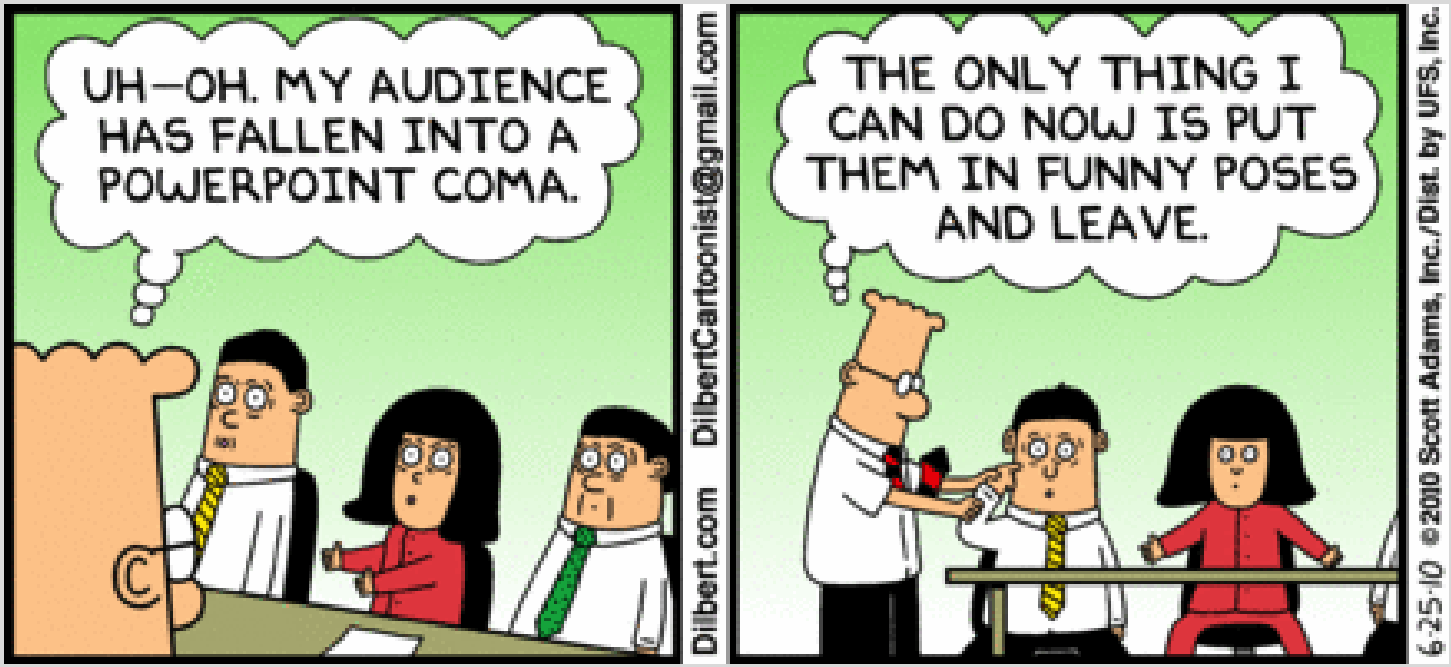
Stats/forest plots/heterogeneity – keep it simple!

Objectives

Show some techniques/tips for critical appraisal of systematic reviews

Help you plan your own 90 min teaching critical appraisal

Help make teaching critical appraisal of systematic reviews fun


UH—OH. MY AUDIENCE HAS FALLEN INTO A POWERPOINT COMA.
THE ONLY THING I CAN DO NOW IS PUT THEM IN FUNNY POSES AND LEAVE.
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Thanks

Publication Bias: Solution

- All trials registered at inception,
  - The National Clinical Trials Registry: Cancer Trials
  - National Institutes of Health Inventory of Clinical Trials and Studies
  - International Registry of Perinatal Trials
- Meta-Registry of trial Registries
  - www.clinicaltrials.org
  - www.controlled-trials.com

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grading quality of evidence and streng
it. »» learn more

Quality assessment							Su	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)	
							With Aspirin vs. Clopidogrel	With Aspirin + Prasugrel
Mortality, All-Cause (CRITICAL OUTCOME)								
13608 (1 study[2]) 15 months	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	undetected	⊕⊕⊕⊕ HIGH[1]	197/6795 (2.9%)	188/6813 (2.8%)
Mortality, Cardiovascular (CRITICAL OUTCOME)								

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METHODOLOGY

Understanding GRADE: an introduction

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Keywords
Evidence-based medicine; GRADE; randomized controlled trial; systematic review.

Correspondence

Abstract

Objective: Grading of recommendations, assessment, development, and evaluations (GRADE) is arguably the most widely used method for appraising studies to be included in systematic reviews and guidelines. In order to use the GRADE system or know how to interpret it when reading reviews, reading several articles and

JEBM; 6:50-54

PRISMA (QUOROM)

***P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-**A**nalyses*

- Consists of a 27-item checklist and four phase flow diagram
- Evidence-based minimum set of items for reporting in systematic reviews and meta-analyses
- Can be used for critical appraisal but not designed for it

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

RESEARCH METHODS & REPORTING

Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement

David Moher,[1,2] Alessandro Liberati,[3,4] Jennifer Tetzlaff,[1] Douglas G Altman,[5] for the PRISMA Group

David Moher and colleagues introduce PRISMA, an update of the QUOROM guidelines for reporting systematic reviews and meta-analyses

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Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their specialty,[1 2] and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research,[3] and some medical journals are moving in this direction.[4] As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews.

Several early studies evaluated the quality of review reports. In 1987 Mulrow examined 50 review articles published in four leading medical journals in 1985 and 1986 and found that none met all eight explicit scientific criteria, such as a quality assessment of included studies.[5] In 1987 Sacks and colleagues evaluated the adequacy of reporting of 83 meta-analyses on 23 characteristics in six domains.[6] Reporting was generally poor; between one and 14 characteristics were adequately reported (mean 7.7, standard deviation 2.7). A 1996 update of this study found little improvement.[7]

In 1996, to address the suboptimal reporting of meta-analyses, an international group developed a guidance called the QUOROM statement (QUality Of Reporting Of Meta-analyses), which focused on the reporting of meta-analyses of randomised controlled trials.[8] In this article, we summarise a revision of these guidelines, renamed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses), which have been updated to address several conceptual and practical advances in the science of systematic reviews (see box).

Terminology

The terminology used to describe a systematic review and meta-analysis has evolved over time. One reason for changing the name from QUOROM to PRISMA was the desire to encompass both systematic reviews

Conceptual issues in the evolution from QUOROM to PRISMA

Completing a systematic review is an iterative process

The conduct of a systematic review depends heavily on the scope and quality of included studies: thus systematic reviewers may need to modify their original review protocol during its conduct. Any systematic review reporting guideline should recommend that such changes can be reported and explained without suggesting that they are inappropriate. The PRISMA statement (items 5, 11, 16, and 23) acknowledges this iterative process. Aside from Cochrane reviews, all of which should have a protocol, only about 10% of systematic reviewers report working from a protocol.[9] Without a protocol that is publicly accessible, it is difficult to judge between appropriate and inappropriate modifications.

Conduct and reporting of research are distinct concepts

This distinction is, however, less straightforward for systematic reviews than for assessments of the reporting of an individual study, because the reporting and conduct of systematic reviews are, by nature, closely intertwined. For example, the failure of a systematic review to report the assessment of the risk of bias in included studies may be seen as a marker of poor conduct, given the importance of this activity in the systematic review process.[10]

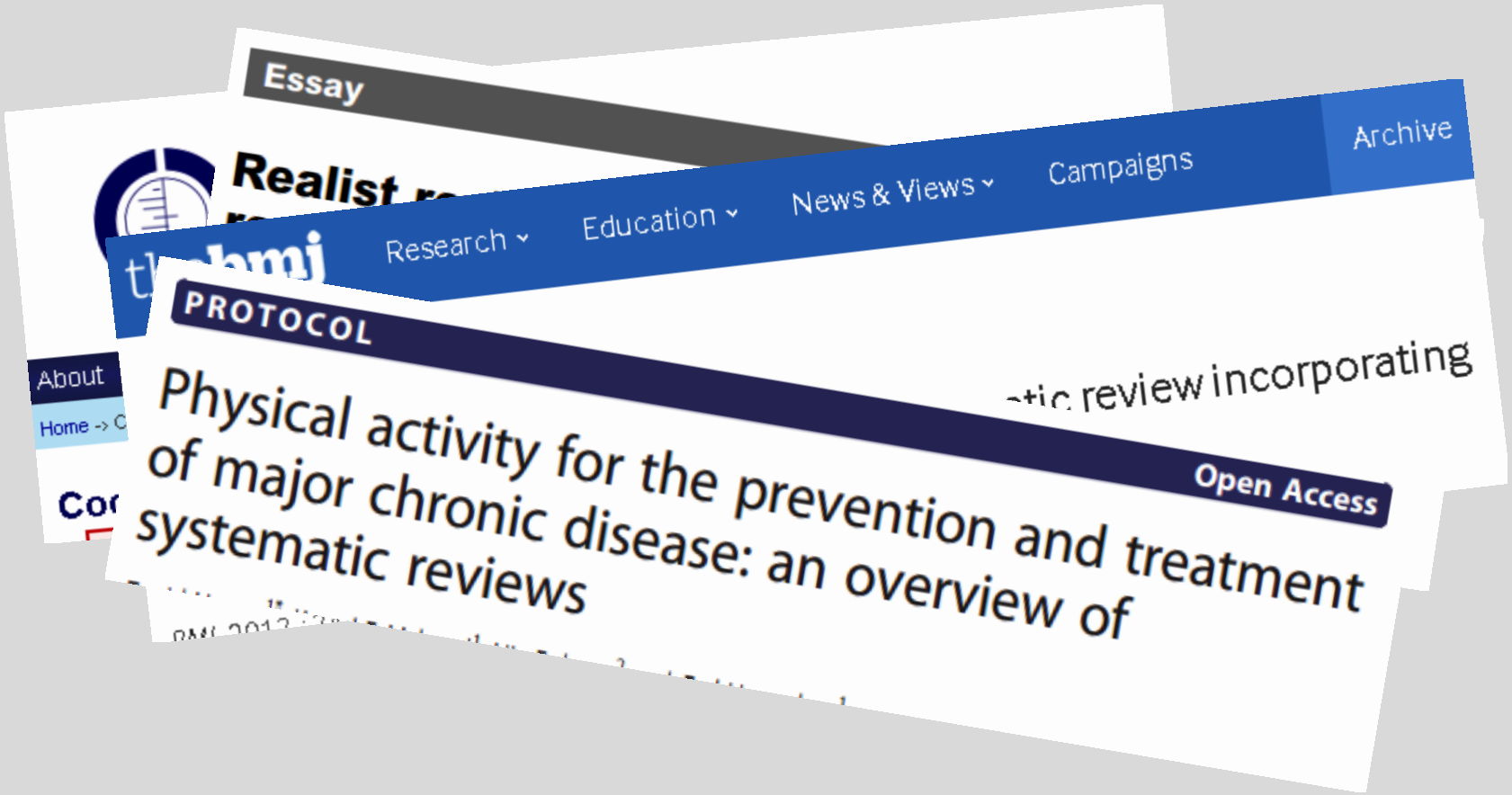
Study level versus outcome level assessment of risk of bias

For studies included in a systematic review, a thorough assessment of the risk of bias requires both a study level assessment (such as adequacy of allocation concealment) and, for some features, a newer approach called outcome-level assessment. An outcome-level assessment involves evaluating the reliability and validity of the data for each important outcome by determining the methods used to assess them in each individual study.[11] The quality of evidence may differ across outcomes, even within a study, such as between a primary efficacy outcome, which is likely to be carefully and systematically measured, and the assessment of serious harms,[12] which may rely on spontaneous reports by investigators. This information should be reported to allow an explicit assessment of the extent to which an estimate of effect is correct.[11]

Importance of reporting biases

Different types of reporting biases may hamper the conduct and interpretation of systematic reviews. Selective reporting of complete studies (such as publication bias),[13] as well as the more recently empirically demonstrated "outcome reporting bias" within individual studies,[14 15] should be considered by authors when conducting a systematic review and reporting its results. Although the implications of these biases on the conduct and reporting of systematic reviews themselves are unclear, some research has identified that selective outcome reporting may occur also in the context of systematic reviews.[14]

Coming soon….already here?



Fixed effects model

Assumptions:

- Studies do not differ in design and how they are conducted.
- Any variation between the results of the studies is due to chance.
- That large studies will have less variation and so are given a heavier weight.
- That bigger studies are better (this is not always the case).

It's more precise than a random-effects model, because in the presence of statistical heterogeneity it usually has narrower confidence intervals.

Random effects model

- Assumes the studies are not all estimating the same intervention effect.
- Can be used to incorporate heterogeneity among studies.
- Not a substitute for a thorough investigation of heterogeneity - is intended primarily for heterogeneity that cannot be explained.
- Accounts for heterogeneity but does not explain it.
- Provides a more conservative estimate of effect.
- Studies are given a more equal weighting.

Risk and odds ratios

Both the odds ratio and the relative risk compare the likelihood of an event between two groups. Consider the following data on survival of passengers on the Titanic. There were **462 female passengers: 308 survived and 154 died**. There were **851 male passengers: 142 survived and 709 died** (see table below).

	Alive	Dead	Total
Female	308	154	462
Male	142	709	851
Total	450	863	1,313

Clearly, a male passenger on the Titanic was more likely to die than a female passenger. But how much more likely? You can compute the odds ratio or the relative risk to answer this question.

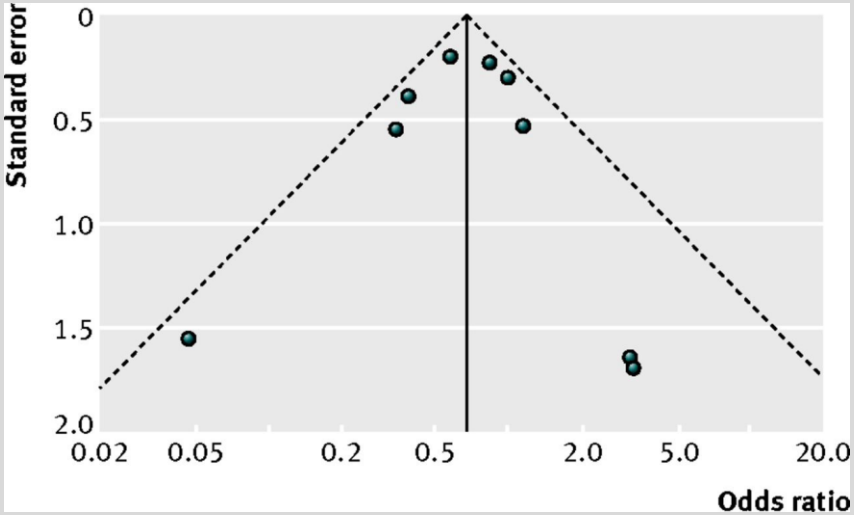
The odds ratio compares the relative odds of death in each group. For females, the odds were exactly **2 to 1 against dying (154/308=0.5)**. For males, the odds were almost **5 to 1 in favor of death (709/142=4.993)**. The odds ratio is **9.986 (4.993/0.5)**. There is a **ten fold greater odds of death for males than for females**.

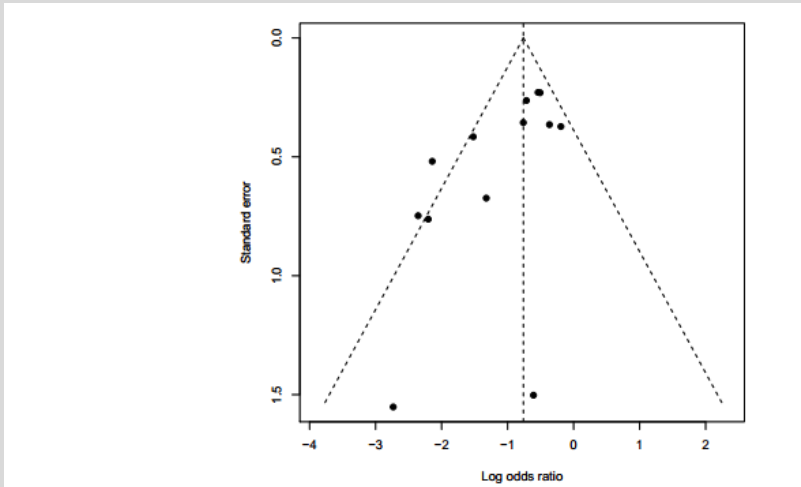
The relative risk (sometimes called the risk ratio) compares the probability of death in each group rather than the odds. For females, the probability of death is **33% (154/462=0.3333)**. For males, the probability is **83% (709/851=0.8331)**. The relative risk of death is **2.5 (0.8331/0.3333)**. There is a **2.5 greater probability of death for males than for females**.

Publication bias

- Occurs when publication of research results depends on their nature and direction
- Often happens because smaller (n and effect size) studies not submitted/rejected, selective reporting, selective citation (of +ve results)
- Funnel plots help identify if there is a bias:
  - Treatment effect vs. study size
  - Smaller the study = wider the effects
  - Largest studies will be near the average (truth), small studies will spread on both sides = symmetric funnel
  - Asymetric funnel indicates publication bias – but not all the time (e.g. heterogeneity)
  - Interpretation difficult if only a few studies in meta-analysis

Funnel plots





⇒ hints for publication bias