FACULTY OF MEDICINE AND HEALTH SCIENCES

Evidence Based Medicine – deel 1

Wim Ceelen - GI Heelkunde

GHENT UNIVERSITY

bloed, ademhaling & spijsvertering

Universitair Ziekenhuis Gent

Overview

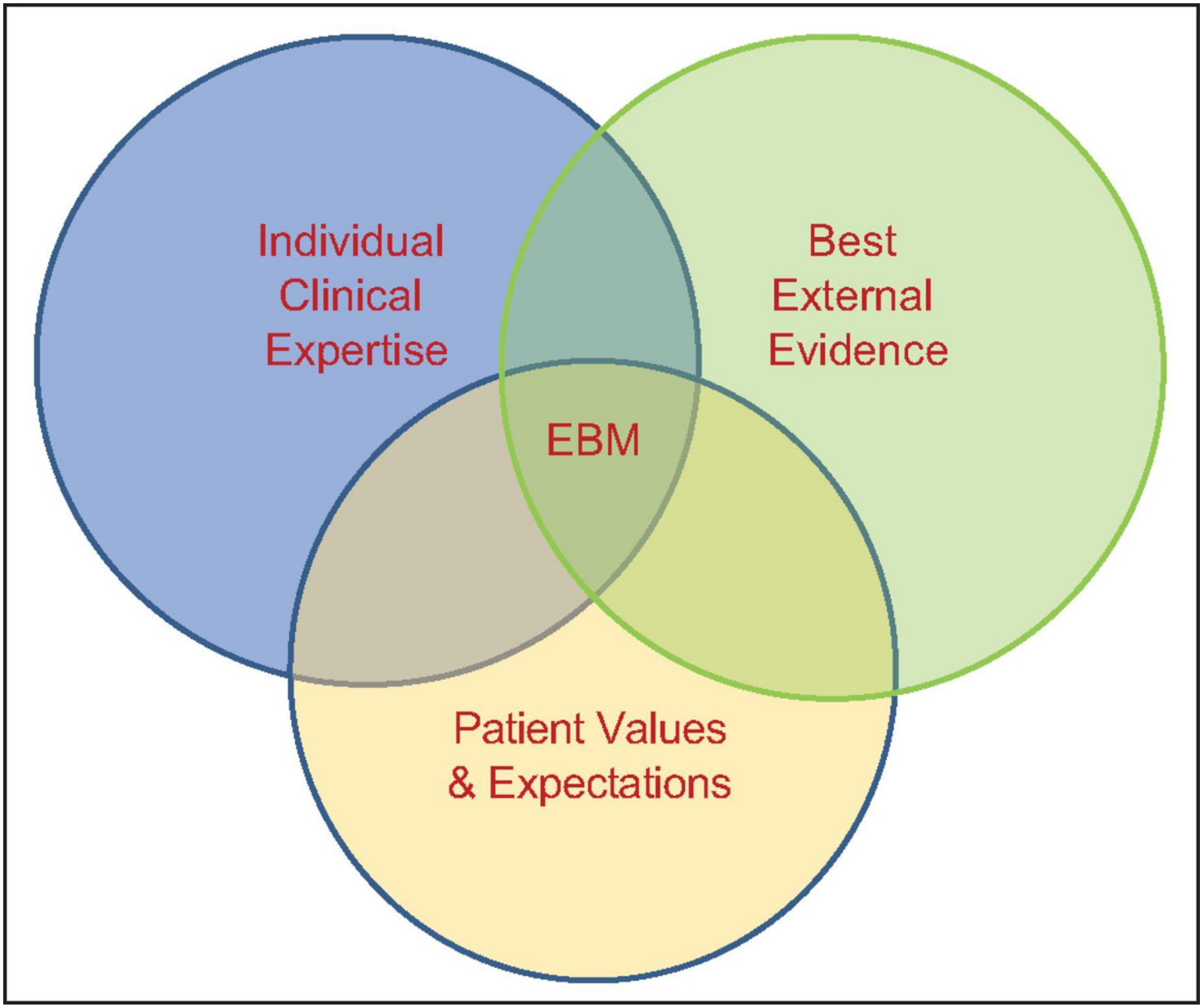
- **Expert**
  - EBM: what, why, how
  - How to interpret results from individual studies
  - How to interpret results from aggregated data (meta-analyses)
- **Expert plus part A**
  - Specific problems and obstacles in the surgical disciplines
  - Alternative study designs
  - How to develop and evaluate practice guidelines
- **Expert plus part B**
  - Ethical and regulatory aspects of research using devices and/or surgical techniques
  - How to measure quality
  - Ethics of surgical interventions: placebo procedures, learning curve,…

https://ebm.mcmaster.ca/

Overview

- Definition
- Why EBHC?
- Critical appraisal of
  - Individual study reports
  - Meta-analyses and systematic reviews

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.


Individual
Clinical
Expertise
Best
External
Evidence
EBM
Patient Values
& Expectations

'The case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue'

Richard Horton, Editor, The Lancet April 2015

'A lie told told often enough becomes the truth'

IS Lenin

Why EBM?

- Scientific arguments
  - ‘information overload’
  - Bias, conflicts of interest, fraud
  - Post-truth: Trumpism
- Medical argument
  - Evidence based practice → better medicine
- Societal/ethical argument
  - Value, justice

Problems with current evidence

- Results from half of all trials are never published, and positive trials are twice as likely to be published
- The cost of drug trials rose fivefold in one decade and is hindering the development of new medicines
- From 2009 to 2014, the drug industry received fines totalling €12bn for *criminal behaviour and civil infringements*
- One third (34%) of scientists report questionable research practices

How is evidence appraised?

- **Hierarchy of study designs**: meta-analysis of well performed and adequately powered RCT's to 'eminence based medicine'
- Individual **scoring systems:**
  - Jadad score
  - Delphi List
  - CONSORT statement
  - Cochrane Collaboration criteria
- Often incomplete/problematic
- **GRADE**: evaluate quality of evidence (4-tier) and formulate treatment recommendation (strong or weak)

NEWS

HOW PAXIL KILLED OUR SON

By Susan Edelman

September 19, 2004 | 4:00am

JAKE Steinberg had bitten his nails since childhood, but when a doctor noticed the California college student's antsy habit, he prescribed a medication to stop it: Paxil.

"It was a terrible mistake," his father, Robert Steinberg, told The Post.

ADVERTISING

TRENDING NOW IN NEWS

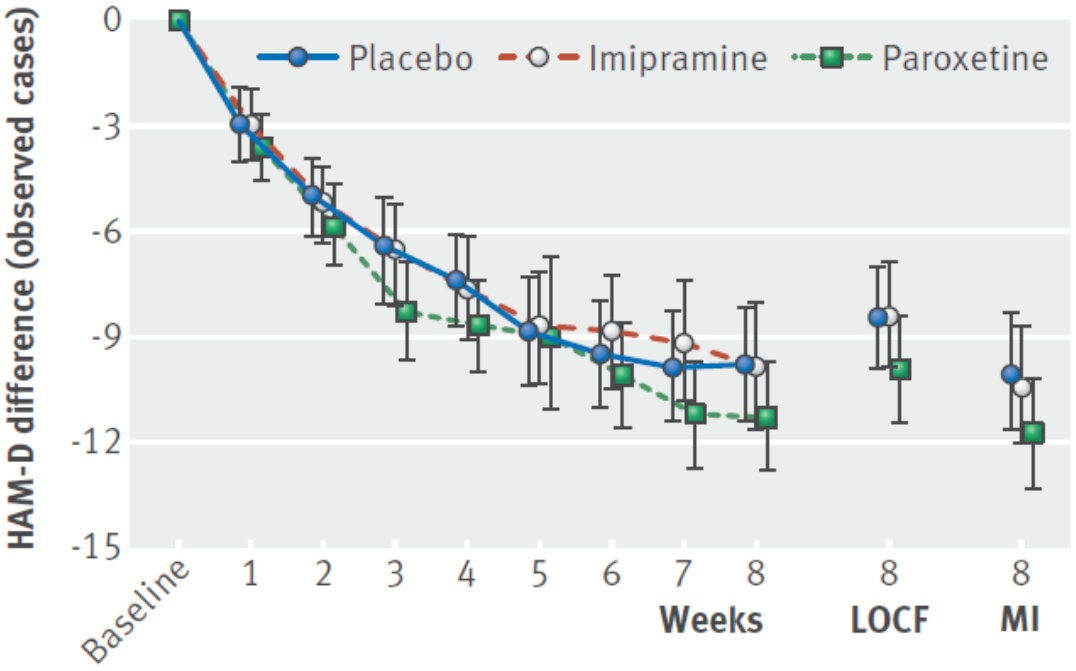
The media loves Hillary — and it could cost her the election

OPEN ACCESS

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

Joanna Le Noury,[1] John M Nardo,[2] David Healy,[1] Jon Jureidini,[3] Melissa Raven,[3] Catalin Tufanaru,[4] Elia Abi-Jaoude[5]

BMJ 2015;35



‘Paroxetine…showed no efficacy for major depression in adolescents, and there was an increase in harms’

SHARE

223

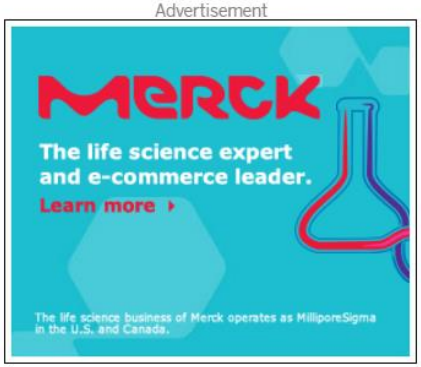
Allegations raised by a Swedish television documentary may prompt the Karolinska Institute to reopen a misconduct investigation involving surgeon and tissue engineering pioneer Paolo Macchiarini.

Conan Fitzpatrick/SVT

Karolinska Institute fires fallen star surgeon Paolo Macchiarini

FOLLOW NEWS FROM SCIENCE

Advertisement



Tweets by @ScienceInsider

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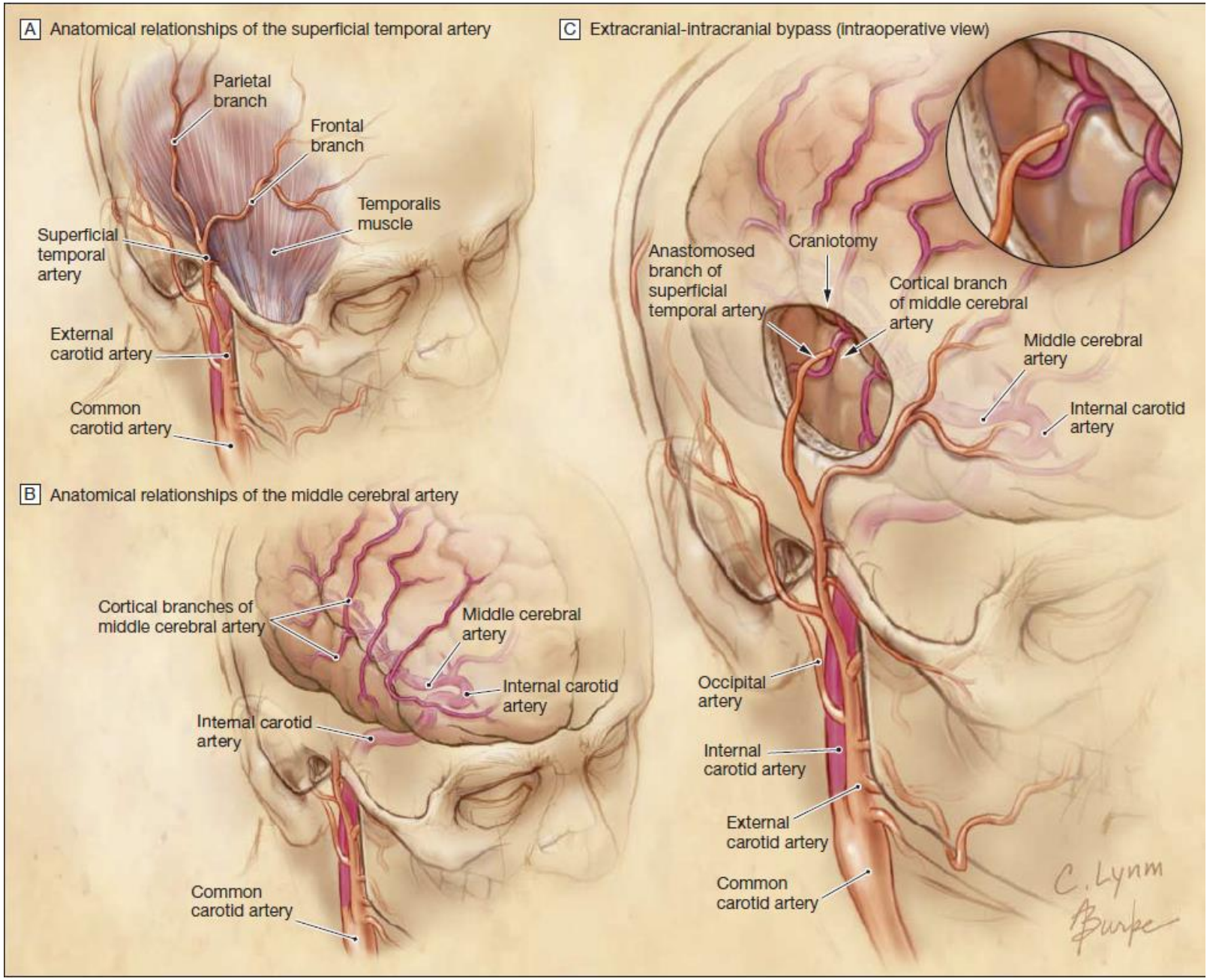
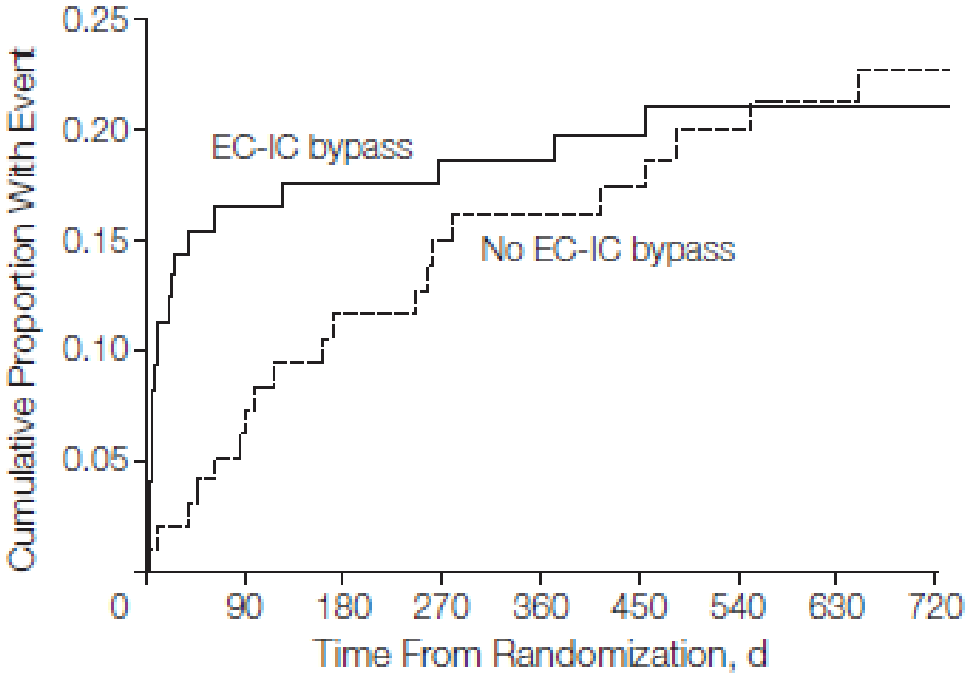
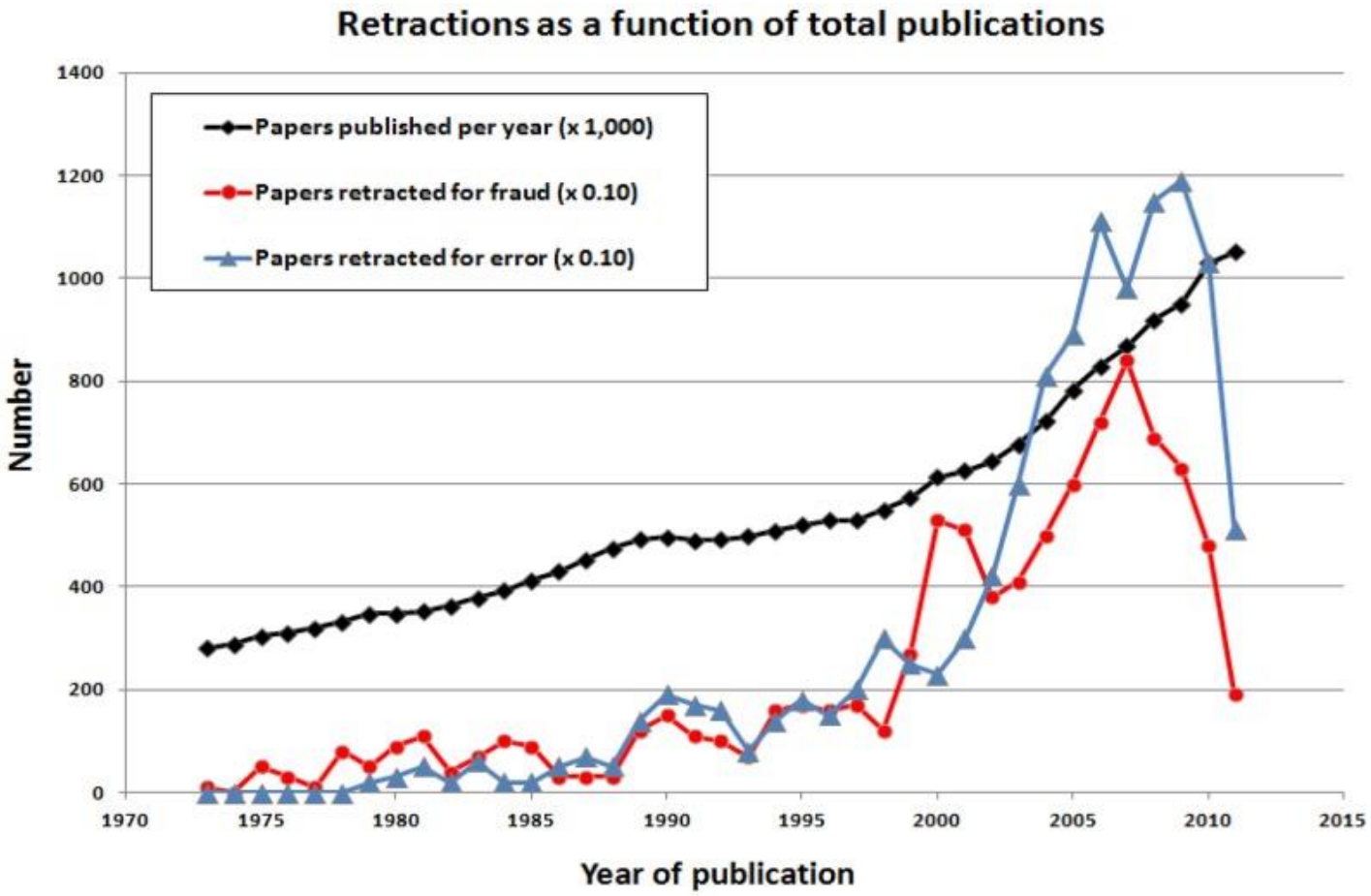
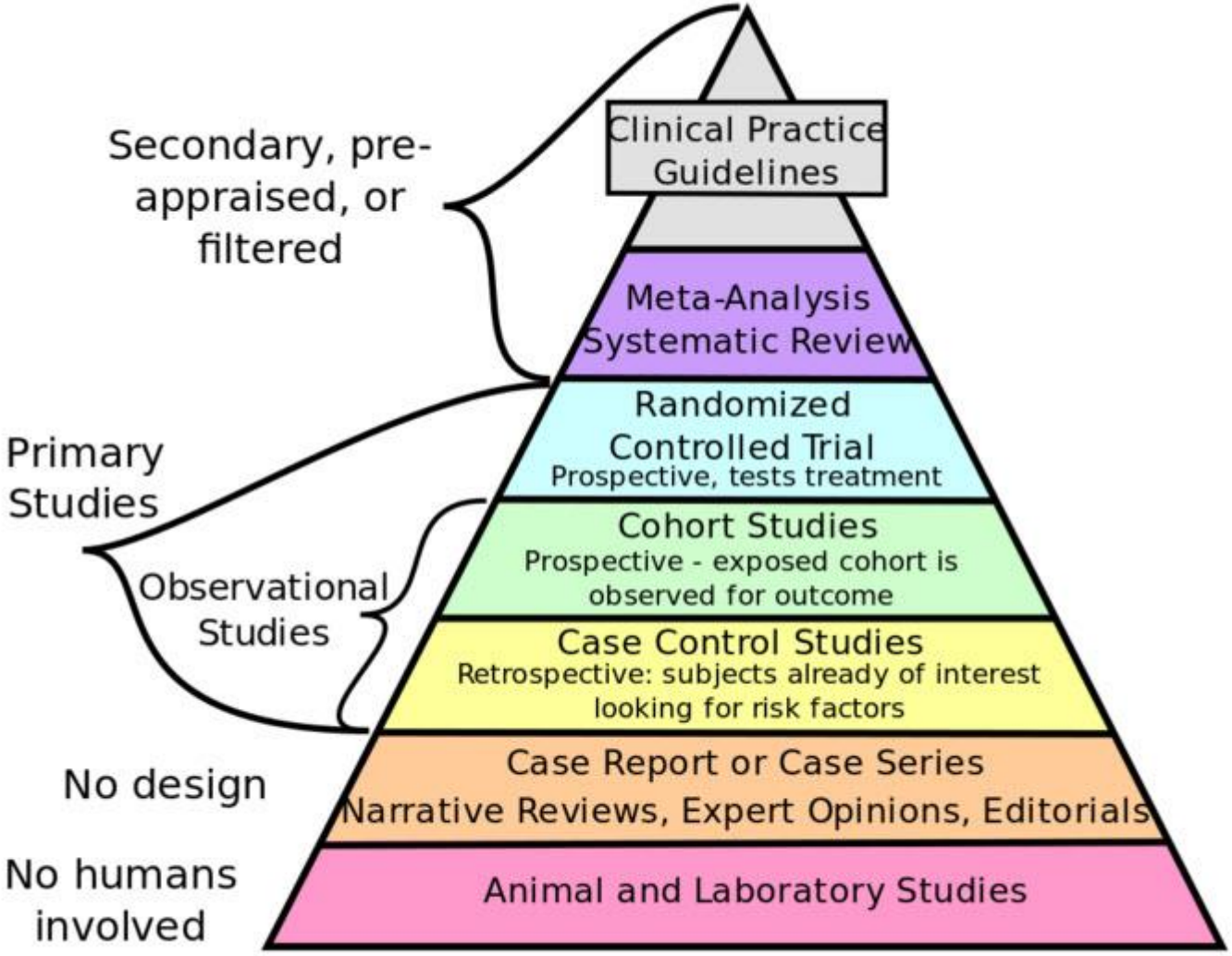

A Anatomical relationships of the superficial temporal artery
Parietal branch
Frontal branch
Temporalis muscle
Superficial temporal artery
External carotid artery
Common carotid artery
B Anatomical relationships of the middle cerebral artery
Cortical branches of middle cerebral artery
Middle cerebral artery
Internal carotid artery
Internal carotid artery
Common carotid artery
C Extracranial-intracranial bypass (intraoperative view)
Anastomosed branch of superficial temporal artery
Craniotomy
Cortical branch of middle cerebral artery
Middle cerebral artery
Internal carotid artery
Occipital artery
Internal carotid artery
External carotid artery
Common carotid artery
C. Lynn Burke



Powers JAMA 2011



Steen PLOSone 2013



"Research design and evidence" by CFCF - Own work. Licensed under CC BY-SA 4.0 via Wikimedia Commons -

Item	Score
Was the Study Described as Randomized (This Includes Words Such as Randomly, Random, and Randomization)?	0/1
Was the Method Used to Generate the Sequence of Randomization Described and Was It Appropriate (eg, Table of Random Numbers and Computer Generated)?	0/1
Was the Study Described as Double Blind?	0/1
Was the Method of Double Blinding Described and Was It Appropriate (eg, Identical Placebo, Active Placebo, and Dummy)?	0/1
Was There a Description of Withdrawals and Dropouts?	0/1
Deduct 1 Point if the Method Used to Generate the Sequence of Randomization Was Described and if It Was Inappropriate (Patients Were Allocated Alternately, or According to Date of Birth or Hospital Number, for Example).	0/–1
Deduct 1 Point if the Study Was Described as or Double Blind but the Method of Blinding Was Inappropriate (eg, Comparison of Tablet vs Injection With No Double Dummy).	0/–1

Jadad score calculation

GRADING the evidence

- GRADE (Grades of recommendation, assessment, development and evaluation)
- international group: Australian NMRC, SIGN, USPSTF, WHO, NICE, Oxford CEBM, CDC, Cochrane collaboration
- ~ 40 meetings over last 16 years
- The system – over 100 organizations thus far

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UpToDate

Box 2 | Quality of evidence and definitions

High quality— Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality— Any estimate of effect is very uncertain

Factors that affect the strength of a recommendation

Factor	Examples of strong recommendations	Examples of weak recommendations
Quality of evidence	Many high quality randomised trials have shown the benefit of inhaled steroids in asthma	Only case series have examined the utility of pleurodesis in pneumothorax
Uncertainty about the balance between desirable and undesirable effects	Aspirin in myocardial infarction reduces mortality with minimal toxicity, inconvenience, and cost	Warfarin in low risk patients with atrial fibrillation results in small stroke reduction but increased bleeding risk and substantial inconvenience
Uncertainty or variability in values and preferences	Young patients with lymphoma will invariably place a higher value on the life prolonging effects of chemotherapy than on treatment toxicity	Older patients with lymphoma may not place a higher value on the life prolonging effects of chemotherapy than on treatment toxicity
Uncertainty about whether the intervention represents a wise use of resources	The low cost of aspirin as prophylaxis against stroke in patients with transient ischemic attacks	The high cost of clopidogrel and of combination dipyridamole and aspirin as prophylaxis against stroke in patients with transient ischaemic attacks

Guyatt BMJ 2008

How to interpret results from an individual study

- **General**
  - Study question
  - COI?
- **Methods** (internal validity)
  - Superiority/inferiority
  - Choice of (prespecified) endpoints
  - Sample size, power
  - RCT's: CONSORT criteria
  - Statistical methods
  - Interpretation of the P value
- **Interpretation** – external validity

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

Results at End of Six Months

Four of the 55 S patients (7%) and 14 of the 52 C patients (27%) died before the end of six months. The difference between the two series is statistically significant; the probability of it occurring by chance is less than one in a hundred.

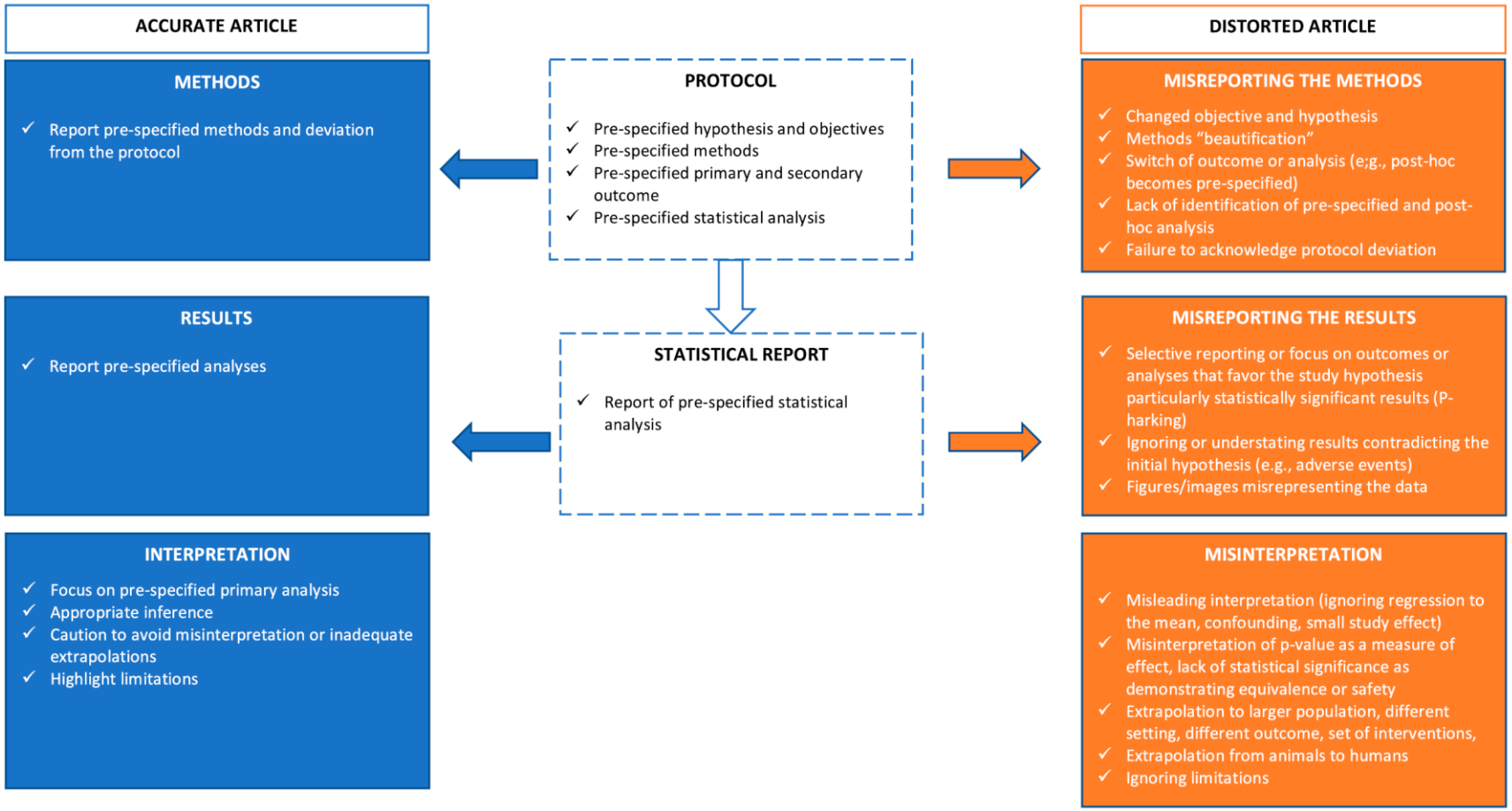


Fig. 1. Practices of spin in published reports.

Boutron PNAS 2018

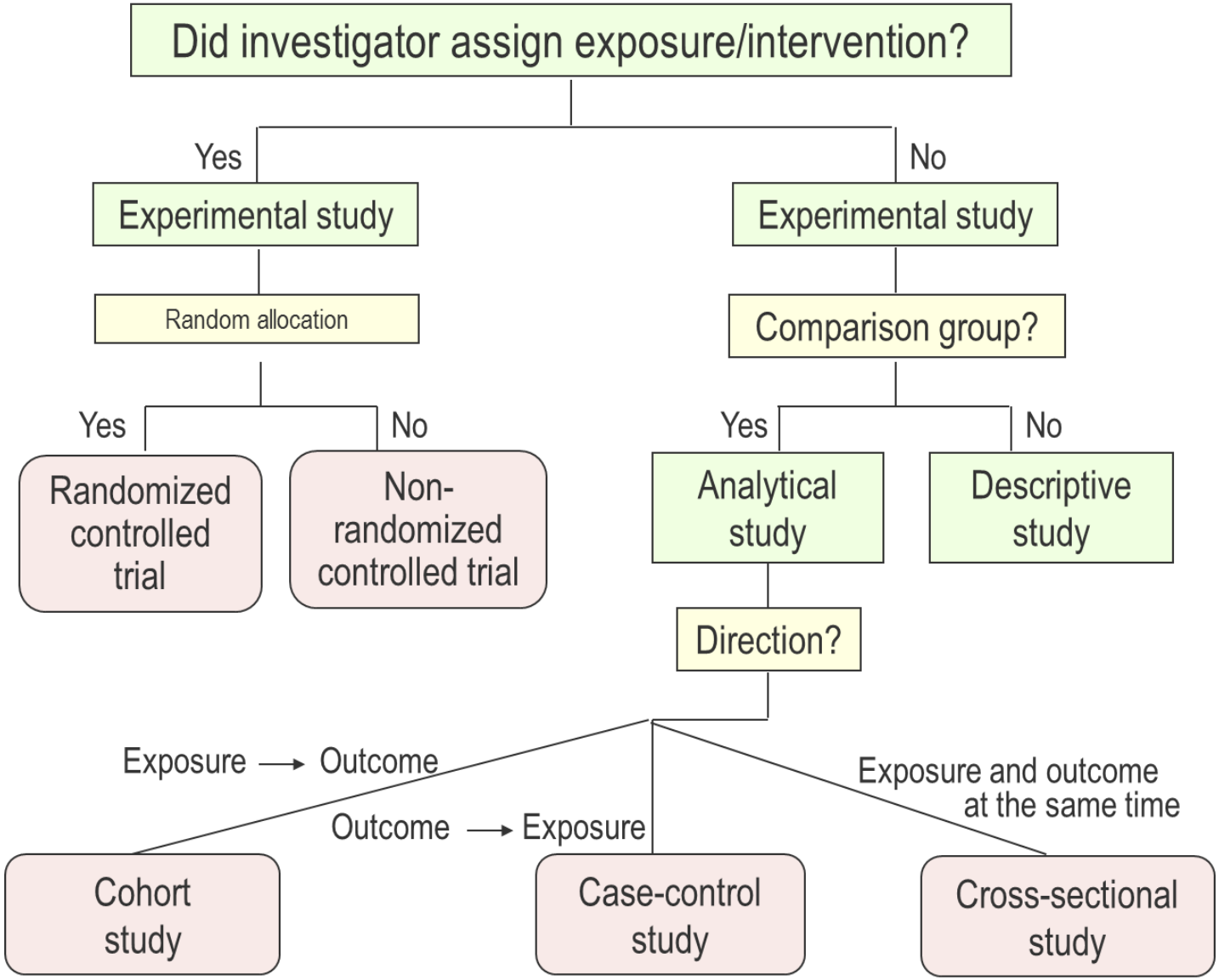
What is a good research question?

Feasible (answerable with a robust method)
Interesting
Novel
Ethical
Relevant

FINER criteria

Clinical trial designs

- Case report
- Retrospective case series, chart review (≠ *cohort study*)
- Prospective trial
  - Observational
  - Interventional (‘controlled’)
    - Non randomized: parallel group, etc
    - RCT


Did investigator assign exposure/intervention?
Yes
No
Experimental study
Experimental study
Random allocation
Comparison group?
Yes
No
Yes
No
Randomized controlled trial
Non-randomized controlled trial
Analytical study
Descriptive study
Direction?
Exposure → Outcome
Outcome → Exposure
Exposure and outcome at the same time
Cohort study
Case-control study
Cross-sectional study

Non inferiority trials

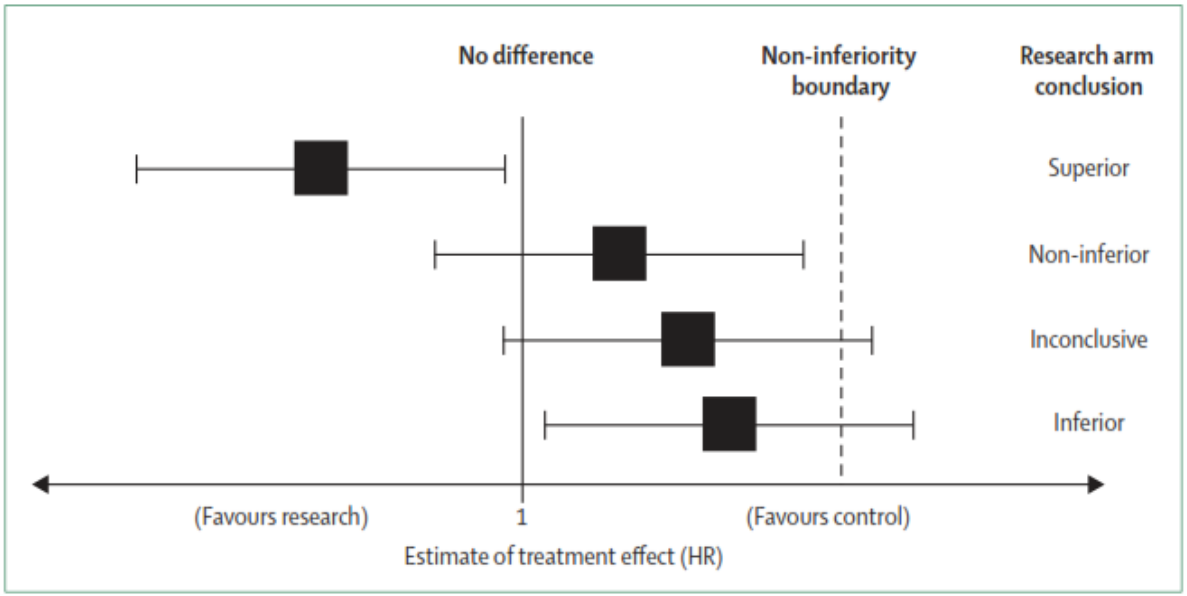
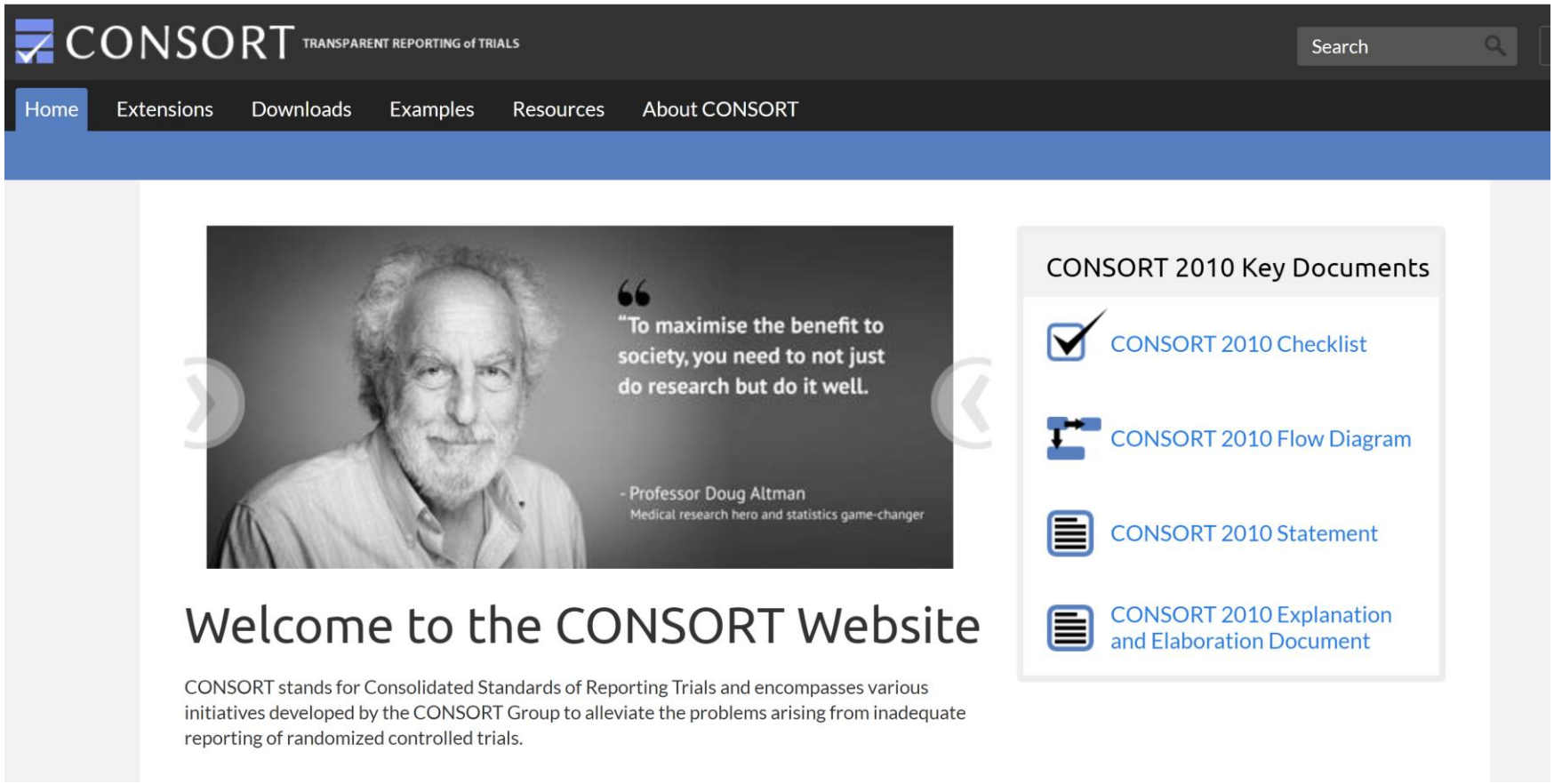


Figure 2: **Conclusions from estimated treatment effect (hazard ratio) in non-inferiority trial**
Lines show estimate of treatment effect and confidence interval. HR<1 favours research group; HR>1 favours control group. HR=hazard ratio.

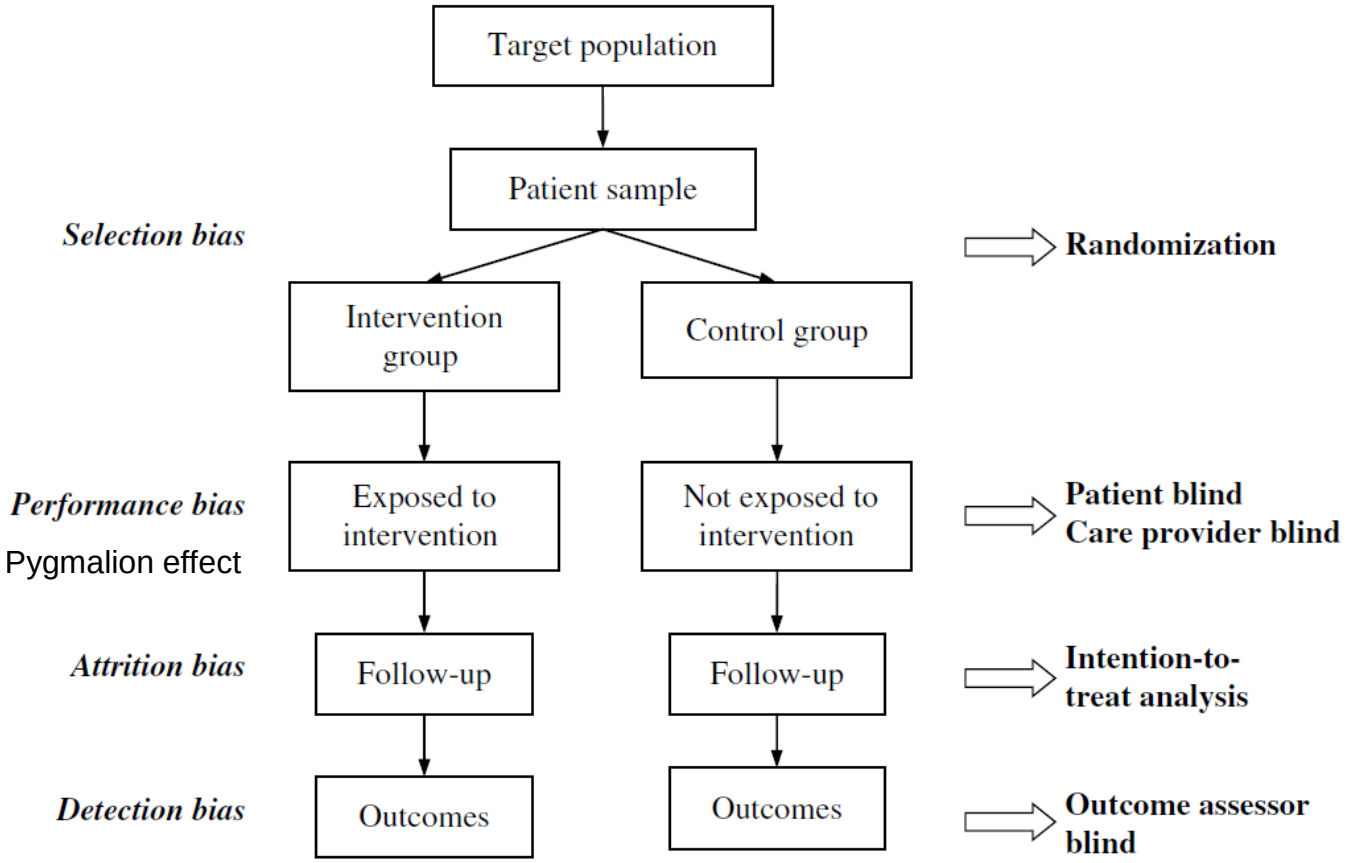
- When comparing against an accepted 'gold standard'; typically: less invasive, less costly…
- Requires <u>larger</u> sample size

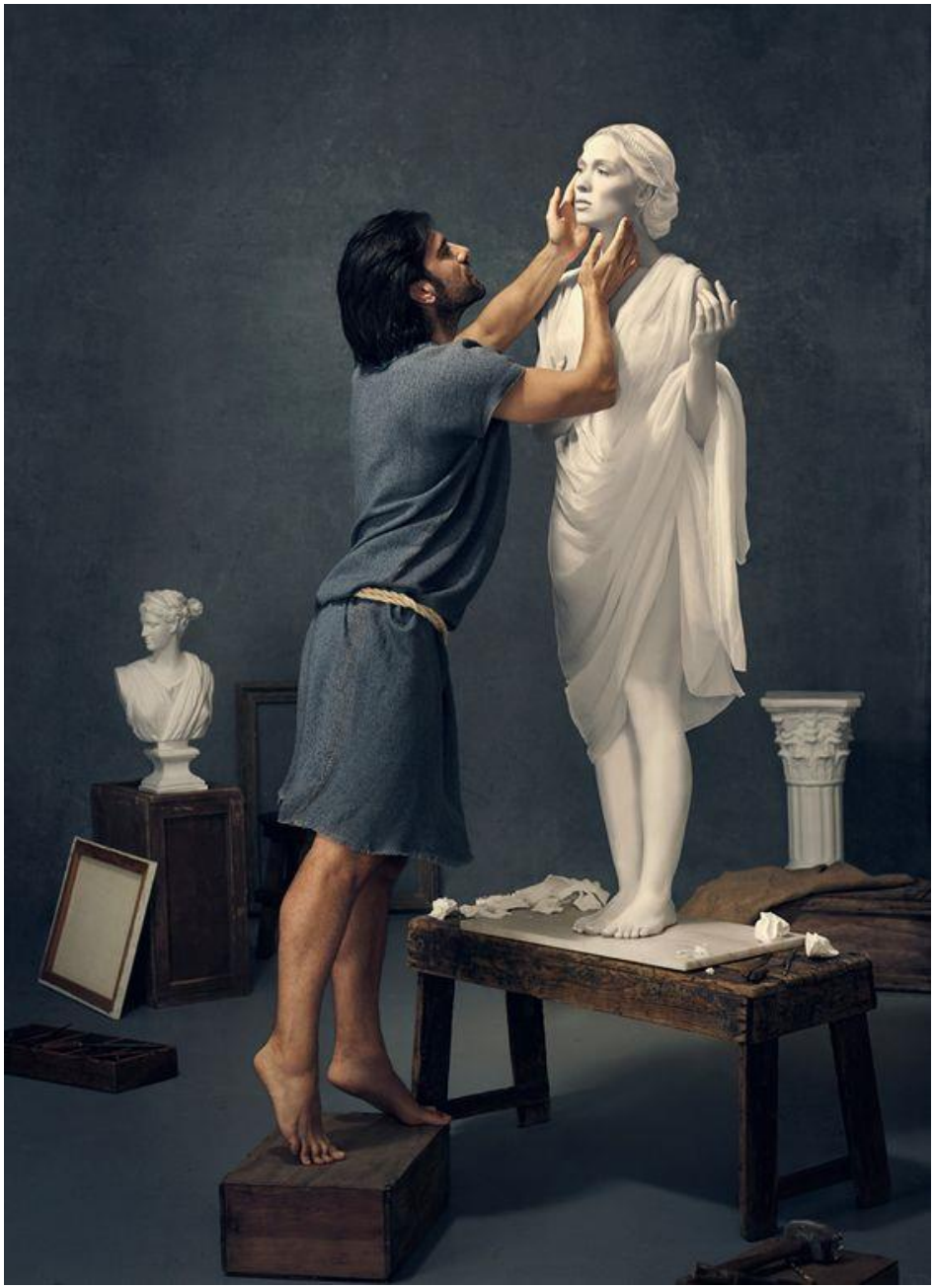
Example: COlon cancer Laparoscopic or Open Resection (COLOR) trial

- RCT comparing open with laparoscopic surgery for colon cancer
- Primary endpoint: DFS @ three years
- Preset non-inferiority margin: 7%
- Result: observed difference (in favour of open surgery) was 2%, with a 95% CI of [-3,2 – 7,2], indicating that non-inferiority **could not be demonstrated.**

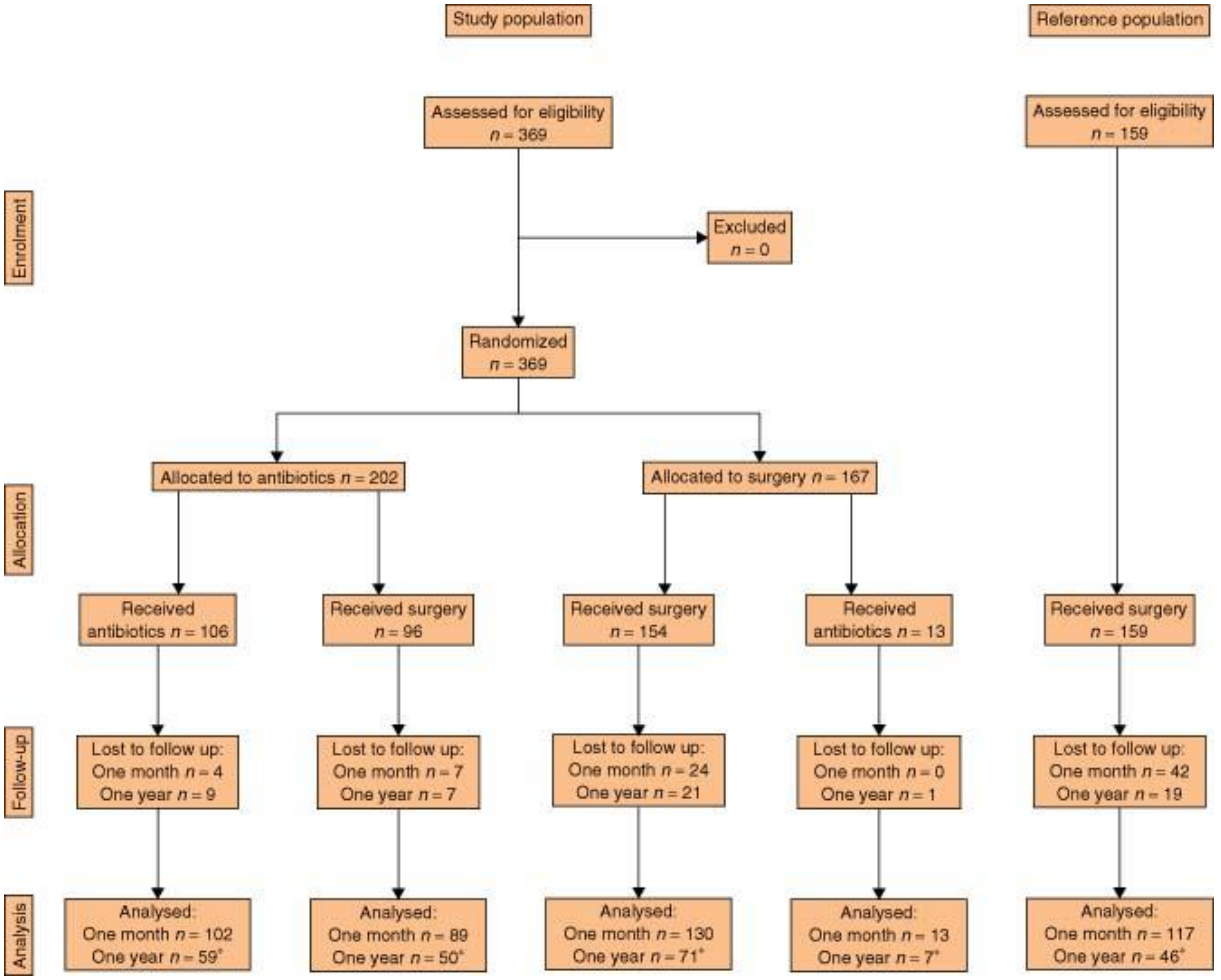


http://www.consort-statement.org/


Target population
Patient sample
Selection bias
Randomization
Intervention group
Control group
Performance bias
Pygmalion effect
Exposed to intervention
Not exposed to intervention
Patient blind
Care provider blind
Attrition bias
Follow-up
Follow-up
Intention-to-treat analysis
Detection bias
Outcomes
Outcomes
Outcome assessor blind



ITT versus ‘as treated’ analysis (Hansson BJS 2009)



- Primary outcome: no need for surgery within a median follow-up of 1 year
- ‘As treated’ analysis: primary endpoint met in 93/119 (78%) in AB group and 223/250 (89%) in surgery group
- ITT analysis: 83 of the 202 originally assigned to antibiotics (41%) met primary endpoint, compared to 142/167 (85%) of those originally allocated to surgery

Was the outcome appropriate?

- Unique
  - Defined *a piori*
  - Multiple endpoints: more false positive results
- Clinically relevant
- Reliable and reproducible
- If surrogate endpoint: demonstrated validity?
- Available for all patients

Types of outcomes

- Hard
  - Mortality
  - Quality of Life
  - Amputations, hearing loss, loss of vision
  - Pain reduction/increase
- Surrogate or intermediate
  - DFS, PFS, pCR as surrogate for OS
  - LN harvest or rectal amputation rate as surrogate for surgical quality in colorectal surgery
- Composite
  - ‘Overall complication rate’
  - MACE (major adverse cardiac events)
- Patient reported outcomes

Hard Endpoints

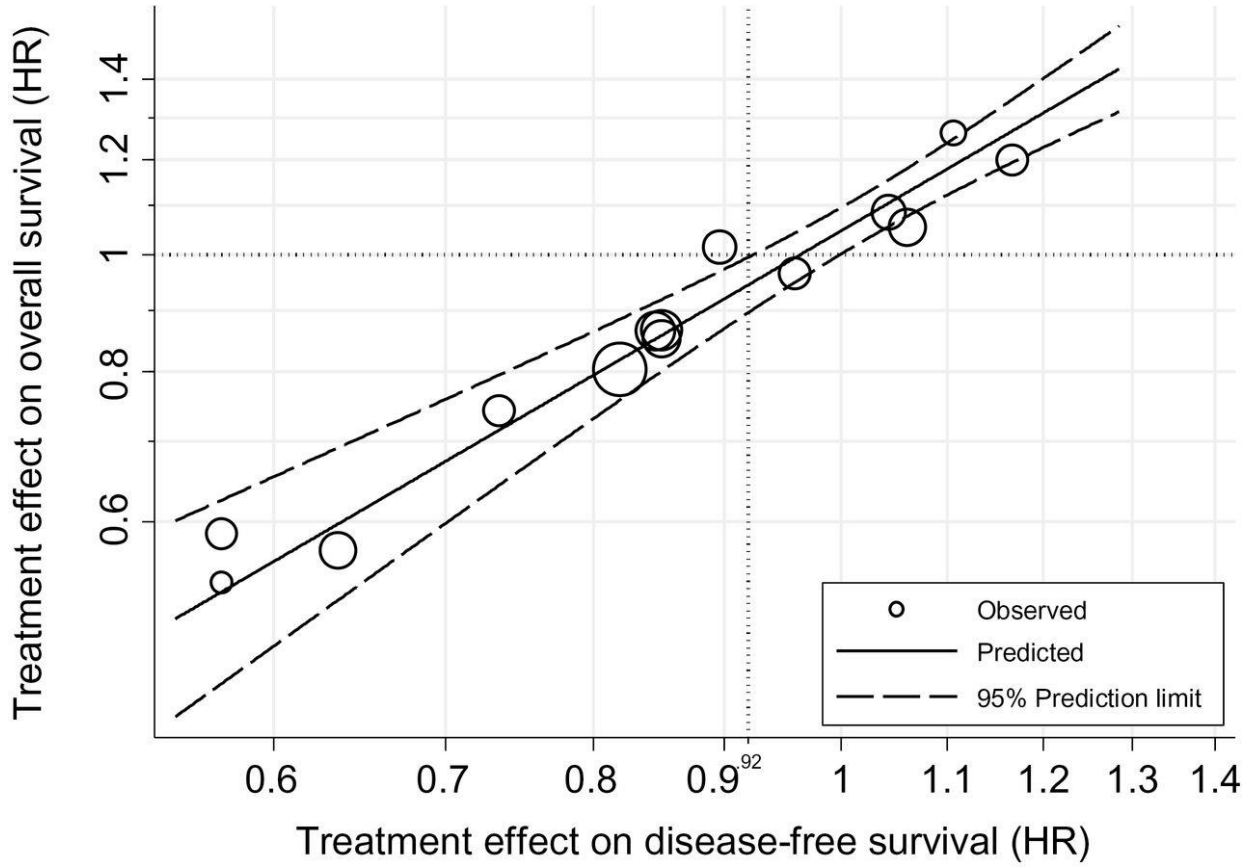
- Mortality
- Quality of Life
- Amputations, hearing loss, loss of vision
- Pain reduction/increase
- *Patient reported outcomes*

Surrogate Outcomes

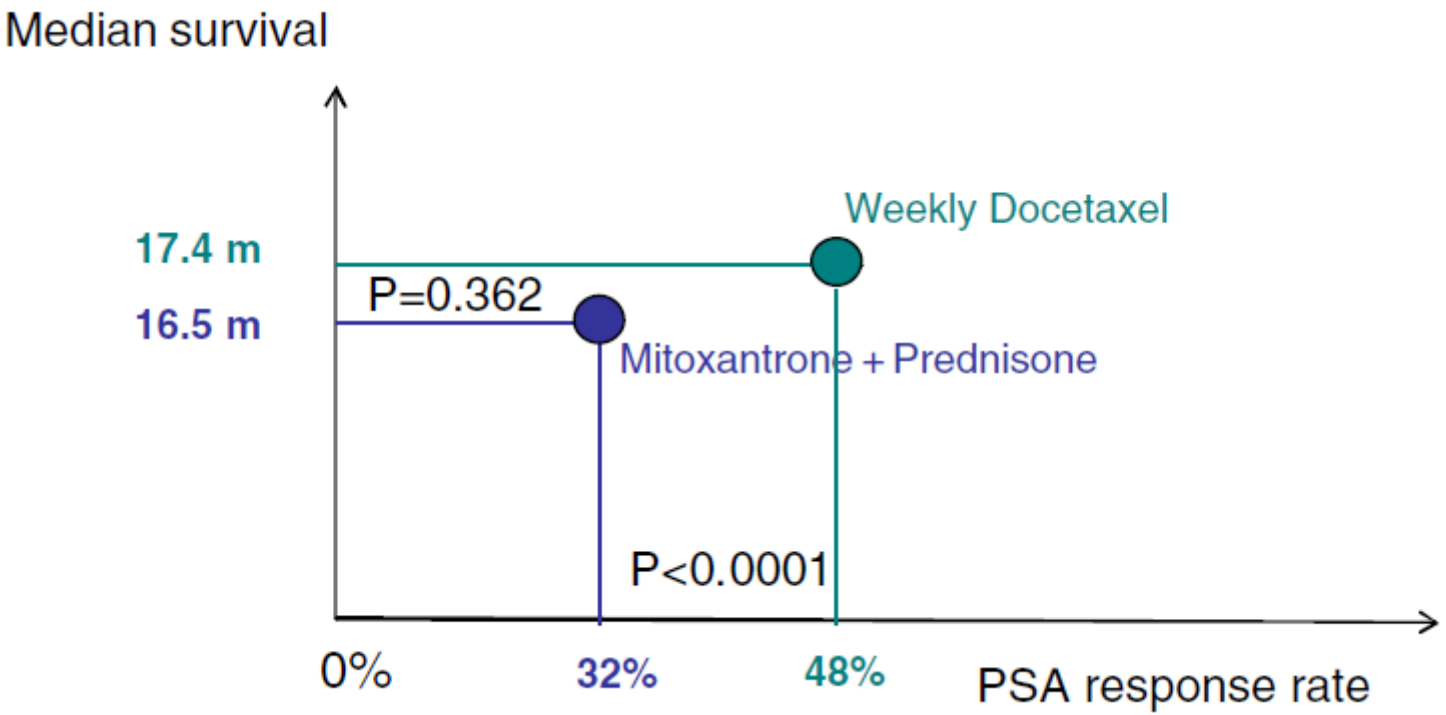
- Valid:
  - the marker is **intermediate** on the causal pathway between exposure and hard outcome AND the association between exposure and surrogate endpoint always results in the same association between the surrogate outcome and the hard endpoint
  - The association between the exposure and the surrogate has always the same extent and sign as that between the exposure and the hard endpoint
- Unvalid
  - The surrogate marker is associated with the exposure, but there is **no causal association** between the surrogate marker and the hard endpoint

Surrogate endpoints: examples

- Oncology trials: DFS, PFS, pCR as surrogate for OS
- LN harvest or amputation rate as surrogate for surgical quality in colorectal surgery
- Prognostic indicators are not always surrogate endpoints!



Oba. Disease-free survival as a surrogate for overall survival in adjuvant trials of gastric cancer: a meta-analysis. JNCI 2013



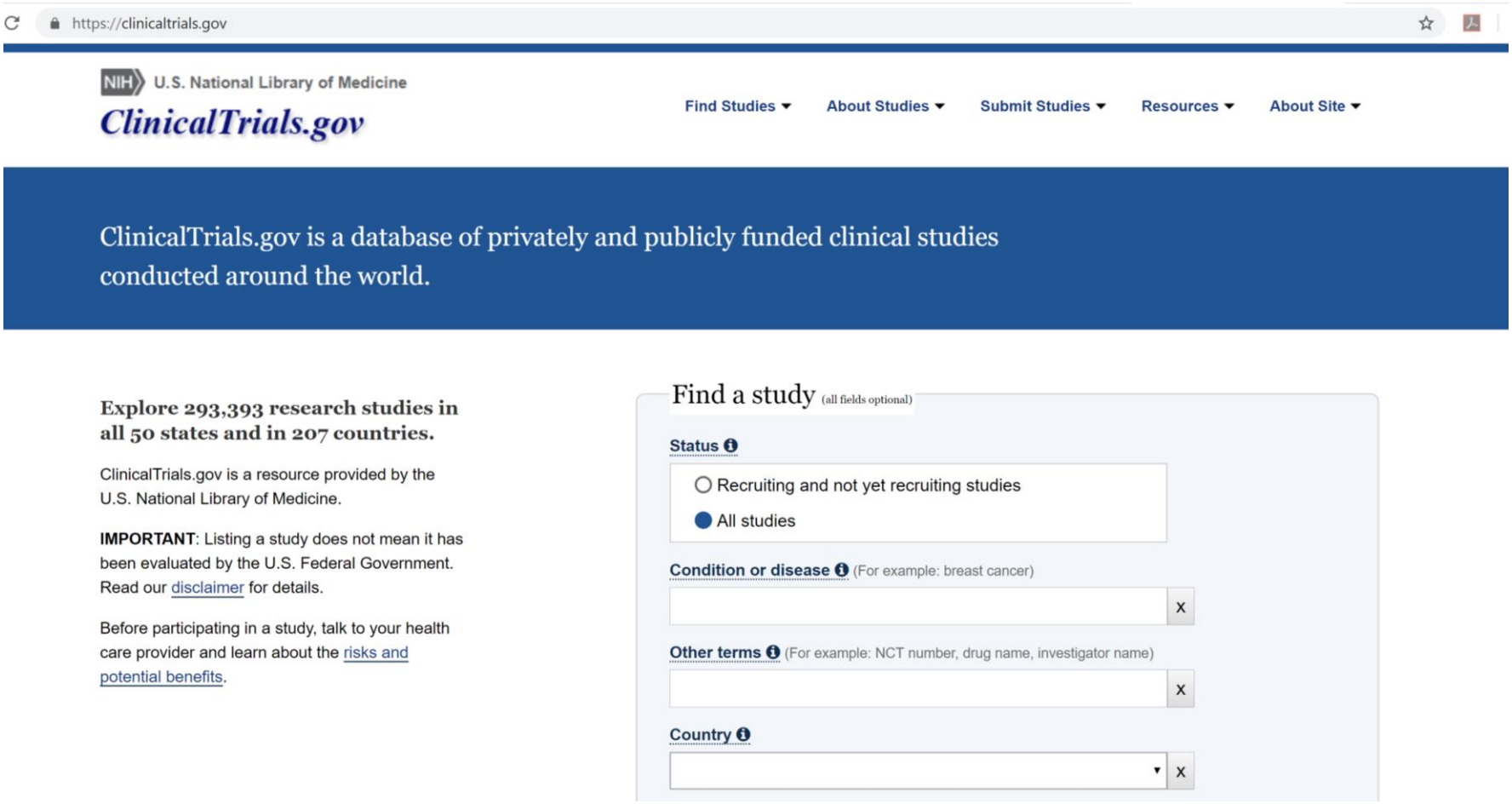
Collette Eur J Cancer 2006

Composite endpoints

- An aggregate of different outcomes rather than one outcome
- Examples
  - ‘Overall complication rate’
  - MACE (major adverse cardiac events)

Selective outcome reporting

- Studies reporting positive or significant results are more likely to be published
- Outcomes that are statistically significant are more likely to be fully reported
- 40–62% of publications had at least one primary outcome changed, newly introduced or omitted compared to protocol [Dwan et al, PLoS ONE 2008]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Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.
Find a study (all fields optional)
Status
Recruiting and not yet recruiting studies
All studies
Condition or disease (For example: breast cancer)
Other terms (For example: NCT number, drug name, investigator name)
Country

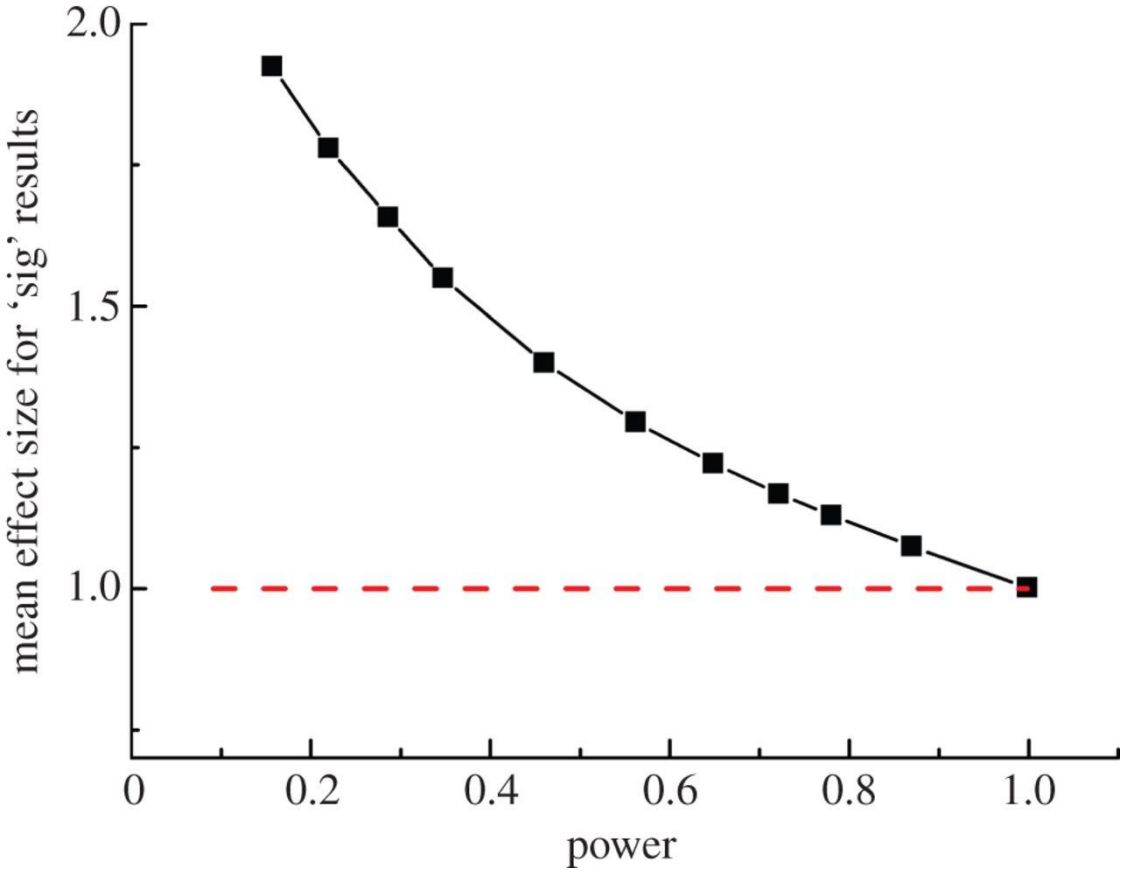
Core Outcome Measures in Effectiveness Trials

www.comet-initiative.org

Was the sample size calculated?

- Sample size calculation should be based on the (single) primary endpoint
- Must be reported:
  - Estimated incidence in control arm (with references)
  - Estimated (clinically relevant) treatment effect size
  - Estimated precision of the estimation
  - Predefined power (80%) = 1-beta
  - Predefined alpha (5%)

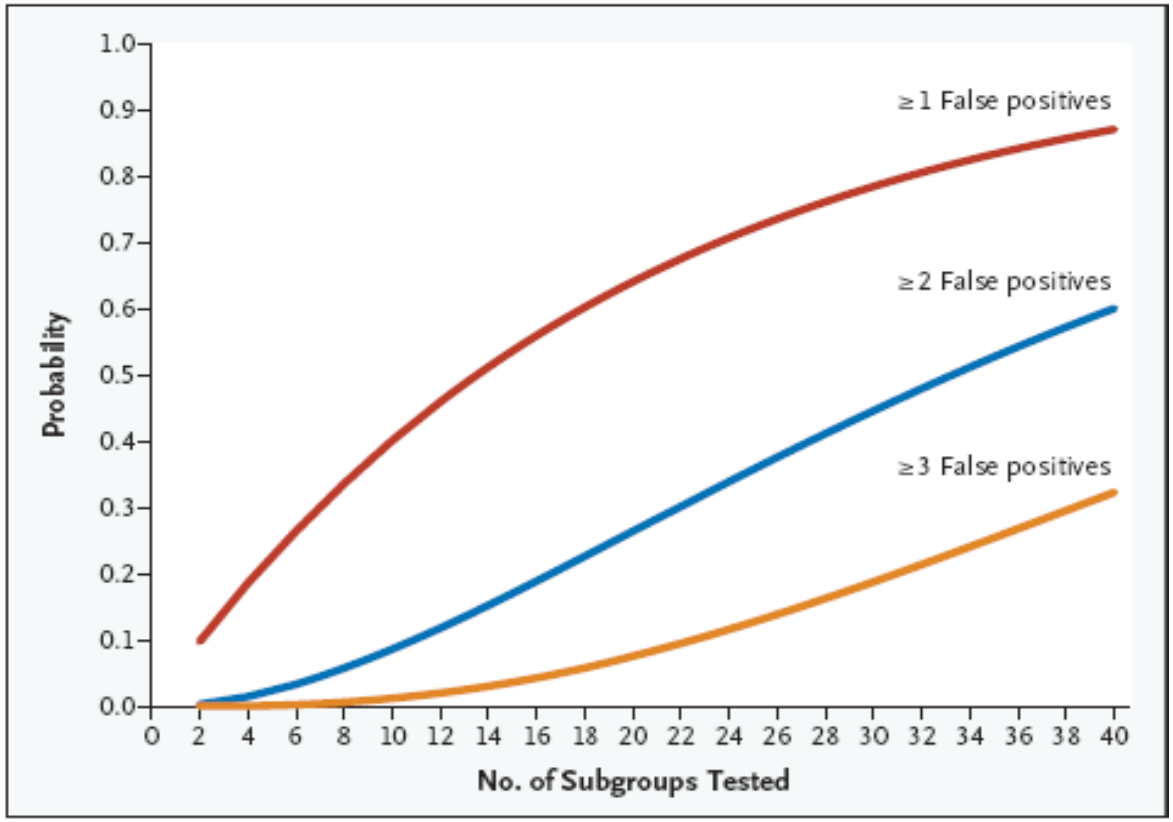
Underpowered studies → ***inflation of effect size***



http://rsos.royalsocietypublishing.org/content/1/3/140216#sec-8

Were subgroups analysed?

- Should be pre-planned
- Results should be interpreted with caution



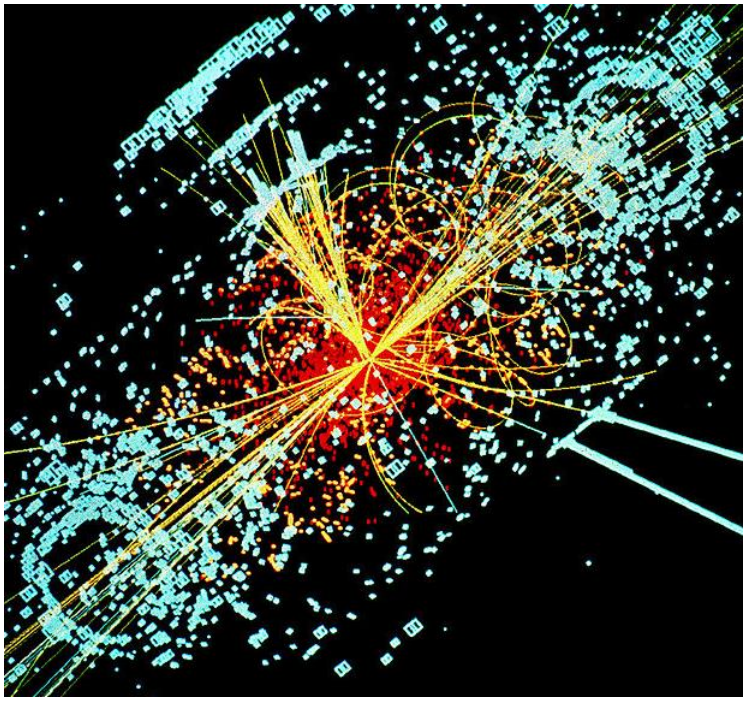
Probability That Multiple Subgroup Analyses Will Yield at Least One (Red), Two (Blue), or Three (Yellow) False Positive Results.

Were the statistical methods appropriate?

- Small sample size → non parametric tests
- Use of SE instead of SD: misleading
- Reporting of ***precision of the estimate*** of the observed effect, in addition to a P value (confidence intervals)
- P values should be two sided
- Correct interpretation of P value

We accept the evidence if the P value is...

- Particle Physics: <5x SD (1/3,5 million)
- Medicine: <2x SD (1/20)



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Physics Letters B 716 (2012) 1–29

Contents lists available at SciVerse ScienceDirect

Physics Letters B

www.elsevier.com/locate/physletb

Observation of a new particle in the search for the Standard Model Higgs boson with the ATLAS detector at the LHC ☆

ATLAS Collaboration *

This paper is dedicated to the memory of our ATLAS colleagues who did not live to see the full impact and significance of their contributions to the experiment.

ARTICLE INFO

Article history:
Received 31 July 2012
Received in revised form 8 August 2012
Accepted 11 August 2012
Available online 14 August 2012
Editor: W.-D. Schlatter

ABSTRACT

A search for the Standard Model Higgs boson in proton–proton collisions with the ATLAS detector at the LHC is presented. The datasets used correspond to integrated luminosities of approximately 4.8 fb^{-1} collected at $\sqrt{s} = 7$ TeV in 2011 and 5.8 fb^{-1} at $\sqrt{s} = 8$ TeV in 2012. Individual searches in the channels $H \to ZZ^{(*)} \to 4\ell$, $H \to \gamma\gamma$ and $H \to WW^{(*)} \to e\nu\mu\nu$ in the 8 TeV data are combined with previously published results of searches for $H \to ZZ^{(*)}$, $WW^{(*)}$, $b\bar{b}$ and $\tau^+\tau^-$ in the 7 TeV data and results from improved analyses of the $H \to ZZ^{(*)} \to 4\ell$ and $H \to \gamma\gamma$ channels in the 7 TeV data. Clear evidence for the production of a neutral boson with a measured mass of $126.0 \pm 0.4\,(\text{stat}) \pm 0.4\,(\text{sys})$ GeV is presented. This observation, which has a significance of 5.9 standard deviations, corresponding to a background fluctuation probability of 1.7×10^{-9}, is compatible with the production and decay of the Standard Model Higgs boson.

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Quizz

- When p = 0.05, there is a 5% chance of a ‘chance finding’, i.e. a false positive result (effect due to random variation and not to intervention)

Correct

Wrong

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Sir Ronald Aylmer Fisher FRS (1890 – 1962)

‘The value for which P = .05 …is convenient to take as a limit in judging whether a deviation is to be considered significant or not’

Interpretation of a P value

- A p value is the (conditional) probability to find a certain data distribution, given a certain hypothesis is true (usually: H_0 or hypothesis of a null effect)
- A p value is **NOT** the probability of a 'chance finding' (false positive)
- P(D|H) ≠ P(H|D)! (*inverted conditional fallacy)*

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Interpretation of the P value

- The risk of a false positive finding depends on **prior probability** (Bayes)

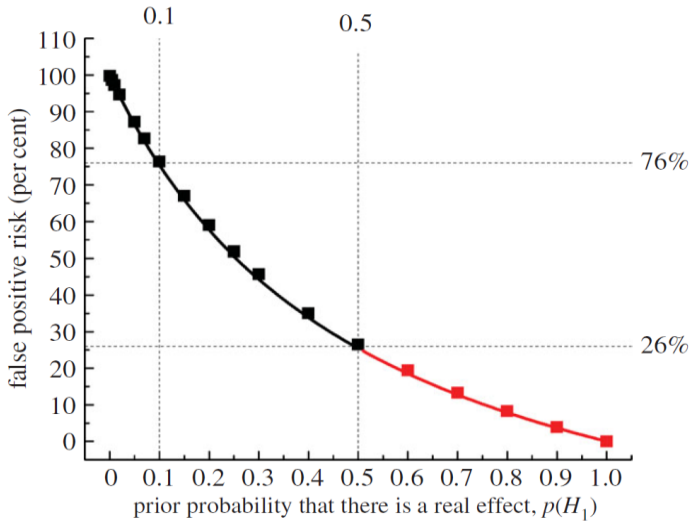

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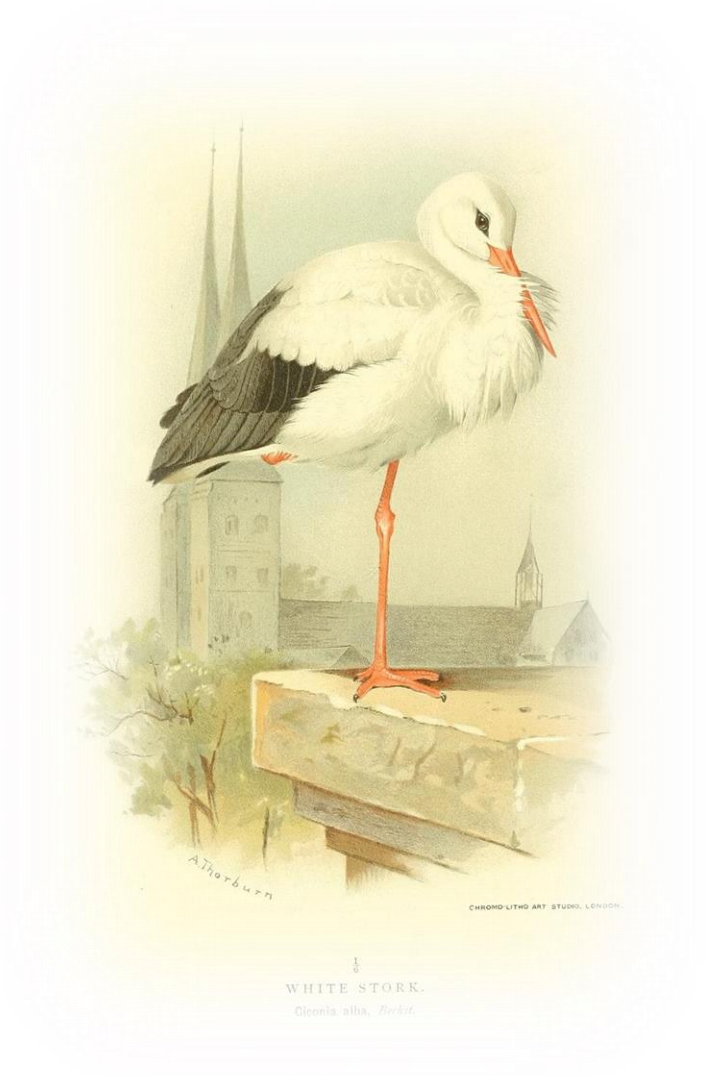
Table. Various Proposed Solutions for Improving Statistical Inference on a Large Scale

	Apply to Past Literature: Easy or Fast Solution?	Apply to Future Research and Publications: Easy or Fast Solution?
Lower *P* value thresholds	A rather simple temporizing solution	Has potential collateral harms (see text) and success depends on adoption or enforcement by stakeholders (eg, journals, funders, societies)
Abandon *P* value thresholds and instead use exact *P* value	Many published *P* values have only been reported with thresholds	Success depends on extent of adoption or enforcement by stakeholders
Abandon *P* values entirely	Not easy because often nothing or little else has been provided; many articles did not report effect sizes and most lacked confidence intervals *P* values are still a good choice for some research applications	Previous pleas have not been successful to gain traction May succeed more easily in some fields (eg, assessment of diagnostic performance or choosing of predictors for prognostic models in which use of *P* values makes little or no sense)
Use alternative inference methods (eg, Bayesian statistics)	Partly doable (eg, one may convert *P* values to Bayes factors, but needs sophisticated training)	Would be suitable for most studies; increase in use of Bayesian methods (and other inferential approaches such as false-discovery rates) has been substantial recently, but would need to accelerate in the future
Focus on effect sizes and their uncertainty	Often not reported at all, but has become more common in more recent literature, particularly in clinical trials and meta-analyses	Relevant to the vast majority of the clinical literature, should be heavily endorsed as more directly linked to decision making, and it may be easier to promote than more sophisticated solutions
Train the scientific workforce	Takes time and major commitment to achieve sufficient statistical literacy.	Can lead to a more definitive solution, choosing fit for purpose statistics and inference tools, but may require major recasting of training priorities in curricula
Address biases that lead to inflated results	Requires major training; biases are often impossible to detect from published reports	Preemptively dealing with biases is ideal, but needs concerted commitment of multiple stakeholders to promote and incentivize better research practices

Ioannidis JAMA 2018

Observational Studies

- Problem: unbalanced groups → systematic error (bias) → incorrect inference
- Solutions
  - Multivariable models
  - Propensity score analysis
  - Instrumental variable approach



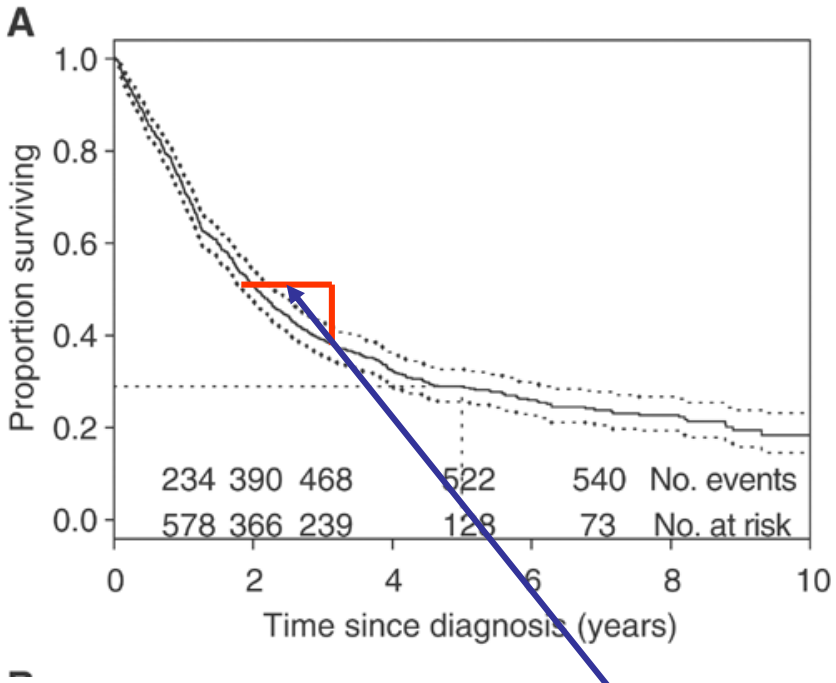
Correlation versus causation: storks and childbirths in 19th century London

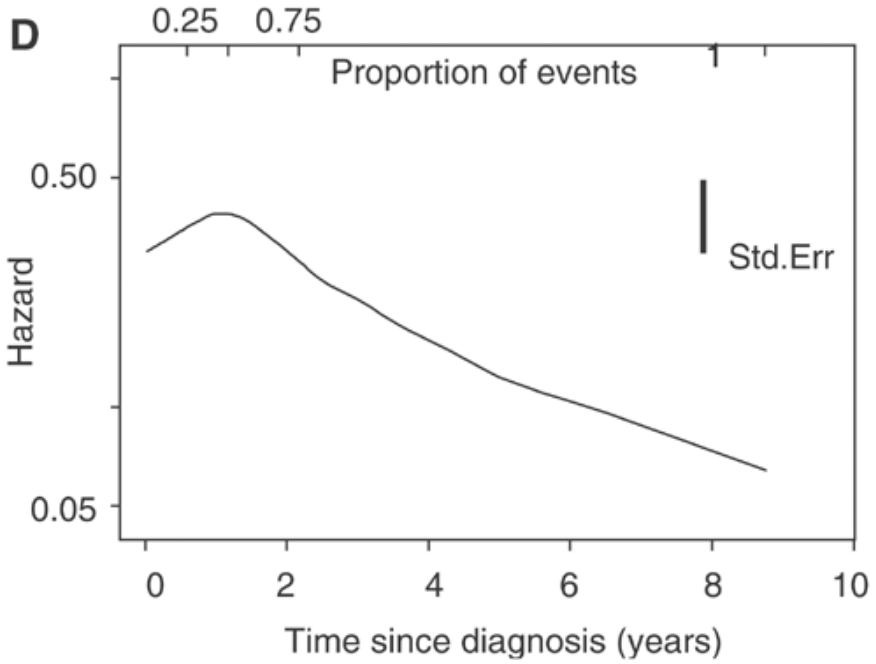
Multivariable models

Dependent variable	Model type
Continuous	Multiple linear regression
Binary	Logistic regression
Time dependent	Cox PH regression
Counts	Poisson regression

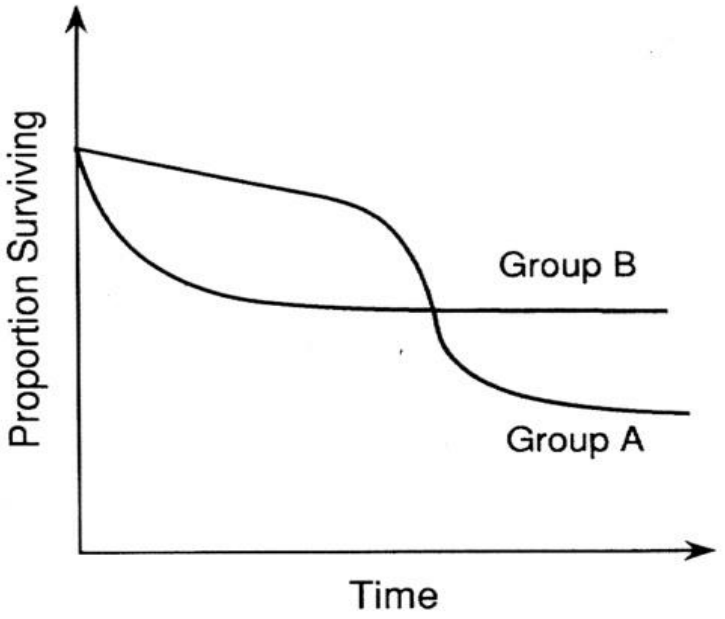
Beware of MV analyses!

- Why/how were independent variables entered?
- Multicollinearity? (correlation statistic)
- Is a measure of goodness of fit included?
- Cox model: are hazards proportional over time? (Log-log plots and Schoenfeld residuals)
- Is sample size sufficient? Rule of thumb:
  - Multiple linear regression: at least 20 **subjects** per independent variable entered
  - Logistic regression, Cox regression: at least 10 **events** per variable entered





$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \le T < t + \Delta t \mid T \ge t)}{\Delta t}$$



Non proportional Hazards

Are the results **clinically significant (important)**?

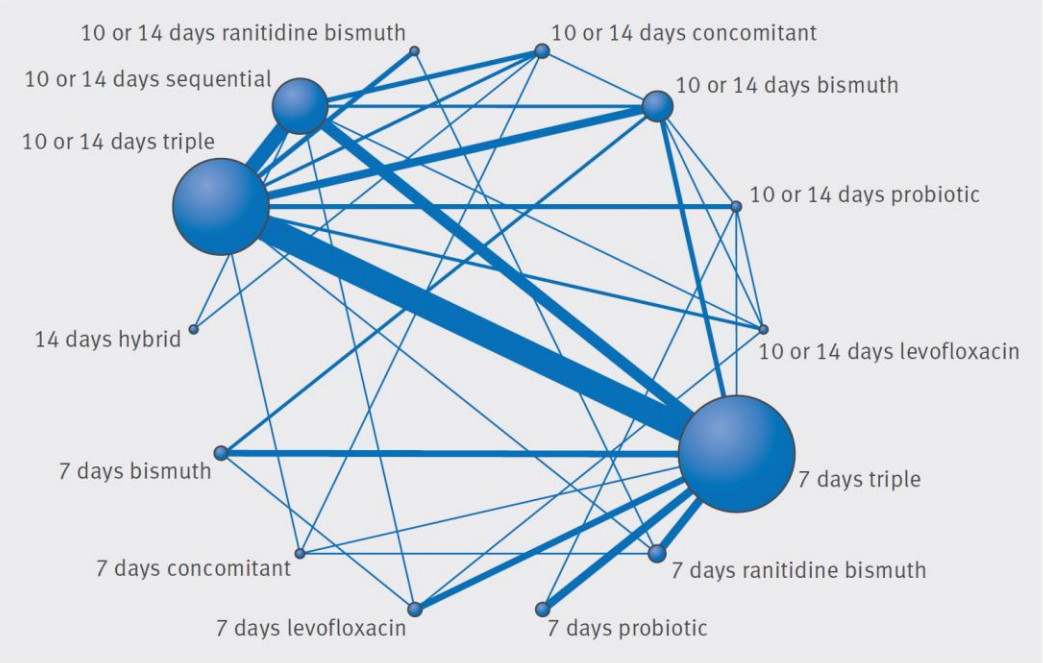
- Large sample size → even small effect magnitude becomes clinically significant
- Examples
  - Tx of hypertension: mean decrease of 2 mm in RR
  - OS in lung cancer: 5 weeks improvement
- Efficacy versus value

How to appraise systematic reviews and meta-analyses

Types of Review

- Narrative review
- Systematic review (from comprehensive, systematic literature search)
  - Int. Register: //www.crd.york.ac.uk/PROSPERO/
- Meta-analysis: SR with calculation of **summary statistics**
- Meta-analysis based on individual patient data (IPD)
- Network meta-analysis

Comparative effectiveness and tolerance of treatments for Helicobacter pylori: systematic review and network meta-analysis



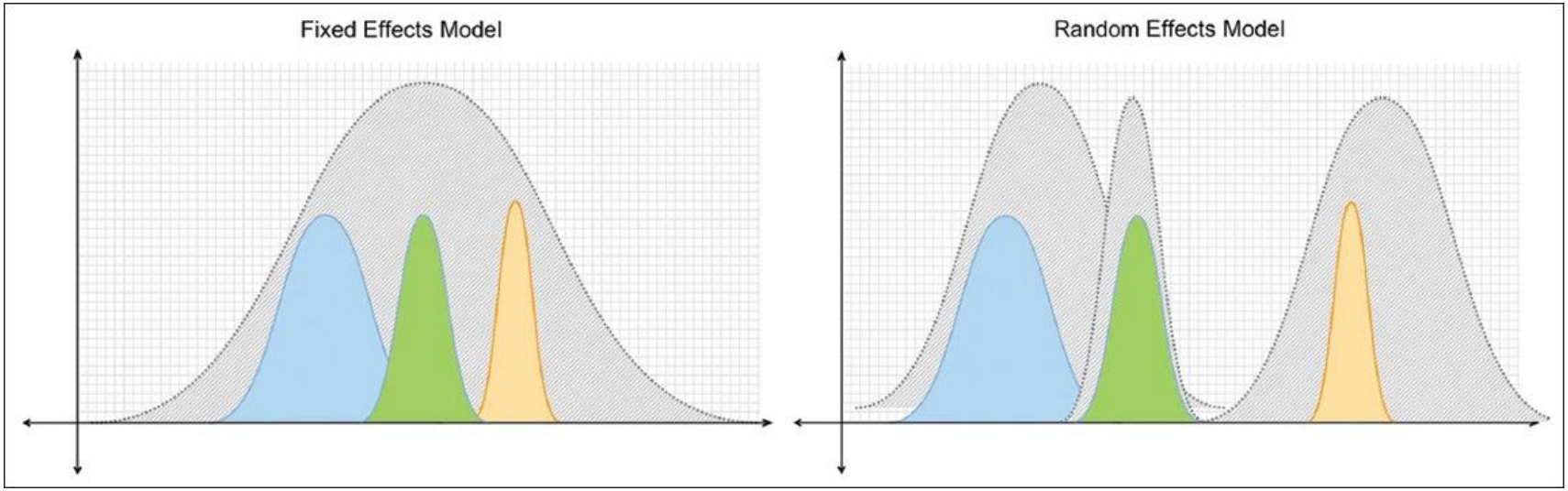
Li BMJ 2015

What to appraise in SR/MA

- Search strategy: encompassing?
- Inclusion/exclusion criteria; restrictions
- Statistical heterogeneity
- Fixed versus random effects meta-analysis
- Test for publication bias
- Sensitivity analyses

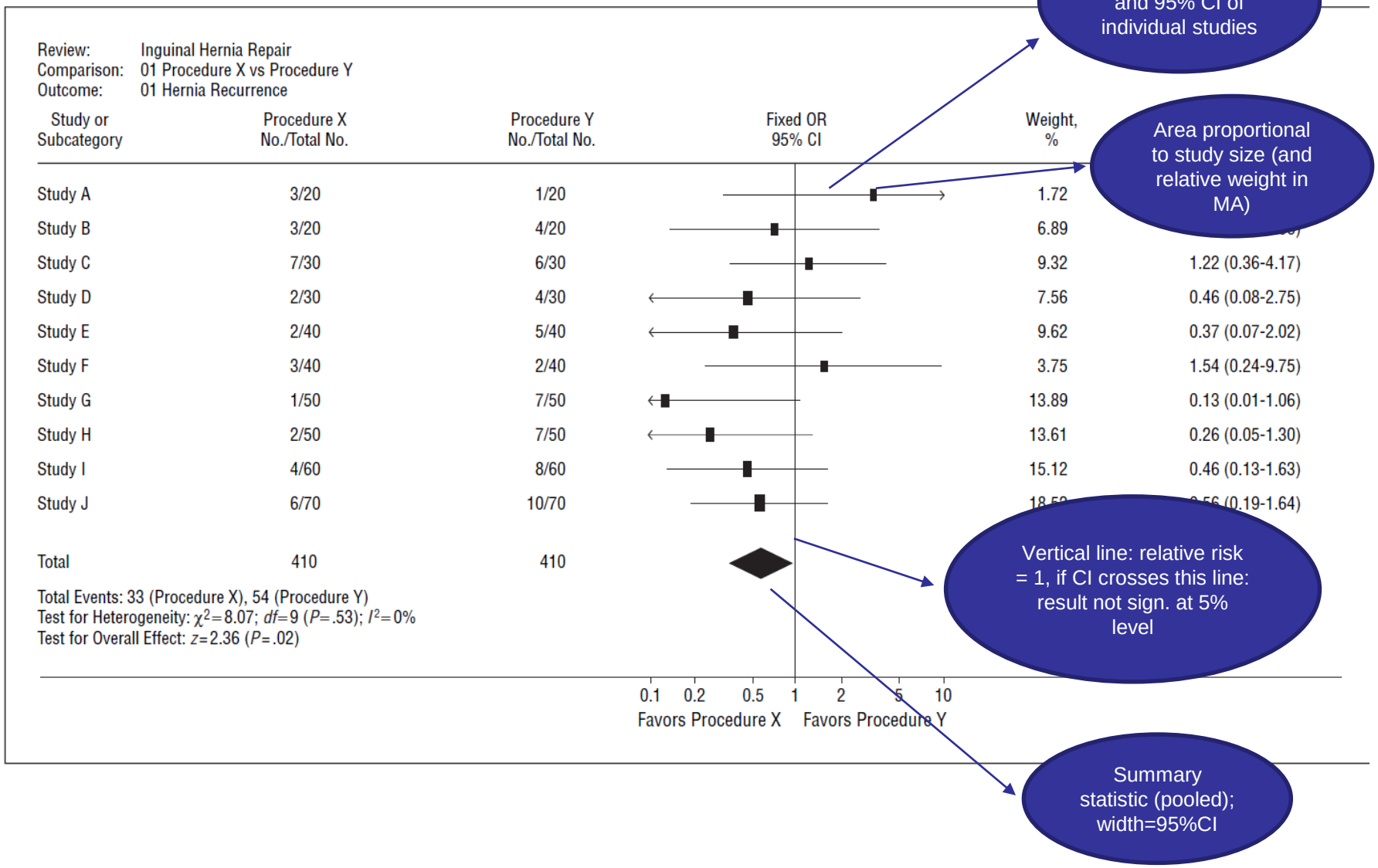
Meta-analysis

- Outcome measures
  - Binary: OR or RR
  - Continuous: weighted mean difference
- Calculation of overall effect
  - Fixed effects model
    - considers that variability is exclusively due to random variation, i.e. if all the studies were infinitely large they would give identical results and estimate the same treatment effect
    - More power to reject the null hypothesis
    - Justified when the test for heterogeneity is **not significant**
  - Random effects model
    - assumes a different underlying effect for each study and takes this into consideration as an additional source of variation
    - 95% CI wider than that of a fixed effects analysis: both inter-patient variability and inter-study variability
    - Results in **more weight given to smaller studies**!



Fixed effects models assume that each trial represents a random sample of a single population with a single response to treatment. Random effects models assume that the different trial results may come from different populations with varying responses to treatment.

Forest Plot



Point estimate and 95% CI of individual studies

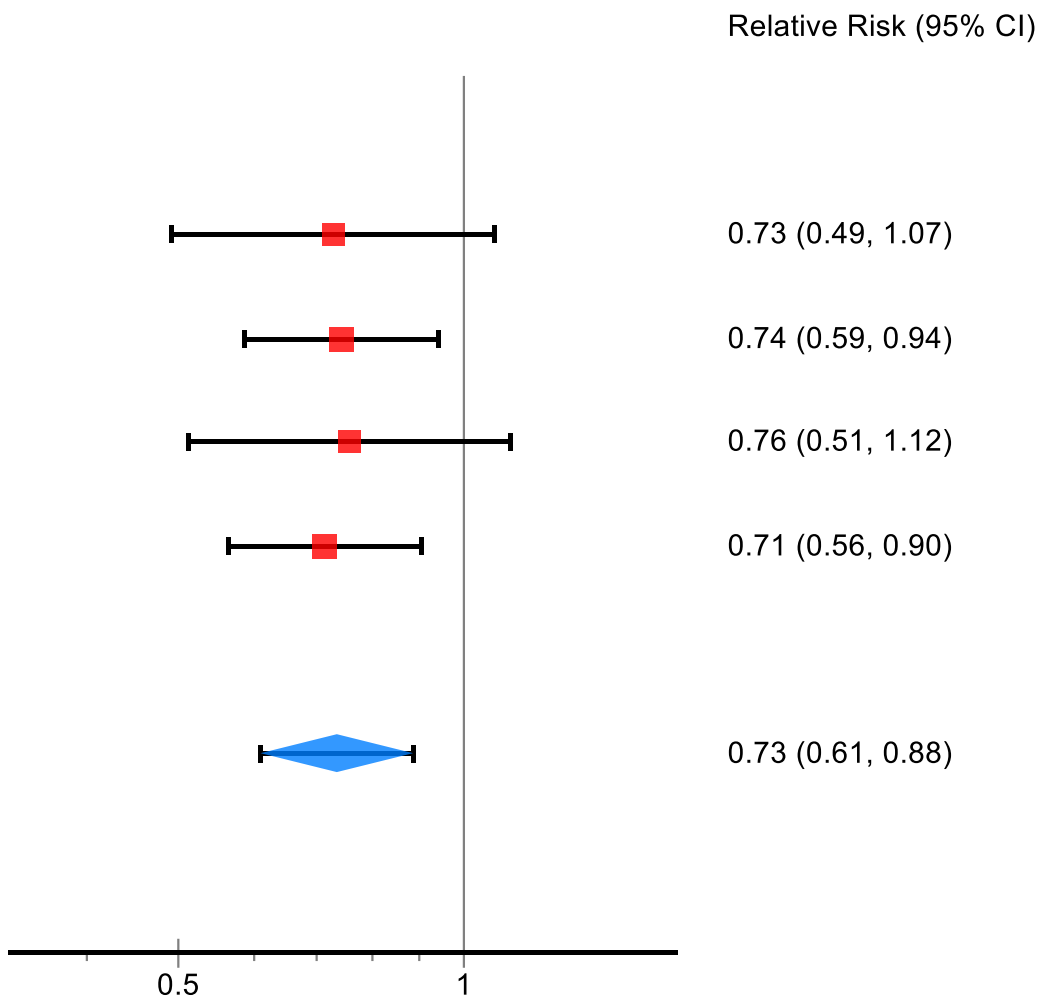
Area proportional to study size (and relative weight in MA)

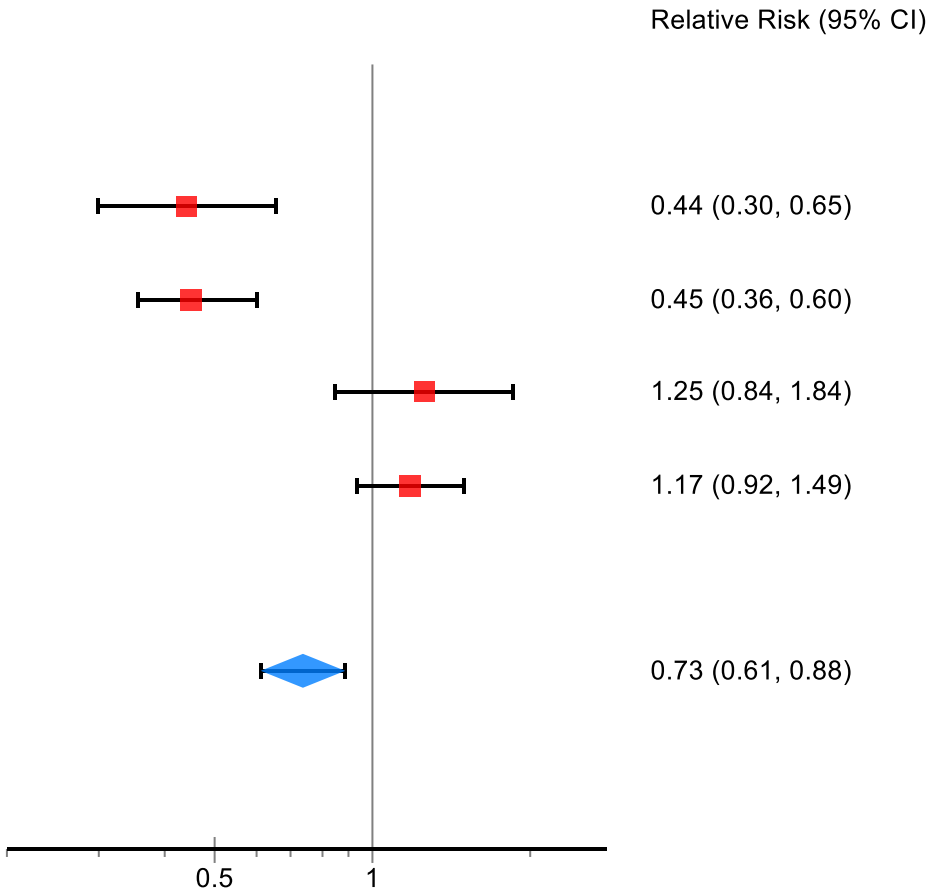
Vertical line: relative risk = 1, if CI crosses this line: result not sign. at 5% level

Summary statistic (pooled); width=95%CI

Meta-analysis

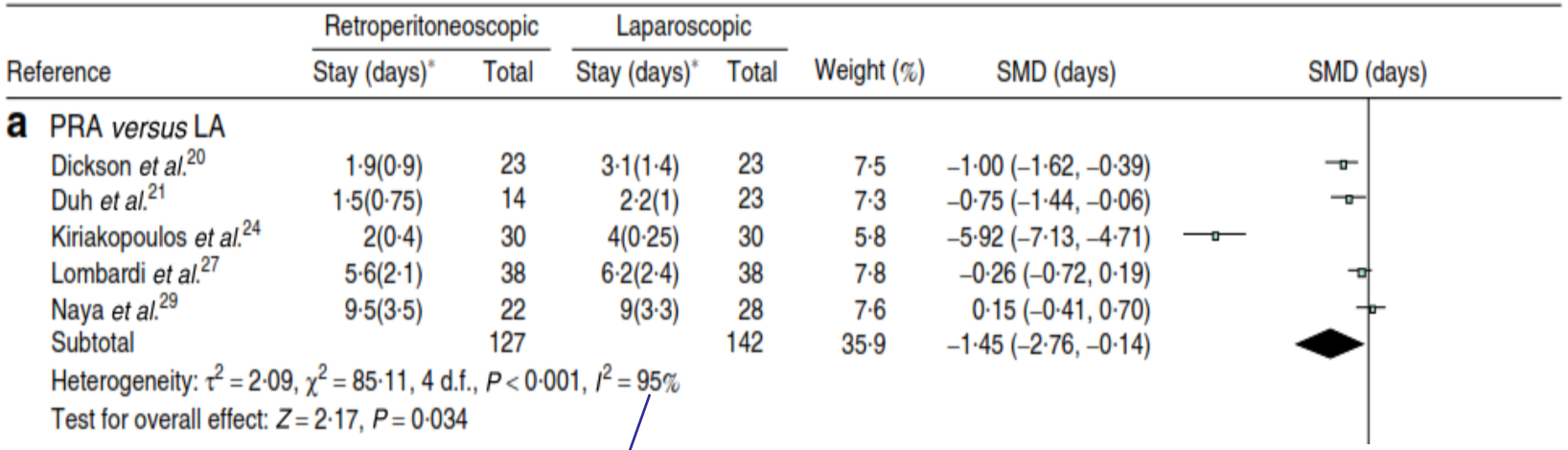
- Heterogeneity
  - Comonly used: I^2 test: [(Q-df/Q)]/ 100, where Q is the chi-square, 0 - 100%.
  - Defines percentage of variability in treatment effect estimates due to between study heterogeneity rather than chance
  - More than 40%: important
- Funnel plots: detect publication bias
  - Large studies→ precise estimates
  - Symmetrical distribution


Relative Risk (95% CI)
0.73 (0.49, 1.07)
0.74 (0.59, 0.94)
0.76 (0.51, 1.12)
0.71 (0.56, 0.90)
0.73 (0.61, 0.88)
0.5
1



p-value for heterogeneity < 0.001

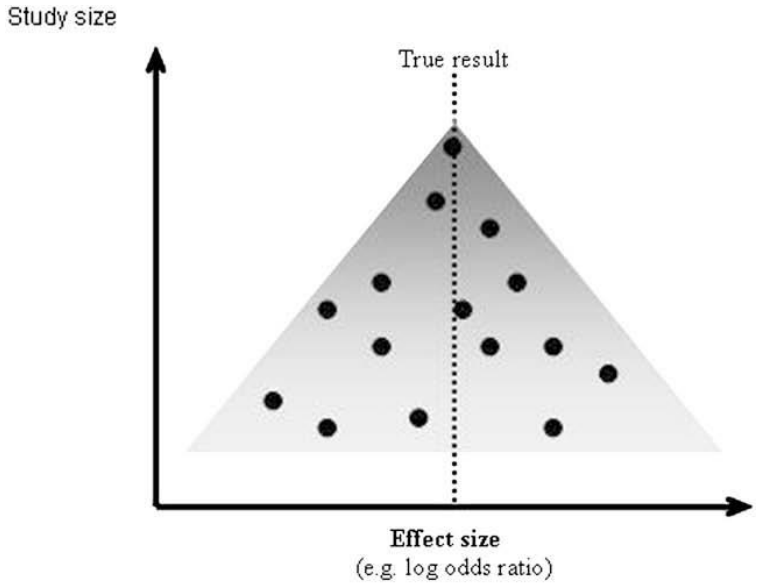
I^2=89%

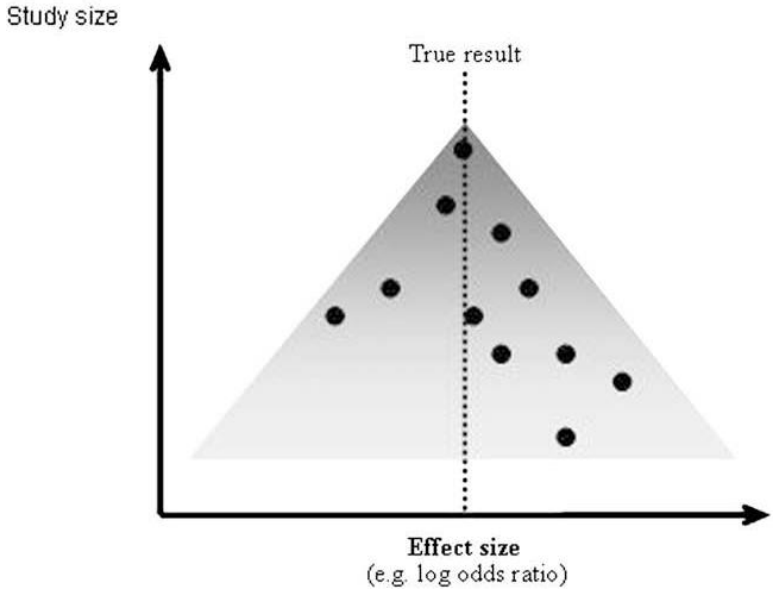


Reference	Retroperitoneoscopic Stay (days)*	Retroperitoneoscopic Total	Laparoscopic Stay (days)*	Laparoscopic Total	Weight (%)	SMD (days)
a PRA *versus* LA						
Dickson *et al.*[20]	1·9(0·9)	23	3·1(1·4)	23	7·5	–1·00 (–1·62, –0·39)
Duh *et al.*[21]	1·5(0·75)	14	2·2(1)	23	7·3	–0·75 (–1·44, –0·06)
Kiriakopoulos *et al.*[24]	2(0·4)	30	4(0·25)	30	5·8	–5·92 (–7·13, –4·71)
Lombardi *et al.*[27]	5·6(2·1)	38	6·2(2·4)	38	7·8	–0·26 (–0·72, 0·19)
Naya *et al.*[29]	9·5(3·5)	22	9(3·3)	28	7·6	0·15 (–0·41, 0·70)
Subtotal		127		142	35·9	–1·45 (–2·76, –0·14)
Heterogeneity: $\tau^2 = 2{\cdot}09$, $\chi^2 = 85{\cdot}11$, 4 d.f., $P < 0{\cdot}001$, $I^2 = 95\%$						
Test for overall effect: $Z = 2{\cdot}17$, $P = 0{\cdot}034$						

Fixed effects MA used even if I^2 = 95%!

Constantinides Br J Surg 2012


Study size
True result
Effect size
(e.g. log odds ratio)


Study size
True result
Effect size
(e.g. log odds ratio)

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- Sealants for preventing dental decay in the permanent teeth
- Vitamin E supplementation in pregnancy
- Topical non-steroidal anti-inflammatory drugs for acute musculoskeletal pain in adults

Critical appraisal of systematic reviews: tools

- AMSTAR 2
- Critical Appraisals Skills Programme (CASP) checklist
- ROBIS tool (Bristol U)

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding methods used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

Opdracht

1. Stel PICO op (mag dezelfde zijn als voor module 1)
2. Selecteer een **recente meta-analyse** over het onderwerp
3. Ga na of er na publicatie van de meta-analyse nog bijkomende trials zijn verschenen (Cochrane database, Embase, WoS, Pubmed) en voeg die toe
4. Beoordeel kwaliteit van de meta-analyse: ROBIS tool (https://www.bristol.ac.uk/population-health-sciences/projects/robis/)
    a. Lees begeleidende informatie en instructies
    b. Vul Word template in
5. Kies en beoordeel één individuele studie op kwaliteit:
    - Voor RCT: Cochrance RoB tool
    - Indien geen RCT's beschikbaar over het onderwerp: gebruik ROBINS-I tool
    - Vul het Word sjabloon in (EBM_checklist)
6. Evalueer evidentie en formuleer besluit met betrekking tot relevantie voor de (eigen) klinische praktijk.

Bezorgen via email (wim.ceelen@ugent.be): opdracht, ROBIS sjabloon, EBM checklist.

Taal: Engels (bij voorkeur) of Nederlands.

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