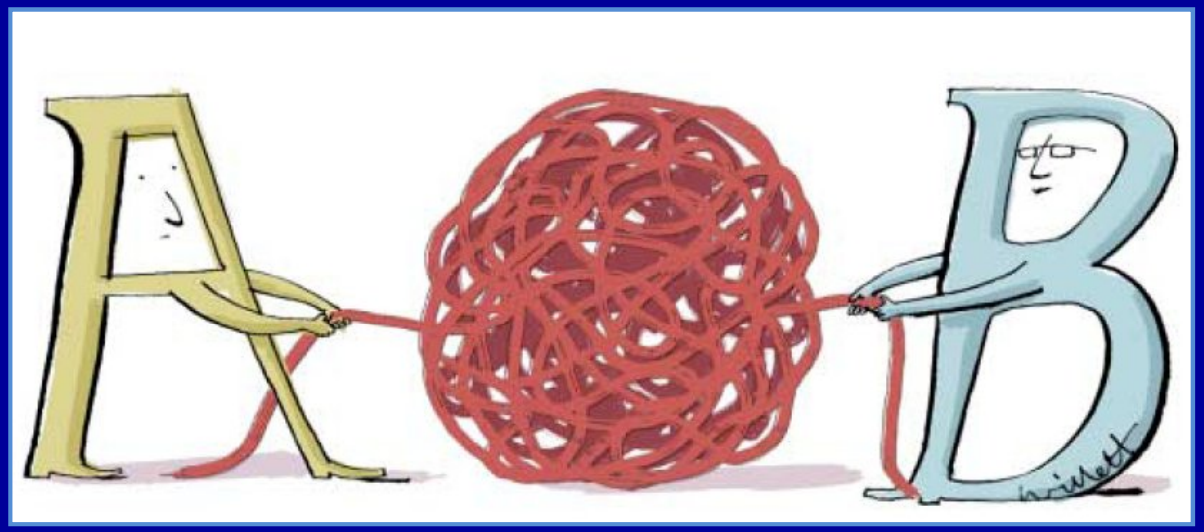
Critical appraisal of randomized clinical trial?

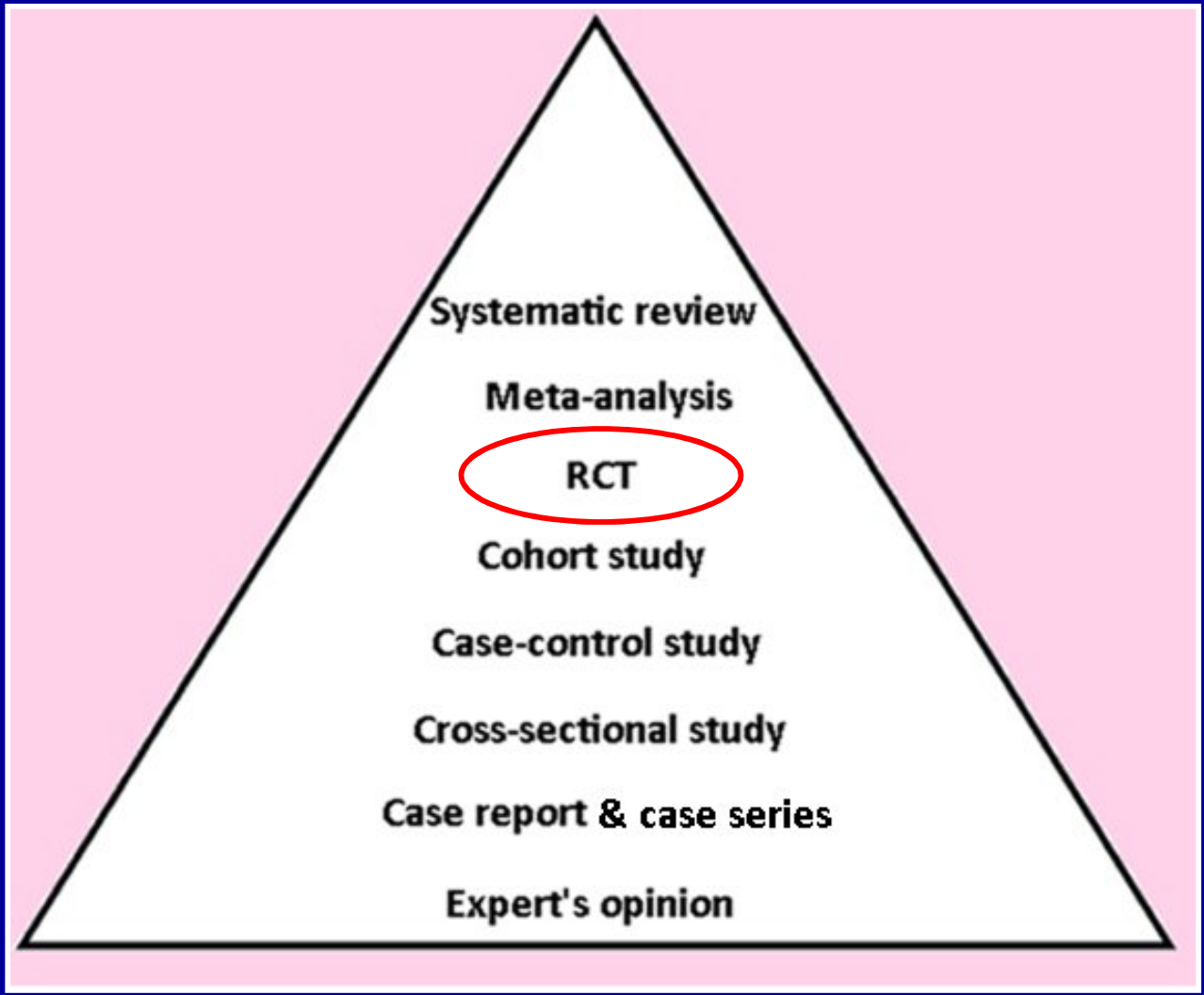


Samir Haffar M.D.

Assistant Professor of Gastroenterology

Al-Mouassat University Hospital – Damascus – Syria

Hierarchy of evidence in quantitative studies



McGovern D, Summerskill W, Valori R, Levi M. Key topics in EBM.
BIOS Scientific Publishers, 1st Edition, Oxford, 2001.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

Perhaps the first large-scale clinical trial using a properly designed randomized schema

Sir Austin Bradford Hill (1897-1991)

British epidemiologist & statistician

The father of modern RCTs

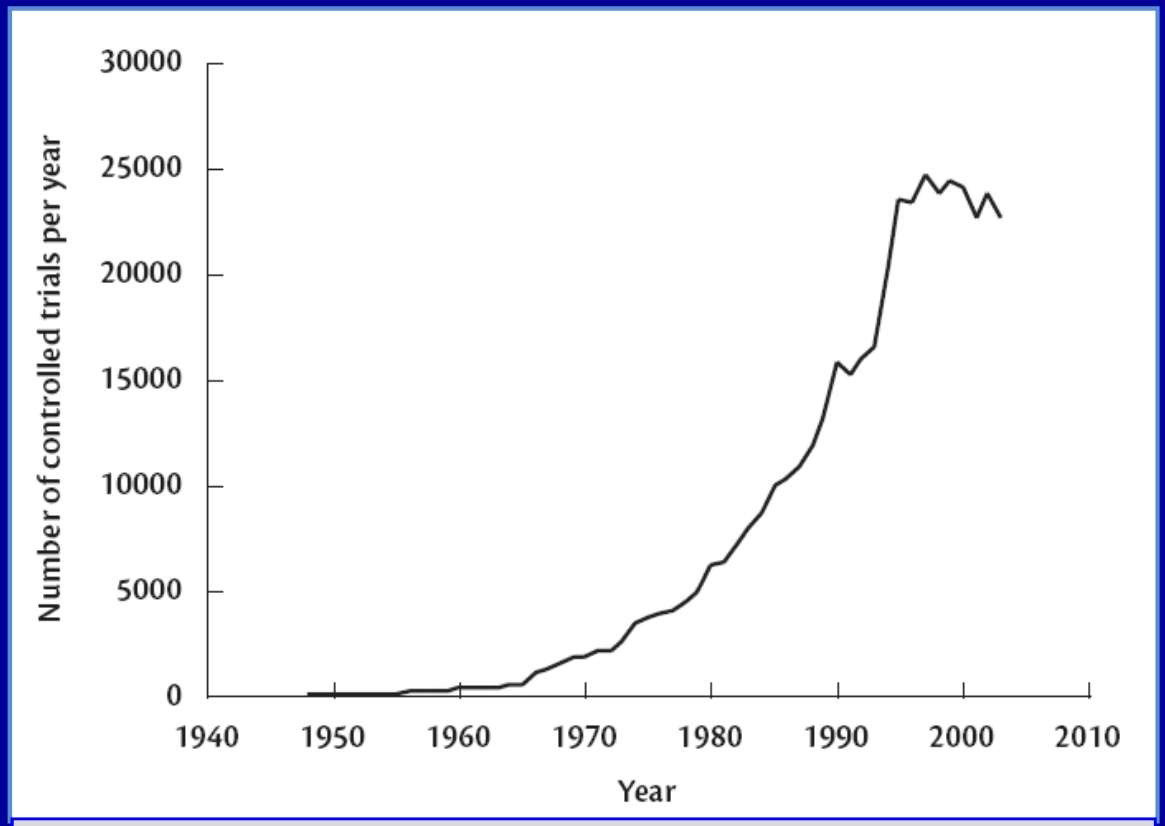
First RCT in the United States

1951

NIH started a study of adrenocorticotropic hormone (ACTH), cortisone & aspirin in the treatment of rheumatic heart disease*

* Rheumatic Fever Working Party. Circulation 1960 ; **22 :** 505 – 15.

Number of RCT per year



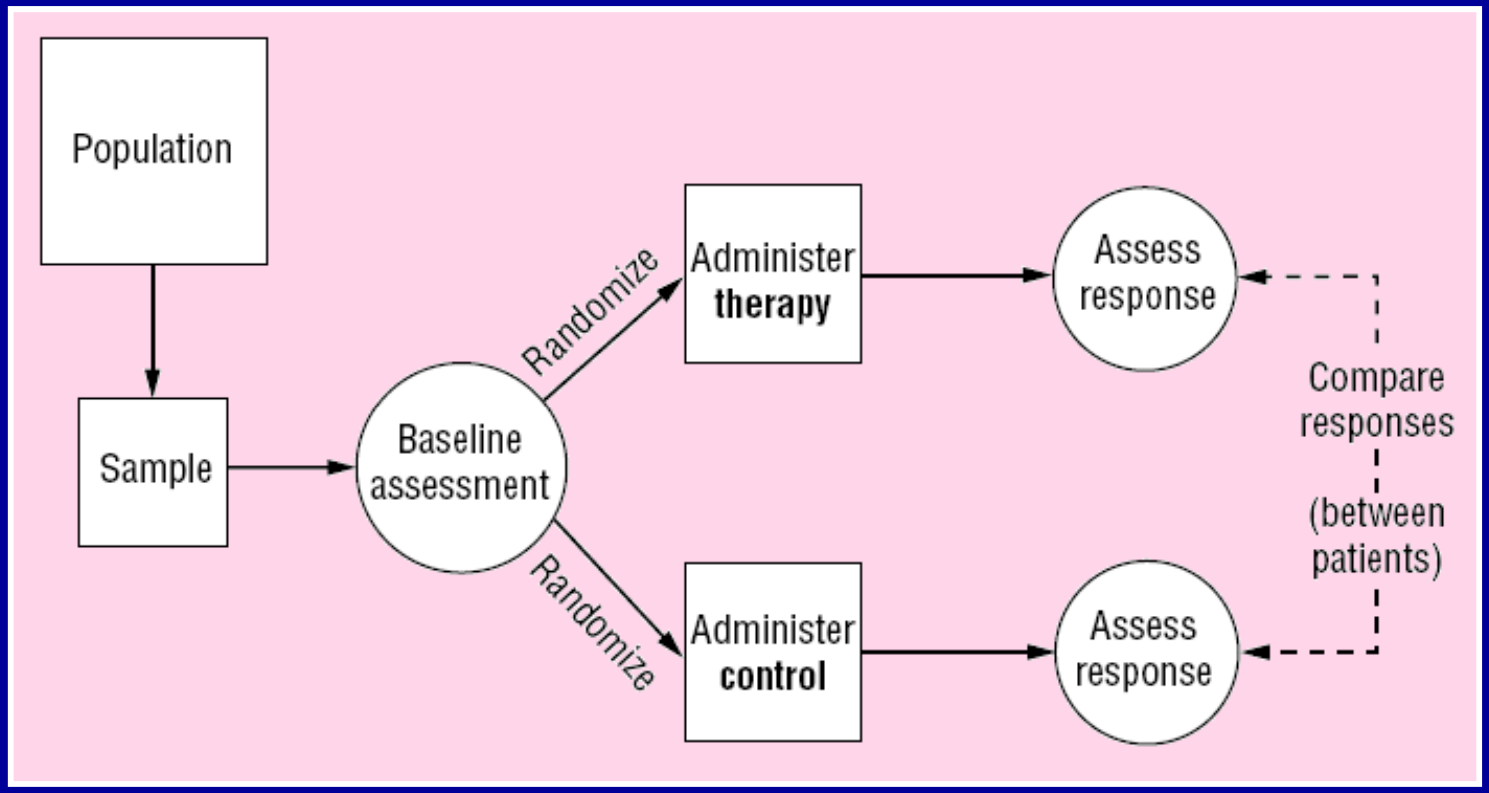
≈ 20,000 trials published each year

> 500,000 trials in total

Glasziou P, Del Mar C. Evidence based practice workbook. Blackwell Publishing, 2nd edition, 2007.

Basic structure of a RCT

Parallel trial



Parallel trial is the most frequently used design

Akobeng AK. Arch Dis Child 2005 ; 90 : 840 – 844.

Basics of RCT – 1

- **Participants**

  Patients – relatives of pts – healthy volunteers – groups

- **Investigators**

  People who design & carry out study & analyze results

- **Interventions**

  Preventive strategies, screening, & **treatments**

Jadad AR, Enkin MW. Randomized control trials.
Blackwell Publishing, 2nd ed, 2007.

Basics of RCT – 2

Control group should receive one of the following:

❶ **Placebo**

Inert pills that appear identical to trial therapy

❷ **Gold standard therapy**

It may be unethical to treat patient with placebo

❸ **New treatment**

Jadad AR, Enkin MW. Randomized control trials.
Blackwell Publishing, 2nd ed, 2007.

Basics of RCT – 3

RCTs are regarded as

- **Quantitative** studies (quantified outcomes)
- Most rigorous method of **hypothesis testing**
- **Experimental** studies versus observational studies
- Gold standard to evaluate **effectiveness of interventions**

Jadad AR, Enkin MW. Randomized control trials.
Blackwell Publishing, 2nd ed, 2007.

Some historical examples of treatments with dramatic effects

- Insulin for diabetes
- Blood transfusion for severe hemorrhagic shock
- Defibrillation for ventricular fibrillation

- Neostigmine for myasthenia gravis
- Tracheotomy for tracheal obstruction
- Drainage for pain associated with abscesses
- Pressure or suturing for arresting hemorrhage

Glasziou P et al. Br Med J 2007 ; 334 : 349 – 351.

Parachutes reduce risk of injury after gravitational challenge

Their effectiveness has not been proved with RCTs

Glasser SP. Essentials of clinical research. Springer, 1st edition, 2008

Ethics committee

- **Include:**

  Layman, religious man, lawyers, researchers & clinicians

- **Responsibilities:**

  Protect rights & welfare of research subjects

  Determine if the potential benefits warrant the risks

  Ensure that **informed consent** is obtained

  Prevent unscientific or unethical research

The trial team

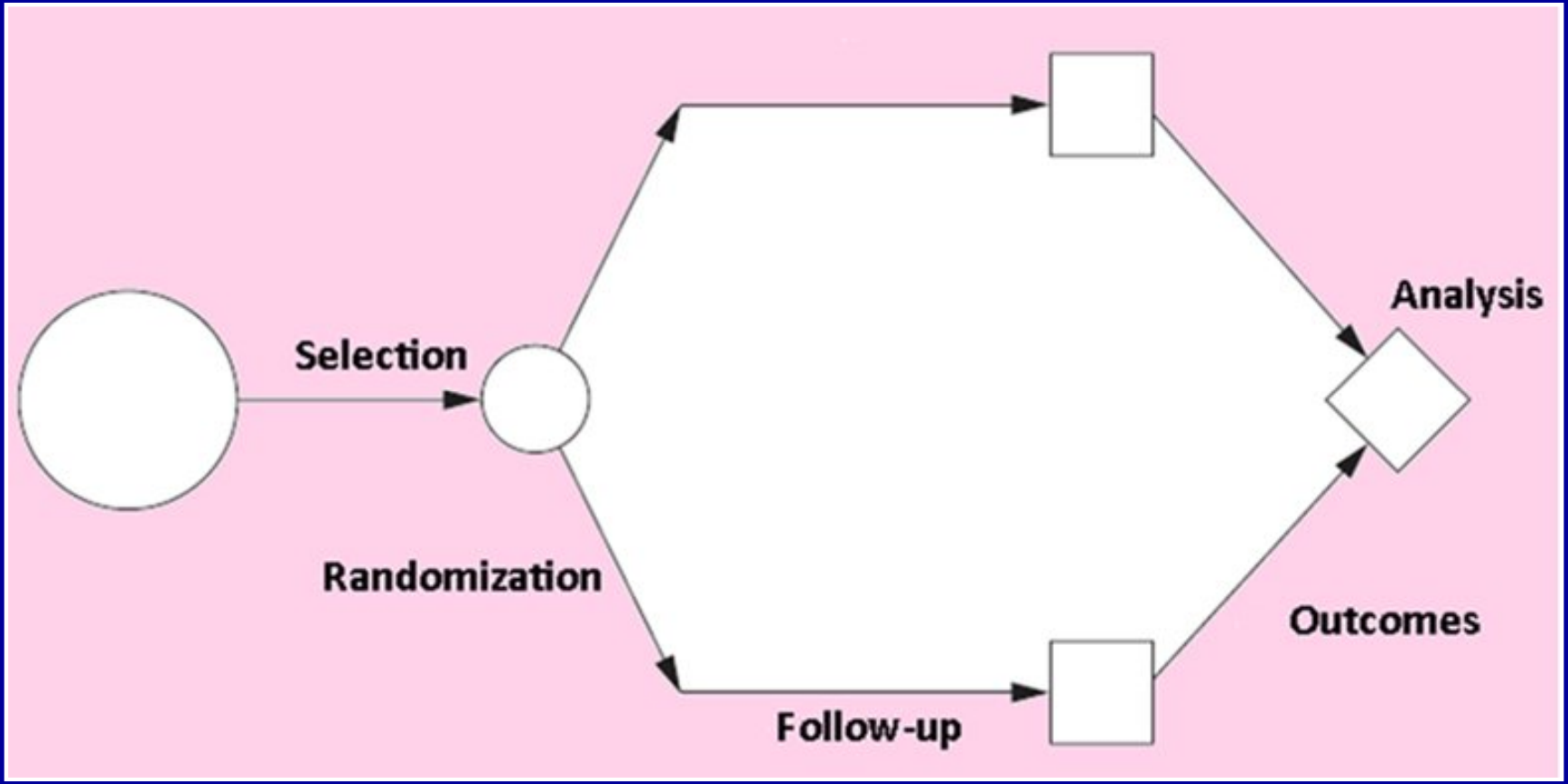
- Principal investigator
- Trial coordinator or manager
- Trial programmer
- Data manager or clerks
- Trial statistician → Planning phase
  - → Interim analyses
  - → Final analysis
- Trial secretary

Randomized controlled trial

1. Sample size
2. Randomization
3. Blinding (Masking)
4. Outcomes
5. Intention to treat analysis (ITT)
6. Measurement of treatment effect
7. Applicability of results to your patients

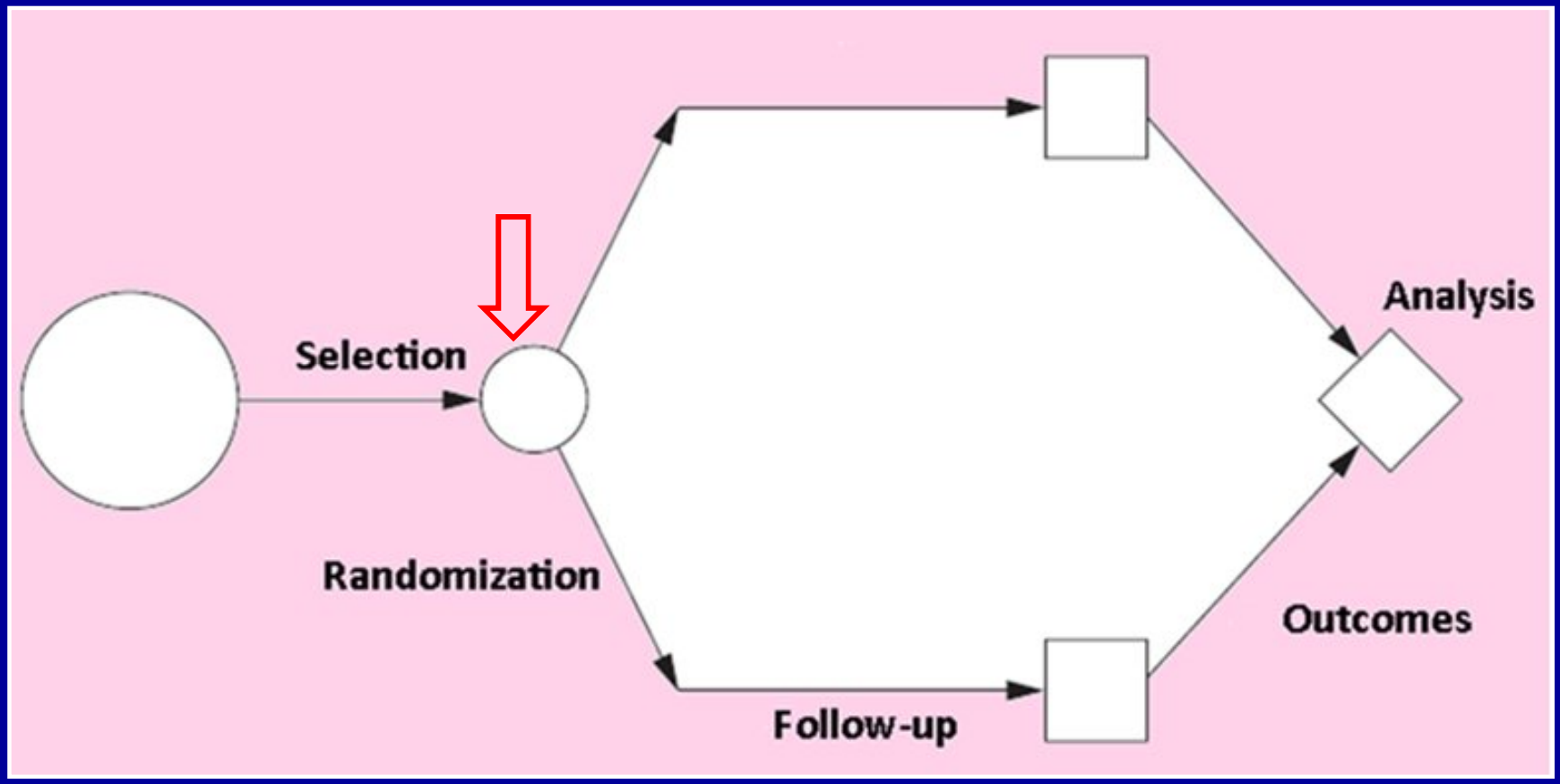
Critical appraisal

Flow diagram for a RCT



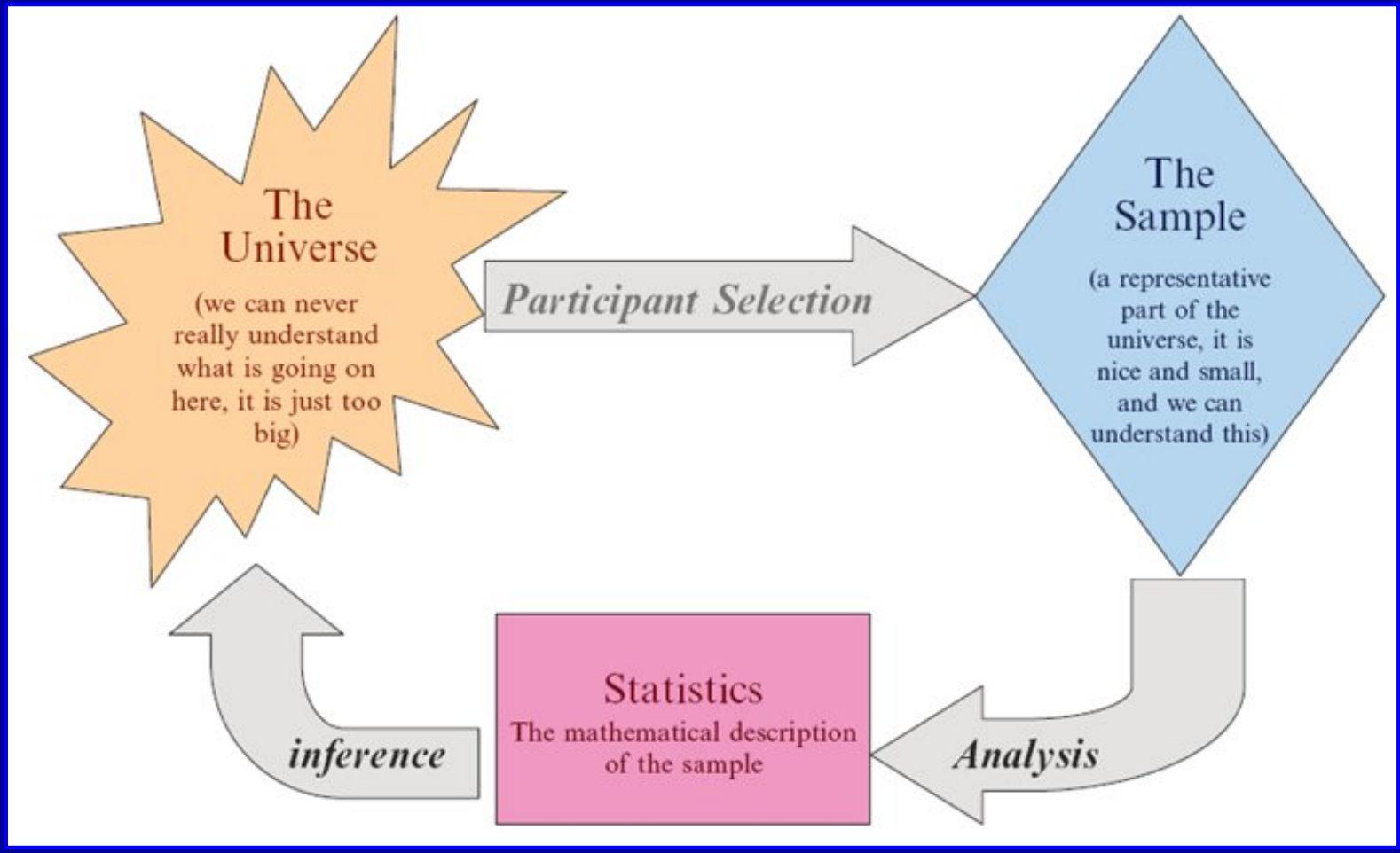
Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

❶ Sample size in RCTs



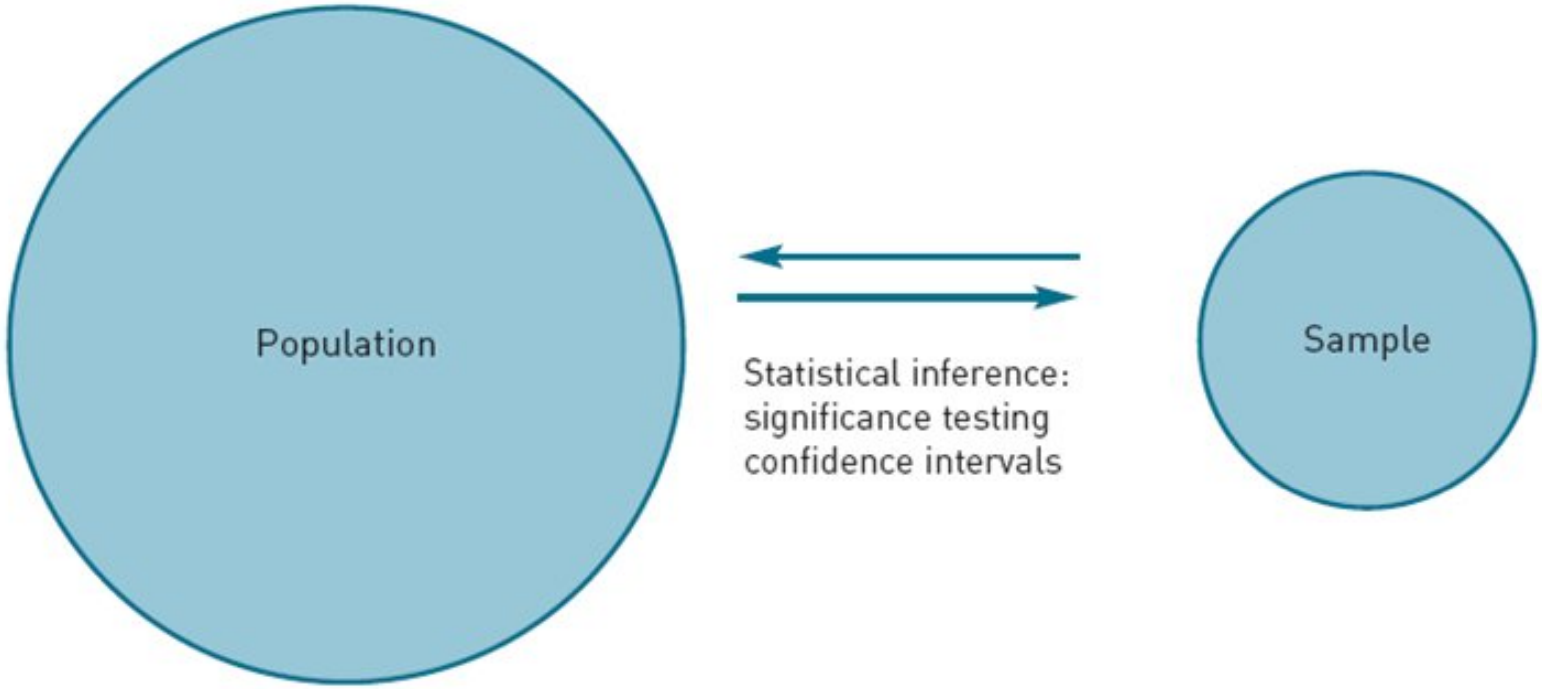
Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

The "Universe" & the "Sample"



Glasser SP. Essentials of clinical research. Springer, 1st edition, 2008

Statistical inference



Making statistical inferences about a population from a sample by means of **significance test & CI**

Wang D, Bakhai A. Clinical trials: practical guide to design, analysis, & reporting. Remedica, London, UK, 1st edition, 2006.

Component of sample size calculation

❶ **Type I error (α)** False positive = **0.05**

❷ **Type II error (β)** False negative = **0.20**

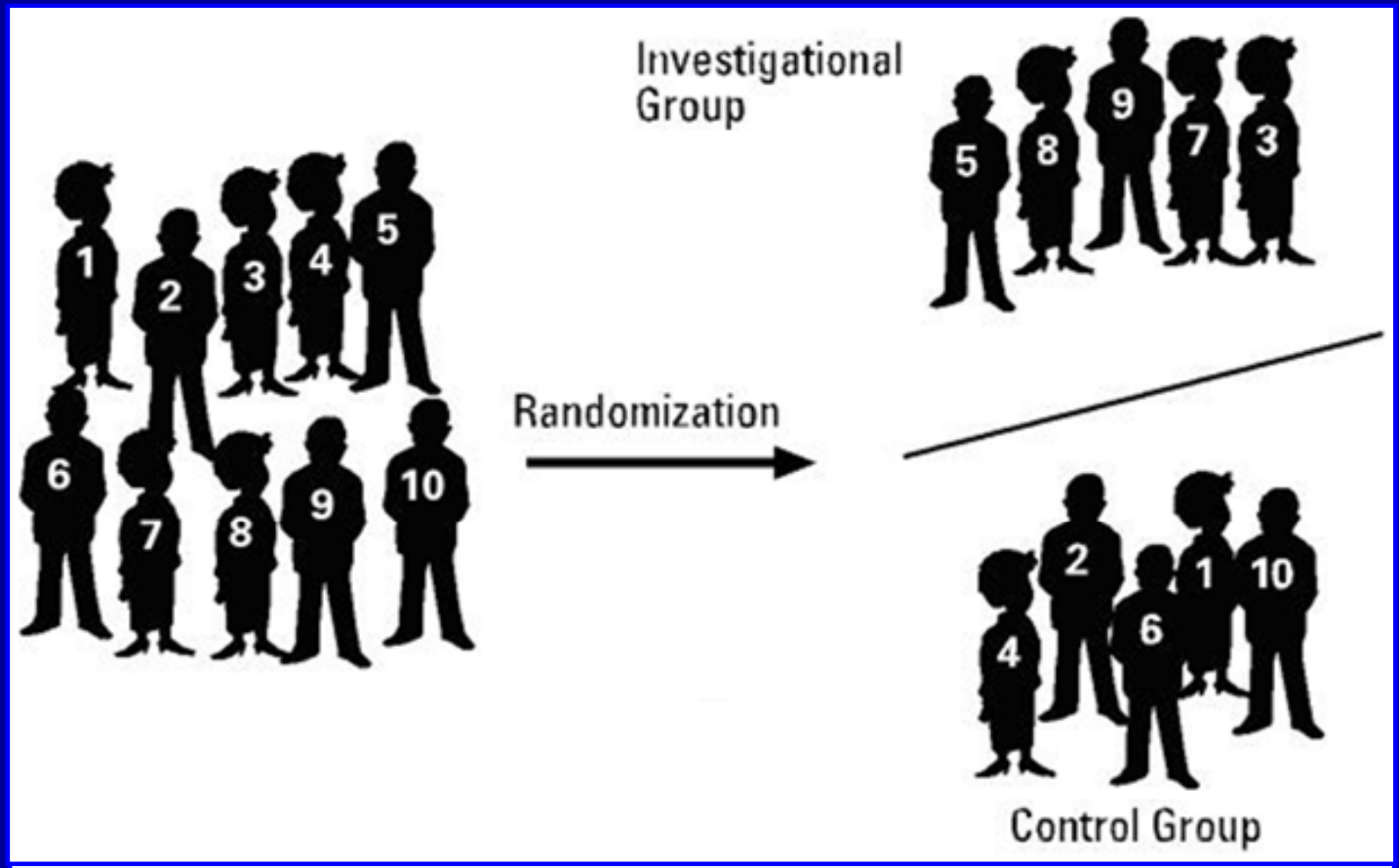
Power (1- β)

❸ **Event rate in control group**

❹ **Event rate in treatment group**

Schulz KF, Grimes DA. Lancet 2005 ; 365 : 1348 – 53.

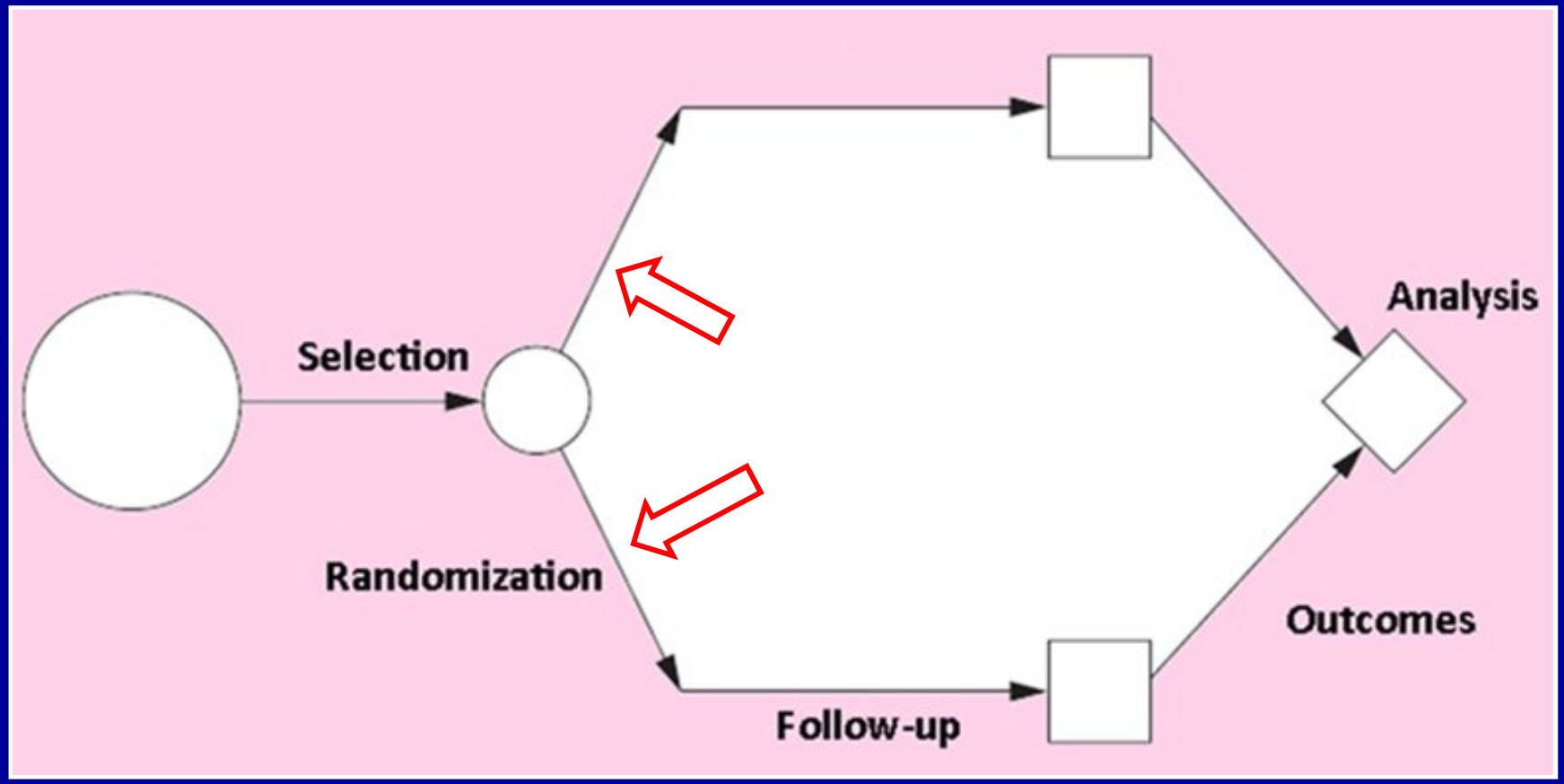
❷ Randomization in RCTs



If the study wasn't randomized

we'd suggest that you stop reading it

❷ Randomization in RCTs



If the study wasn't randomized
we'd suggest that you stop reading it

Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

Goal of randomization

Comparable groups to known prognostic factors

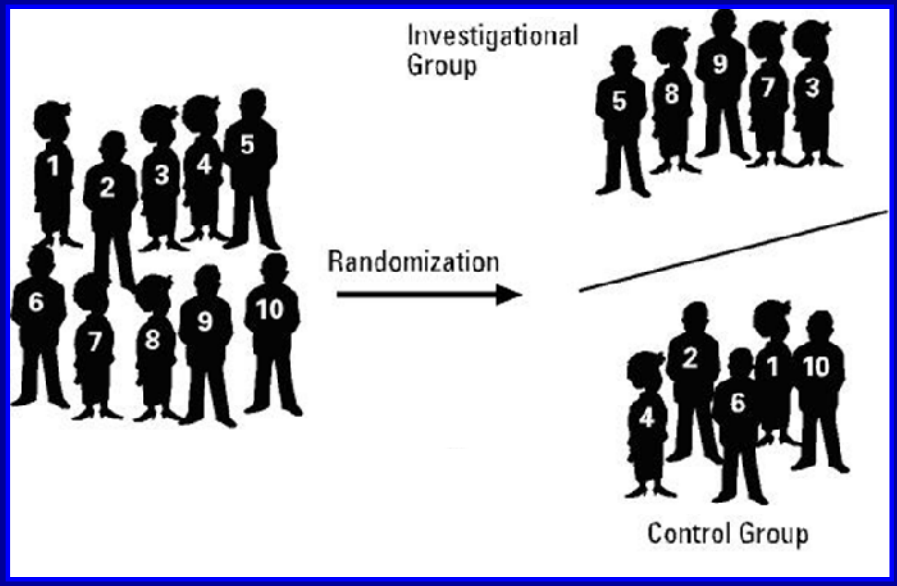
Beta-Blocker Heart Attack Trial - Baseline comparisons

	Propranolol (N-1,916)	Placebo (N-1,921)
Average Age (yrs)	55.2	55.5
Male (%)	83.8	85.2
White (%)	89.3	88.4
Systolic BP	112.3	111.7
Diastolic BP	72.6	72.3
Heart rate	76.2	75.7
Cholesterol	212.7	213.6
Current smoker (%)	57.3	56.8

Table comparing baseline characteristics presented in RCT reports

Randomization

- Simple randomization → Inacceptable
- Random table
- Block randomization
- Stratified randomization
- Minimization method
- Unequal randomization
- Allocation concealment → Preferred



2 principles of randomization

Regardless of the method of randomization used, investigators should follow two principles

- **First** They must define the rules that will govern allocation
- **Second** They should follow the same rules strictly throughout the whole study

Simple randomization

Inacceptable

- **Toss of a coin**
- **Date of birth** (even numbers to group A)
- **Hospital admission number**
- **Date seen in clinic** Patients seen this week (group A)
  Those seen next week (group B)

Problems arise from openness of allocation system

Allocation concealment

- **Sealed opaque envelope**

  Investigator open several envelopes before allocation

  Allocation seen if envelope held against bright light

- **Remote randomization (preferred)**

  Assignment removed from those making assignments:

  By telephone – Over the internet

Randomization should be distant

& separate from clinicians conducting the trial

RCT of open vs. lap appendectomy

- Trial ran smoothly during the day
- Surgeon's presence required for lap procedure at night
- Residents at night held semiopaque envelopes up to light & opened first envelope that dictated open procedure
- First eligible patient in the morning allocated to lap group
- If patients seen at night sicker than those seen in the day, this behavior bias results against open procedure

Hansen J et al. World J Surg. 1996 ; 20 : 17 – 20.

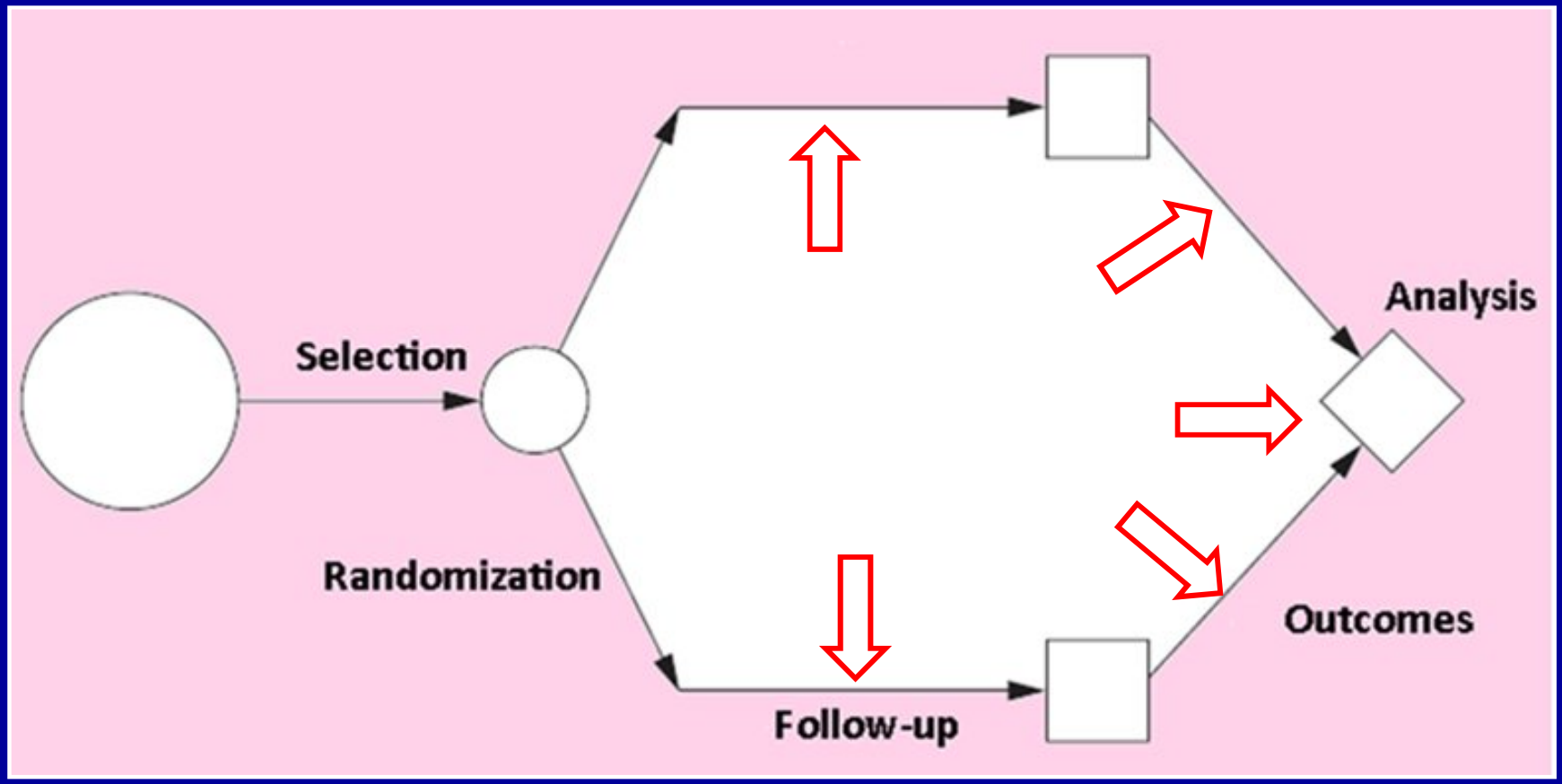
Estimates of treatment effect exaggerated

by 40% in trials with unconcealed

compared with concealed randomization

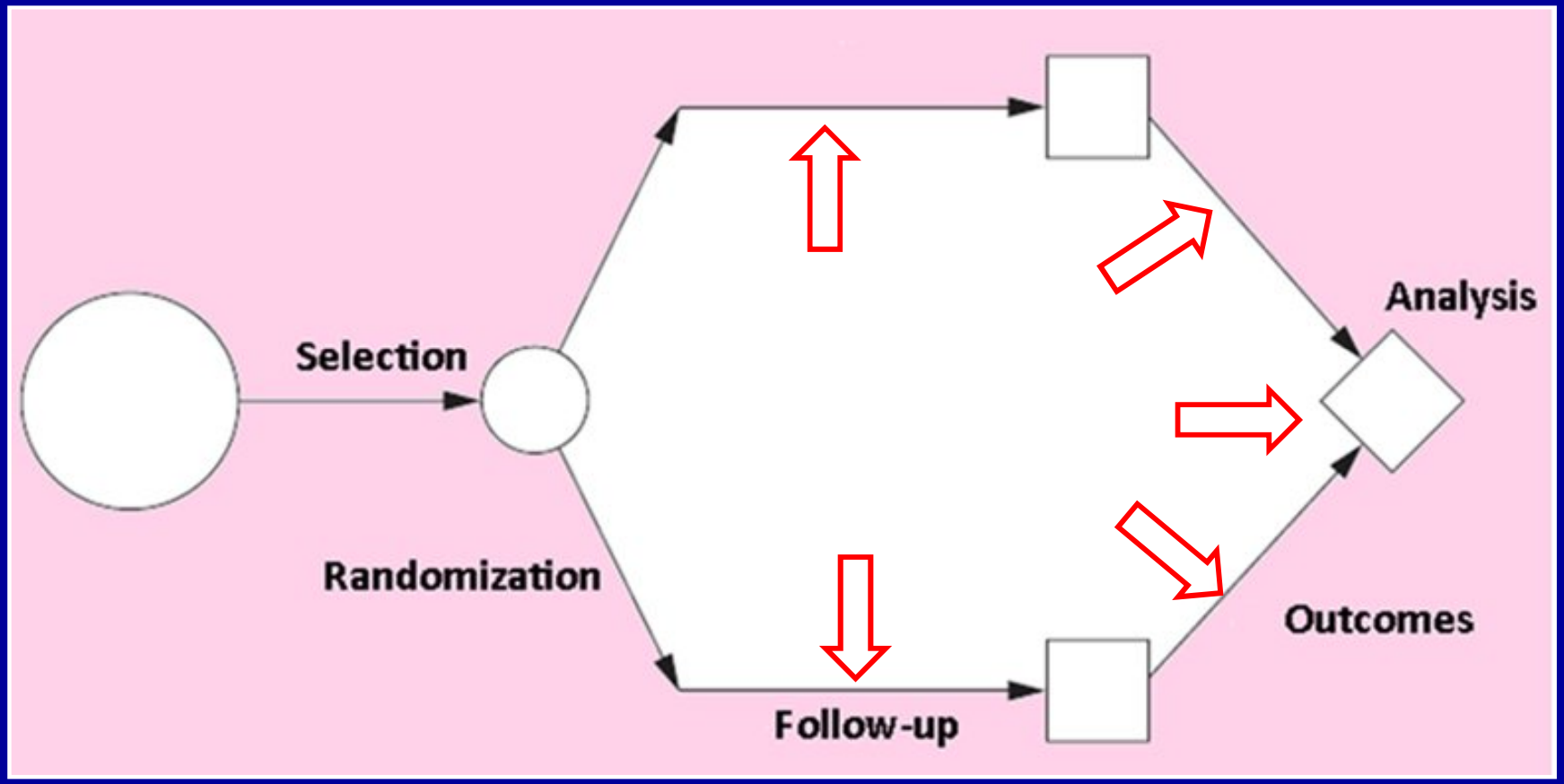
Schulz KF et al. JAMA 1995 ; 273 : 408 – 12.

❸ Blinding in RCTs



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

❸ Blinding /masking in RCTs



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

Blinding or masking

- Keep one or more of the people involved in the trial unaware of the intervention that is being evaluated
- Purpose: decrease risk of **observation bias**

- **What matters**
  Not the number of people blinded during a trial
  But the number & role of those who are **not blinded**

Blinding is not always appropriate or possible

Blinding or Masking

Blinding can be implemented in at least 6 levels in RCTs

- Participants
- Investigators who administer interventions
- Investigators taking care of the participants
- Investigators assessing the outcomes
- Data analyst
- Investigators who write results of the trial

Usually the same

Blinding or masking

Depending on blinding extent, RCTs classified as

- **Open label (everyone aware)**
- **Single-blind**
- **Double-blind**
- **Triple-blind**
- **Quadruple-blind & so on**

The term 'double-blind RCT', so often used to represent the ultimate in design to produce valid results, is confusing

Jadad AR, Enkin MW. Randomized control trials.
Blackwell Publishing, 2nd ed, 2007.

Why is blinding so important?

- Trials that were not double blinded yielded larger estimates of treatment effects than double blinded trials (**OR exaggerated on average by 17%**)

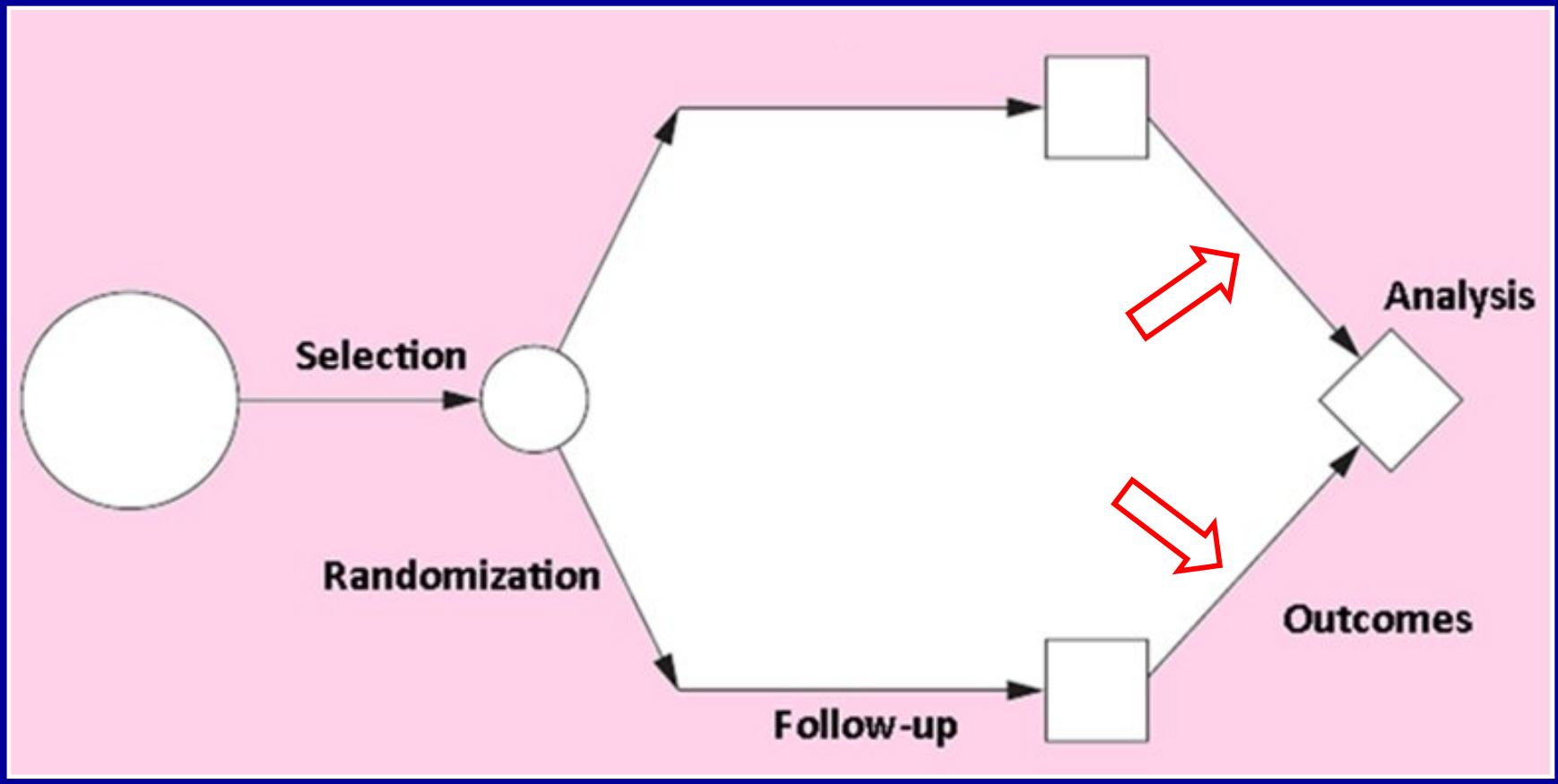
- Blinding is weaker than allocation concealment in preventing biases

Schulz KF. Evid Based Nurs 2000 ; 5 : 36 – 7.

A humorous example of blinding/masking

Glasser SP. Essentials of clinical research. Springer, 1st edition, 2008

❹ Outcomes in RCTs



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

Outcomes in RCTs – 1

Primary outcome

- **One primary outcome** (usually)

  Most important outcome (stroke in carotid endarterectomy)

- **Composite outcomes** (sometimes – can mislead)

  - Drug in MI: death, non fatal MI, hospitalization for ACS
  - Validity depends on similarity in patient importance, treatment effect, & number of events across components
  - Abandoned if large variations exist between components

Montori VM. Br Med J 2005; 330 : 594 – 596.

Outcomes in RCTs – 2

Surrogate outcomes

Used in case of rare events of clinical importance

Studies in cytoprotection of *NSAIDs*

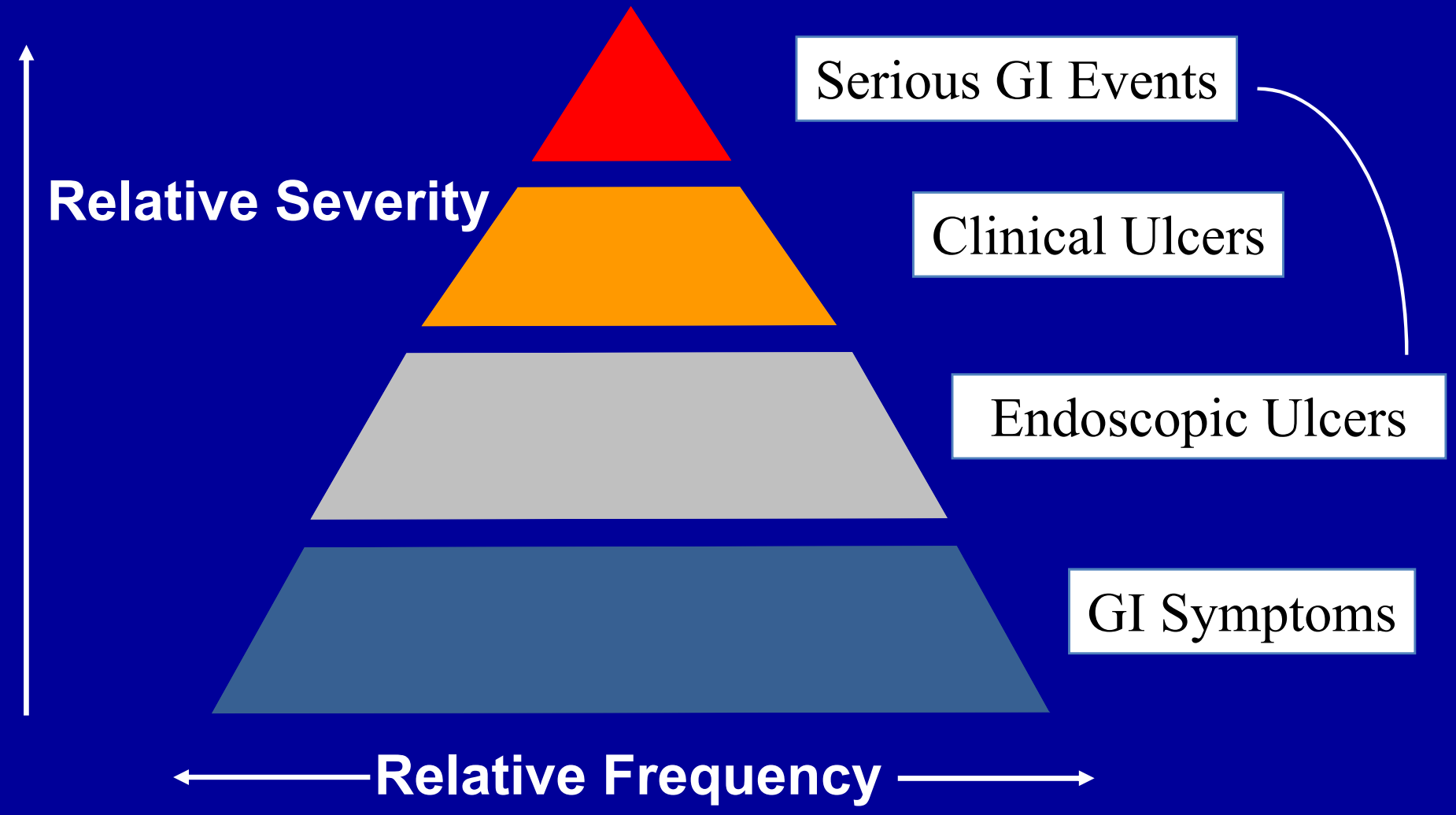
Endoscopic ulcers surrogates of bleeding or perforated PU

Secondary outcomes (usually multiple)

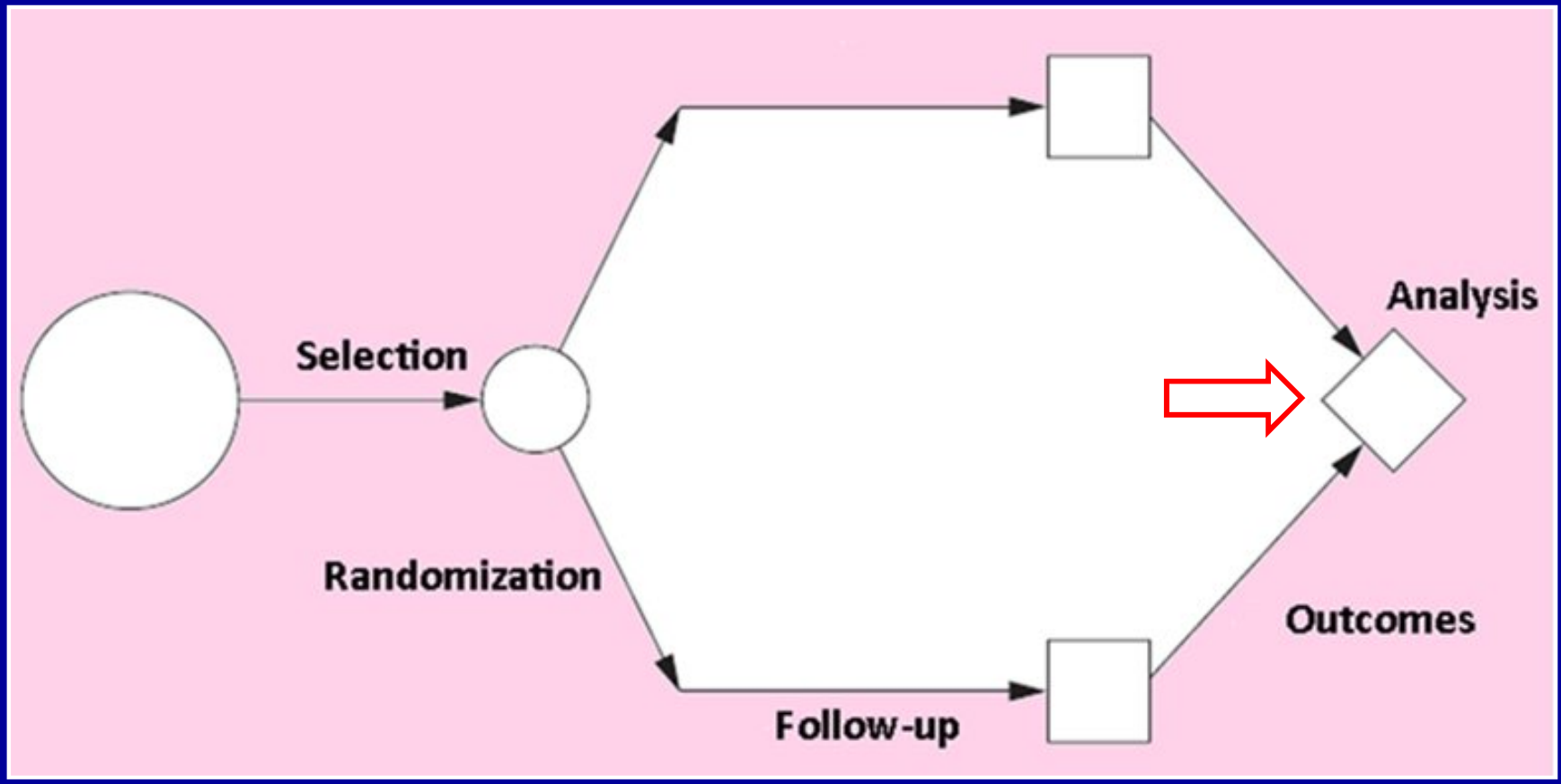
Other variables important to research question (drugs SE)

Too much emphasis if no change in primary outcome

NSAID-related GI side effects



❺ Intention to treat analysis (ITT)



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

Participants who not complete the study

- Some participants would not complete the study because of **misdiagnosis**, **non-compliance**, or **withdrawal**
- When such patients excluded from analysis, we can no longer be sure that important prognostic factors in the 2 groups are similar which lead to potential bias
- To reduce this bias, results should be analyzed on an **'intention to treat'** basis

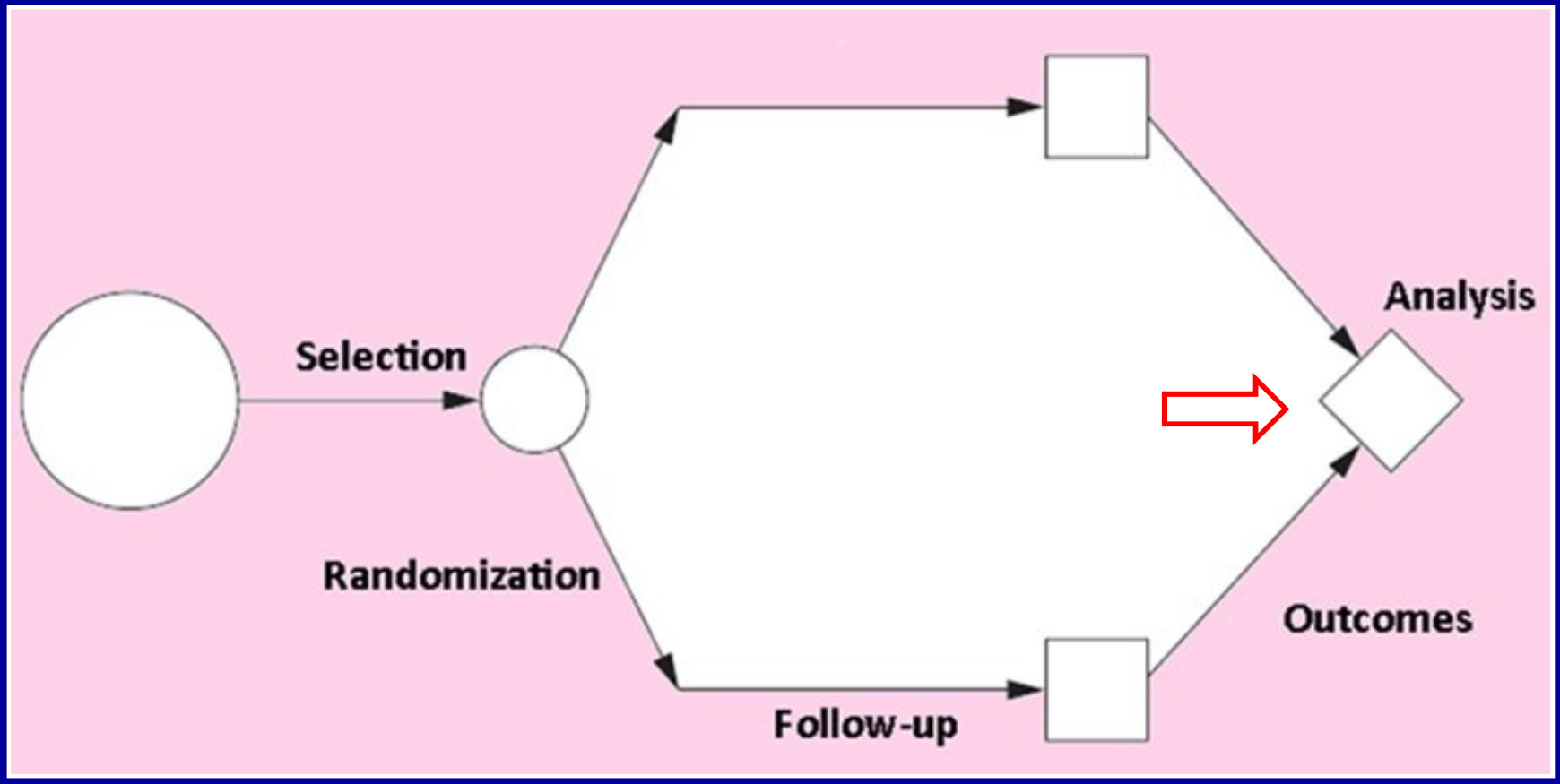
Intention to treat analysis

Form of quality control rather than analytic tool

- Strategy in conduct & analysis of RCT ensuring that all patients allocated to treatment or control groups analyzed together as representing that treatment arm whether or not they received prescribed therapy or completed study
- **Randomized participants = Analyzed participants**

McGovern D, Summerskill W, Valori R, Levi M. Key topics in EBM. BIOS Scientific Publishers, 1st ed, Oxford, 2001.

❻ Measurement of treatment effect



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

Measurement of treatment effect in RCTs

- **p value (p)**
- **Relative Risk (RR)**
- **Odds Ratio (OR)**
- **Confidence Intervals (CIs)**
- **Number Needed to Treat (NNT)**

Data analyzed as trial proceeds (interim analysis) or at the ends of the trial

Probability value (p Value)

- p value is probability that observed difference between 2 treatment groups might occur by chance
- Many use p value of **0.05** as cut off for significance

p < 0.05 Observed difference between groups is so unlikely to have occurred by chance
Considered as **statistically significant**

p > 0.05 Observed difference between groups might have occurred by chance
Considered as **not statistically significant**

Probability value (p value)

- $p > 0.05$ Statistically insignificant
- $p < 0.05$ Statistically significant

Statistically significant → **Doesn't mean** → **Clinically significant**

Statistical versus clinical significance

- Pentoxifylline vs placebo in PAD* (1992)
  40 patients randomized to pentoxifylline or placebo
  Maximum pain-free walking distance longer in pentoxifylline group than in placebo group (**$p < 0.001$**)
  Conclusion: **pentoxiphylline clinically effective**

- Close examination of data:
  Difference in maximum walking distance: **3.5 feet**
  Doctors & patients consider it **not clinically significant**

* PAD: Peripheral Arterial Disease

McGovern D et al. Key topics in EBM. BIOS Scientific Publishers, Oxford, 2001.

Risk & Relative Risk (RR)

- **Risk**

Number of patients fulfill criteria for a given end point divided by total number of patients

i.e.: Diarrhea during tt with antibiotic in 4 of 10 patients

Risk of patients: 4 / 10 = **0.4**

Diarrhea in control group in 1 of 10 persons

Risk of controls: 1 / 10 = **0.1**

- **Relative Risk**

Risk of patient / risk of control group

RR: 0.4 / 0.1 = **4**

Odds & Odds Ratio (OR)

- **Odds**

Number of patients fulfill criteria for given endpoint divided by number of patients who do not

i.e.: Diarrhea during tt with antibiotic in 4 of 10 patients

Odds of patients: 4 / 6 = **0.66**

Diarrhea in control group in 1 of 10 persons

Odds of controls: 1 / 9 = **0.11**

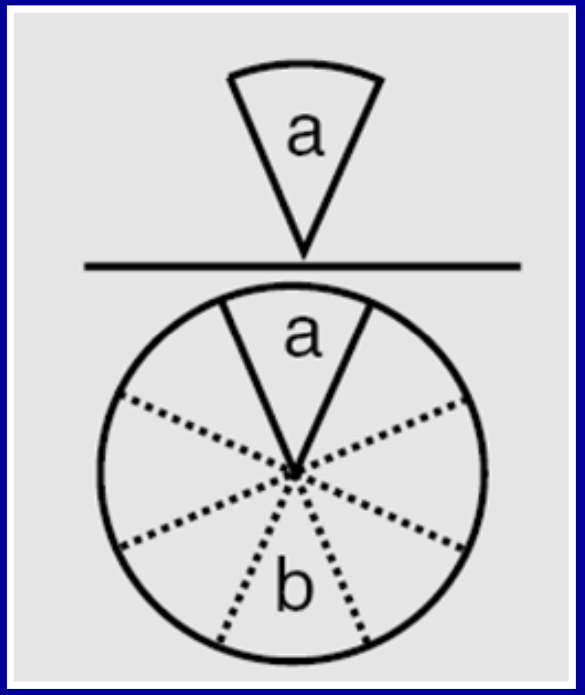
- **Odds Ratio**

Odds of patients / odds of control group

OR = 0.66 / 0.11 = **6**

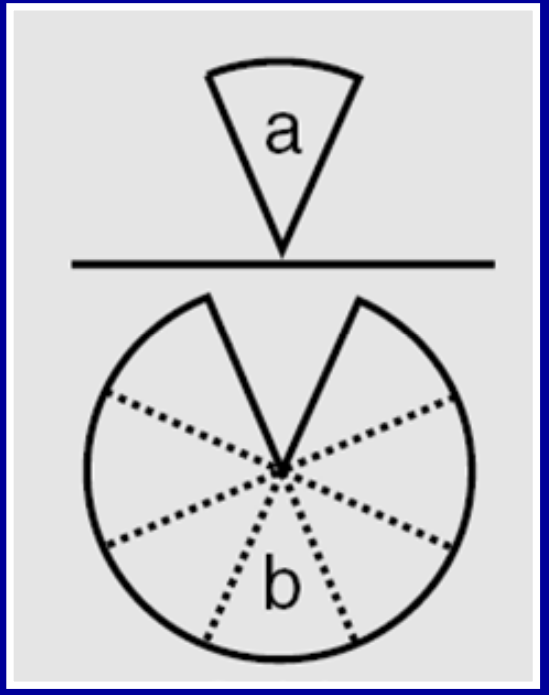
Risk & Odds

Risk



$$\frac{a}{a+b}$$

Odds



$$\frac{a}{b}$$

Interpretation of RR & OR

RR or OR should be accompanied by their CIs

RR or OR > 1

Increased likelihood of outcome in treatment group

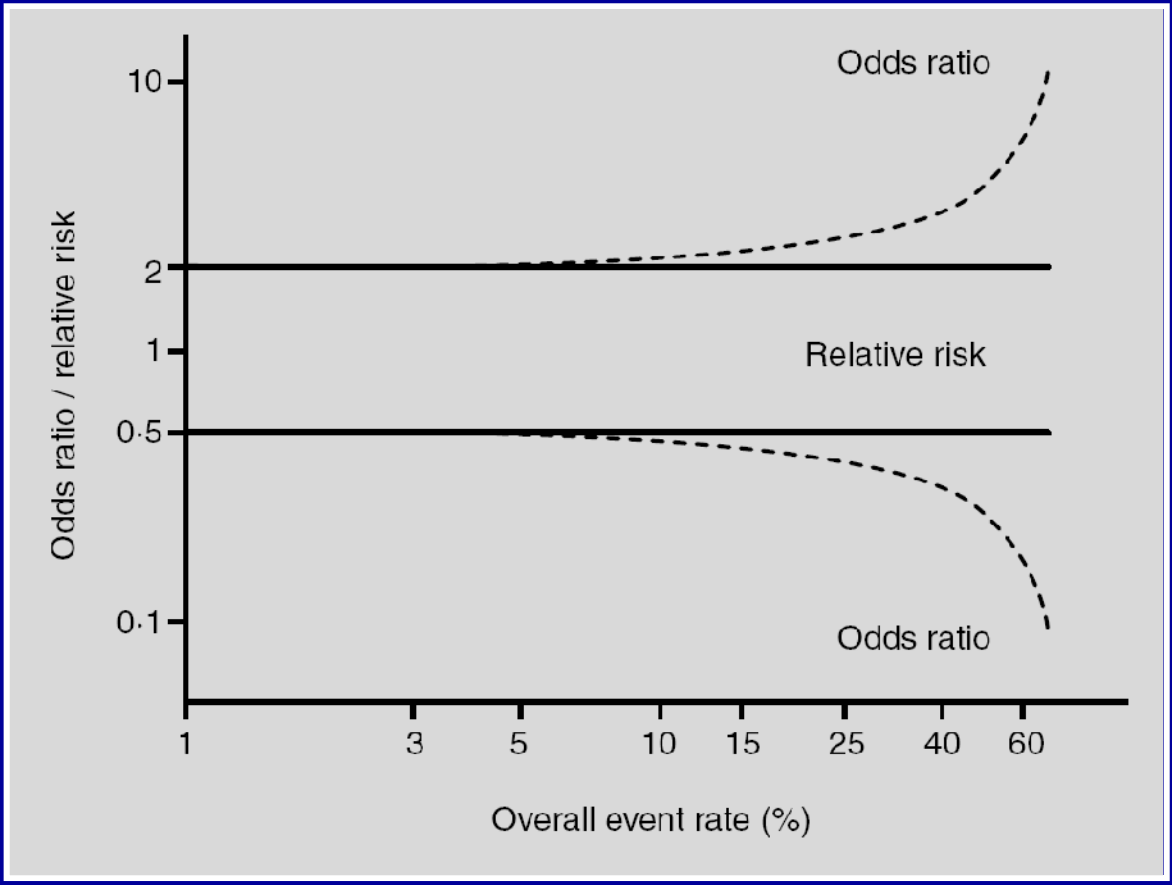
RR or OR < 1

Decreased likelihood of outcome in treatment group

RR or OR = 1

No difference of outcome between tt & control group

Odds ratio or relative risk?



OR will be close to RR if endpoint occurs infrequently (<15%)

If outcome is more common, OR will differ increasingly from RR

Altman DG et all. Systematic reviews in health care: Meta-analysis in context. BMJ Publishing Group, London, 2nd edition, 2001.

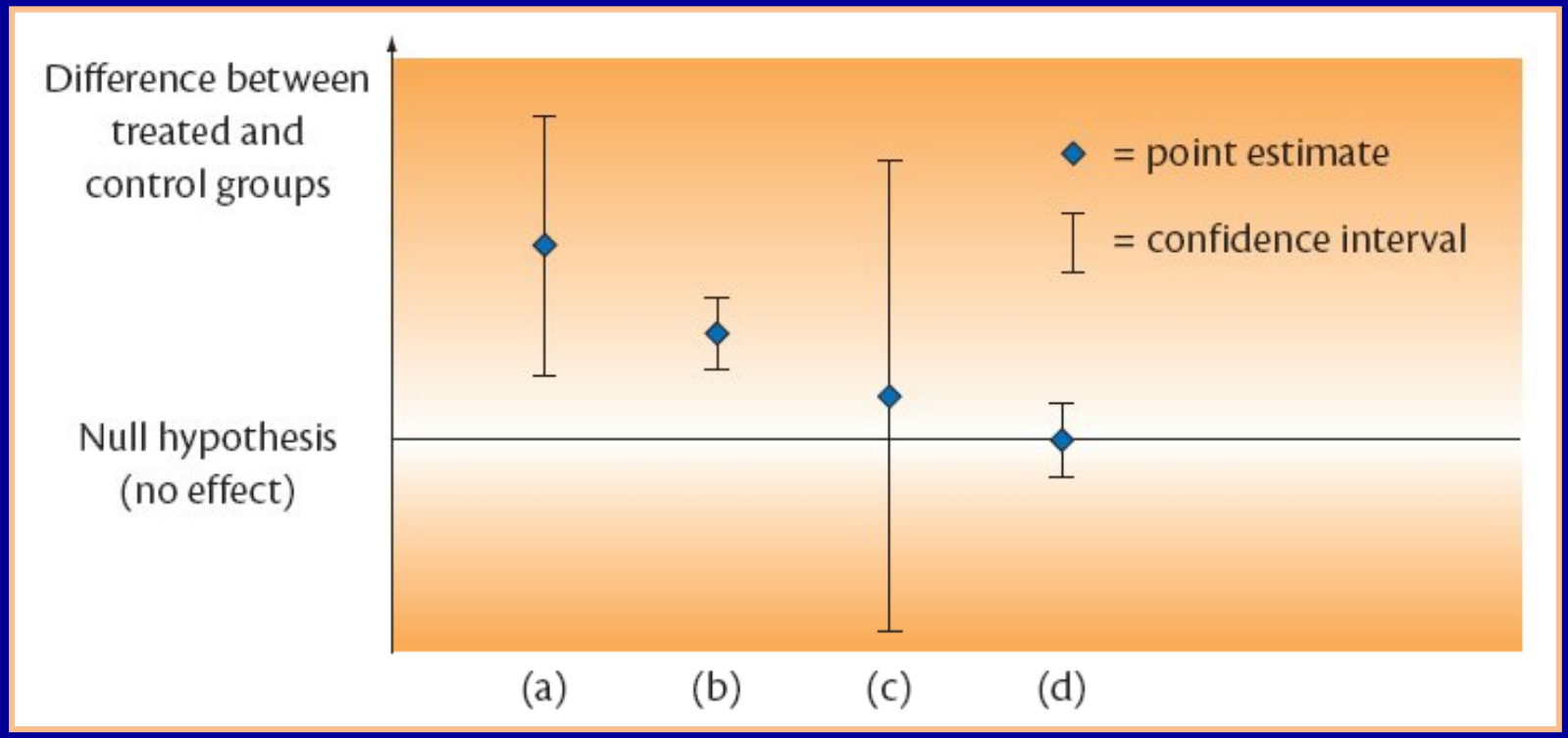
Significance of CI

- When we test a new Crohn's disease drug on randomly selected sample of patients, the treatment effect we will get will be an estimate of the "true" treatment effect for the whole population of patients with CD in the country
- **95% CI** of estimate will be range within which we are 95% certain the true population treatment effect will lie

Confidence intervals

Value	95 % CI are commonly used 90 or 99% CI are sometimes used
Width of CI	Indicates precision of the estimate Wider the interval, less the precision
CI includes 1	No statistically significant difference
CI doesn't include 1	Statistically significant difference

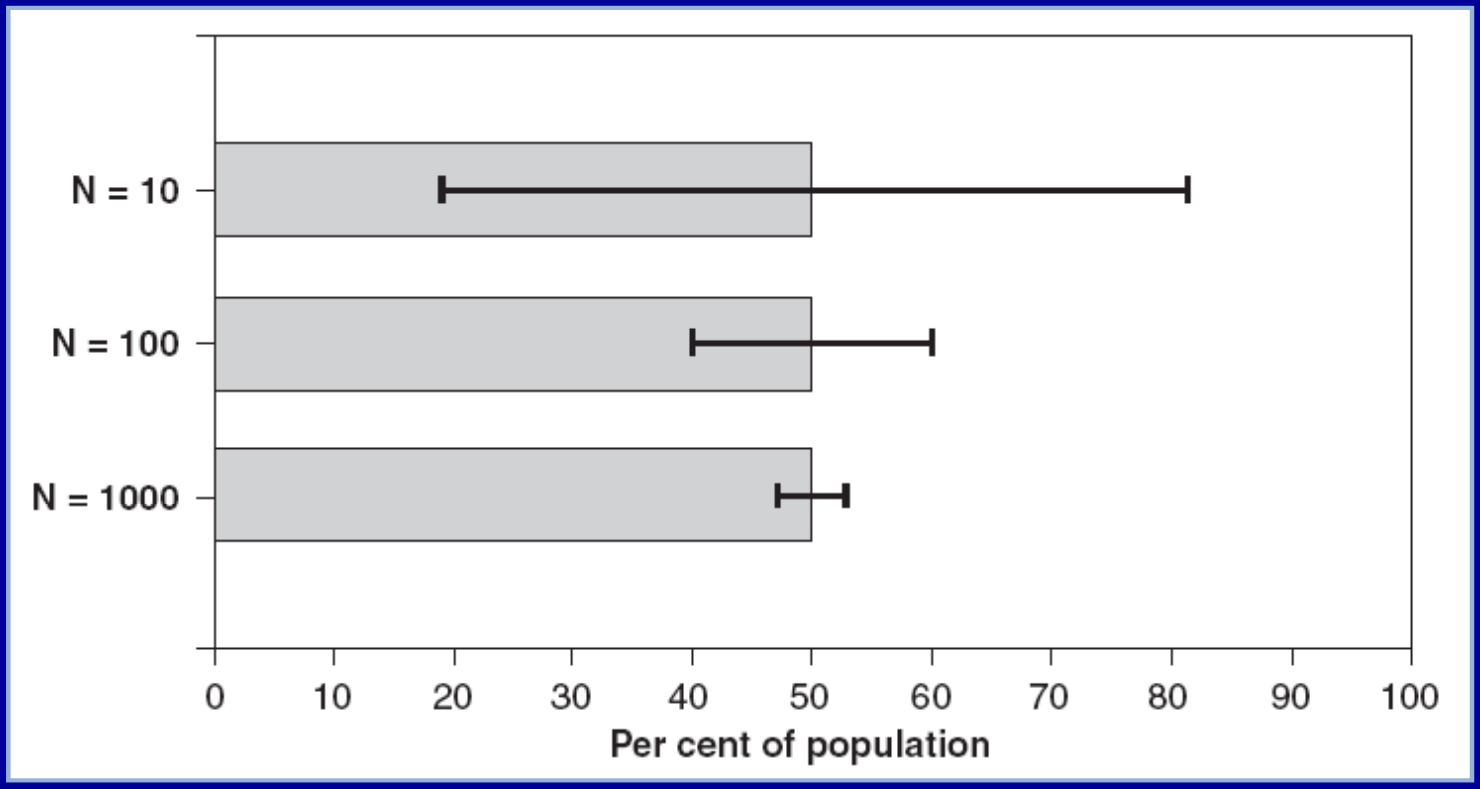
Statistical significance & CI



(a) Statistically significant , low precision
(b) Statistically significant, high precision
(c) Not statistically significant, low precision
(d) Not statistically significant, high precision

Glasziou P et al. Evidence based practice workbook. Blackwell, 2nd edition, 2007.

Influence of sample size on CI precision



Width of CI (precision of the estimate) decreases with increasing sample size

Peat JK, et al. Health science research. Allen & Unwin, Australia, 1st ed, 2001.

Confidence interval or p value?

- Authors of articles could report both p values & CIs
- CI convey more useful information than p values
- **If only one is to be reported, then it should be the CI**
- p value is less important & can be deduced from CI

Number Needed to Treat (NNT)

- **Relative Risk (RR)**

  Risk in treatment group / risk in control group

- **Relative Risk Reduction (RRR)**

  1 – RR

- **Absolute Risk Reduction (ARR)**

  Risk in control group – risk in treatment group

- **NNT** (expressed in clinically relevant way)

  1 /ARR

Measurement of treatment effect in RCTs

- p value (p)
- Relative Risk (RR)
- Odds Ratio (OR)
- Confidence Intervals (CIs)
- Number Needed to Treat (NNT)

Subgroup analysis

Post-hoc analysis

- In large trials not demonstrating overall favorable trend, it is common to conduct subgroup analyses to find one or more subgroups in which treatment "really works"

- Literature is replete with unconfirmed subgroup findings
- Post-hoc results should be regarded as **inconclusive**
- May be of value for **hypothesis generation**

ISIS-2 trial - Subgroup analysis

- Effects of streptokinase &/or aspirin on short-term mortality in patients admitted with AMI
- Mortality benefits for both active interventions
- In subgroup analyses:
  - Patients born under Zodiac signs of **Gemini & Libra**
    5% higher mortality on aspirin vs placebo
  - Patients born under **other Zodiac signs**
    30% lower mortality on aspirin vs placebo

Sleight P. Curr Control Trials Cardiovasc med. 2000;1(1):25-27.

ISIS-2 trial

Streptokinase &/or aspirin on AMI mortality

Furberg B. Evaluating clinical research. Springer, NY, USA, 2007.

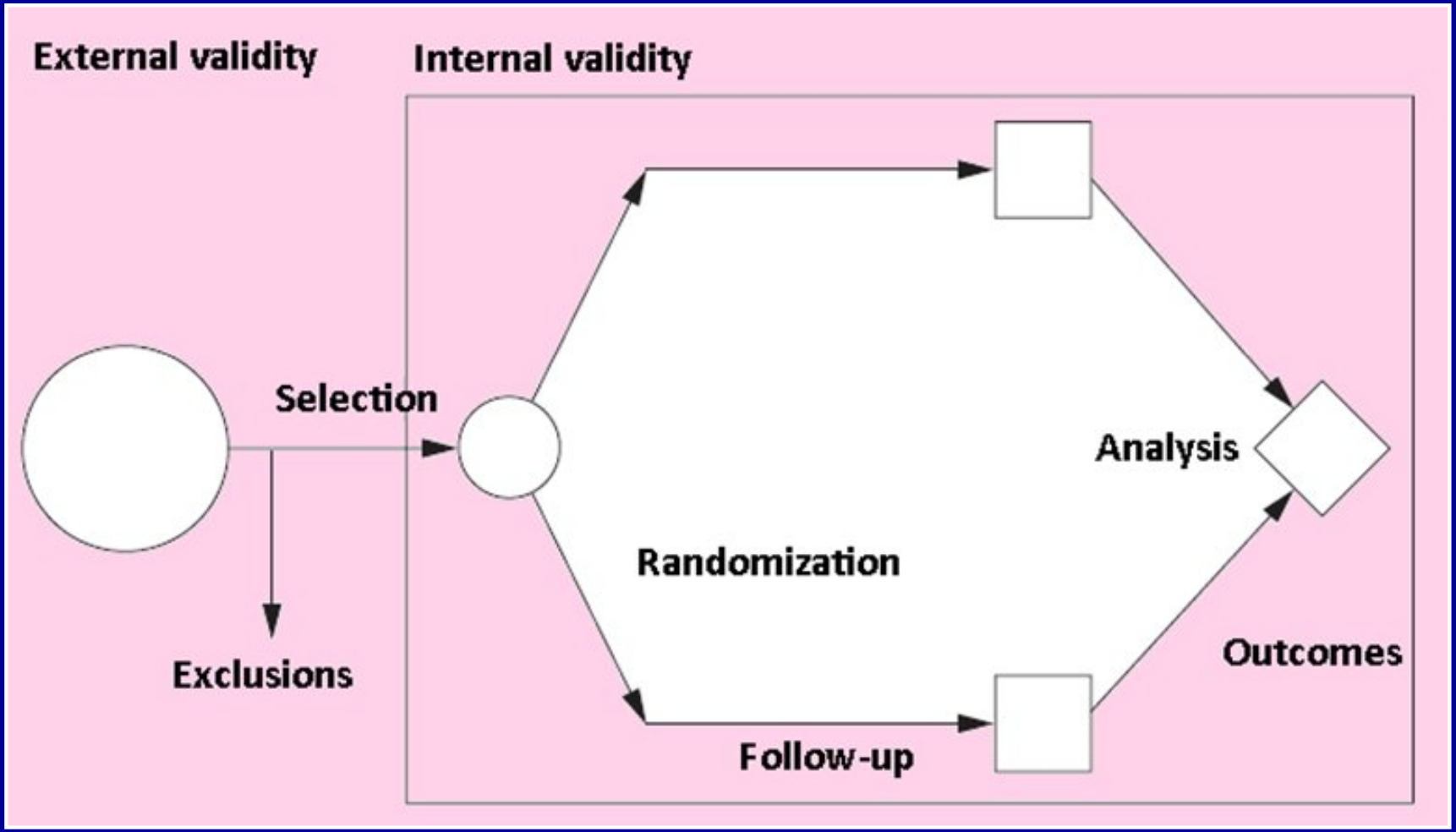
It is very difficult to make a judgment if statistics used in a study are appropriate & applied correctly

Furberg BD & Furberg CD. Evaluating clinical research. Springer Science & Business Media , 1st ed, 2007.

Basic understanding of medical statistics will enable us to detect the more obvious errors

Wang D, Bakhai A. Clinical trials: practical guide to design, analysis, & reporting. Remedica, London, 1st Edition, 2006.

❼ Applicability of results to your patients



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

External validity

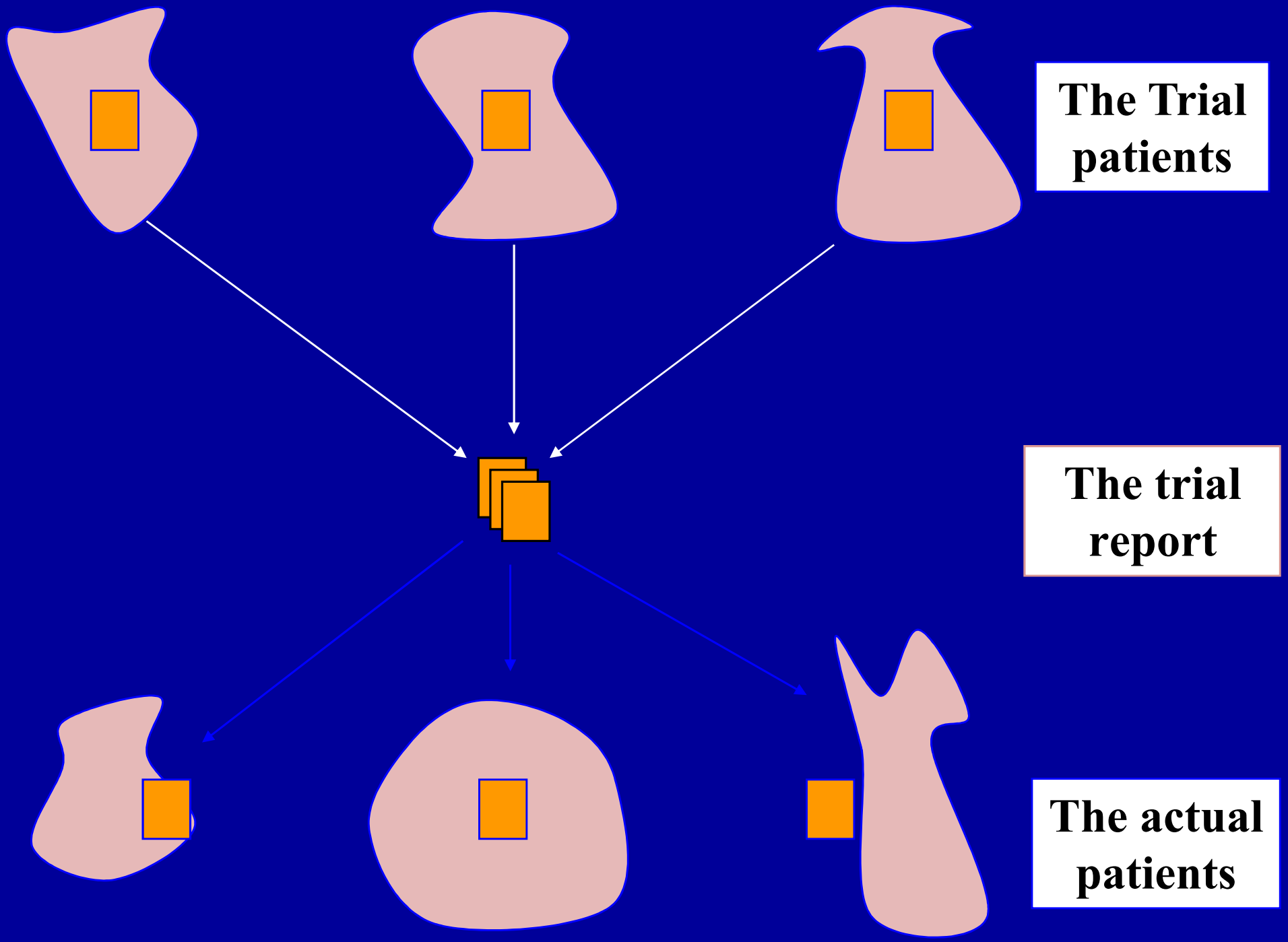
Applicability of results to your patients

Issues needed to consider before deciding to incorporate research evidence into clinical practice

- Similarity of study population to your population
- Benefit versus harm
- Patients preferences
- Availability
- Costs

* Guyatt G, et al. User's guide to the medical literature. Essentials of evidence based clinical practice. Mc Graw Hill, 2nd edition, 2008.

The problem of applying trial results

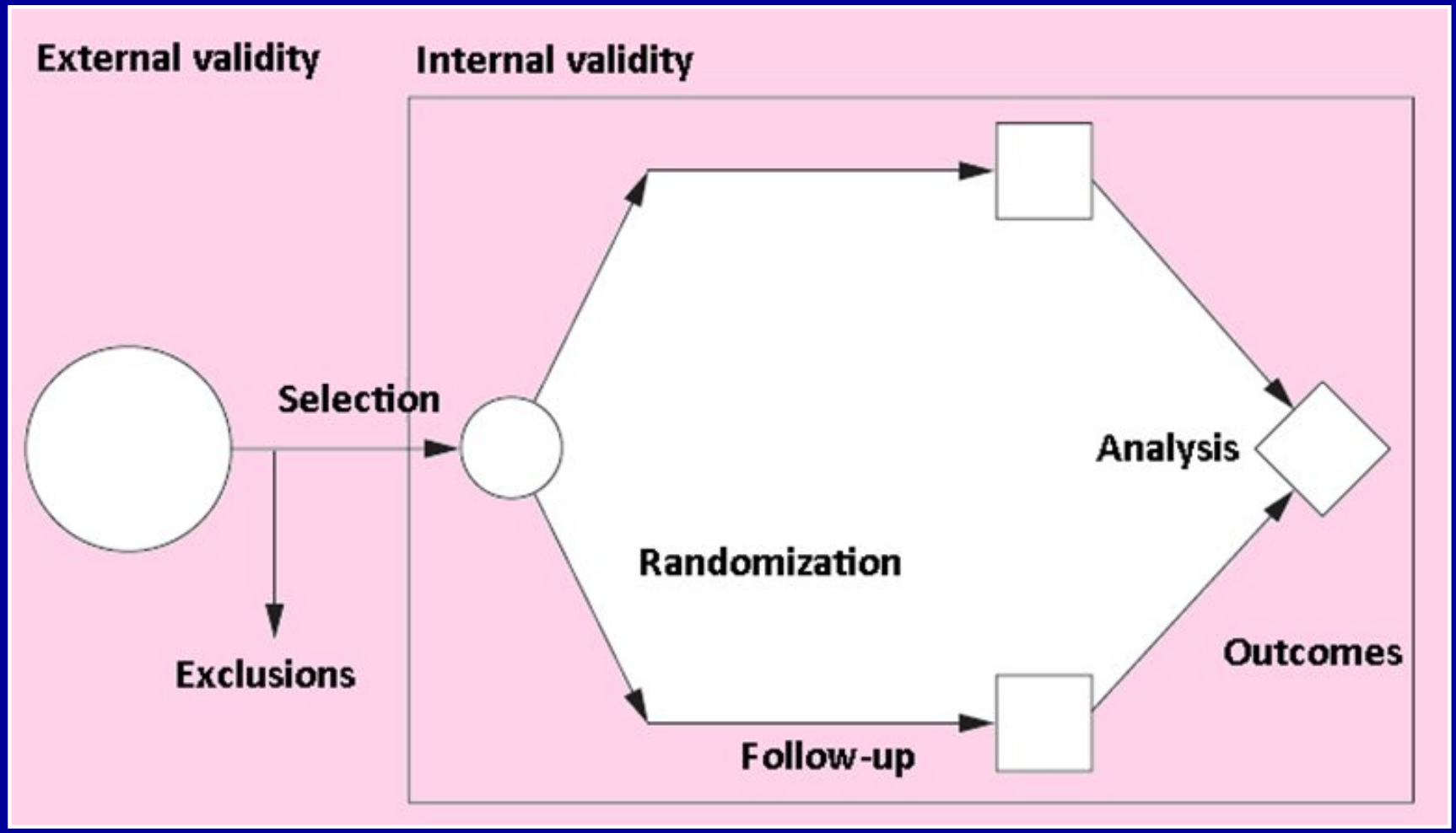


Critical appraisal of a RCT

Glasziou P et al. BMJ 2004 ; 328 : 39 - 41.

Furberg BD & Furberg CD. Evaluating clinical research.
Springer Science & Business Media – First Edition – New York – 2007.

Internal & external validity of a RCT



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 - 69.

Critical appraisal of a RCT

- **Internal validity of a trial**
  - Randomization
  - Blinding (Masking)
  - Follow-up
  - Outcomes
  - Analysis
  - Biases
- **External validity of a trial (generalizability)**
  - Applicability of results to your patients

Bias

- Difference between the study results & the truth
- Of course, we can never know the truth, but we try to come as close as possible by performing & using well-designed & well executed studies
- **Non-systematic bias** (random error or **chance**)
  Occurs to similar extent in all subjects for both group
  Predictable – Less important than systematic bias
- **Systematic bias** (non-random error)
  Most serious type of bias: under or over-estimation

* Guyatt G, et al. User's guide to the medical literature. Essentials of evidence based clinical practice. Mc Graw Hill, 2nd edition, 2008.

Main types of biases in RCTs

Biases	Types
During planning phase of a RCT	Choice-of-question bias Regulation bias Wrong design bias
During course of a RCT	Selection bias Observation bias Population choice bias Intervention choice bias Control group bias Outcome choice bias
During reporting of a RCT	Withdrawal bias Selective reporting bias Fraud bias

Jadad AR, Enkin MW. Randomized control trials. Blackwell Publishing, 2nd ed, 2007.

Fraud bias

John Darsee (Harvard researcher in cardiology)

- Fabricated data in a study on dogs in 1981
- Fabricated data during his:
  - Undergraduate days [**Notre Dame University,** (1966-70)]
  - Residency & fellowship [**Emory University,** (1974-79)]
  - Fellowship [**Brigham & Women's**, Harvard, (1979-81)]
- **> 100 papers & abstracts** most in prestigious journals
- His coauthors had too little contact with the research
  Listed over their objections (had been helpful in the past)

Lessons learned from the Darsee's affair

1. Little can be done to stop unscrupulous scientist even when he collaborates with knowledgeable colleagues
2. Inability of **peer review** to detect the fraud
3. Need for explicit guidelines & oversight for collection, maintenance, & analysis of data in clinical trials
4. Focus on responsibilities & contributions of **coauthors**
5. Misconduct investigations may need to **examine a researcher's entire work** over many years

Lock S, Wells F, Farthing M. Fraud & misconduct in biomedical research. BMJ Publishing Group, London, 3rd Edition, 2001.

One of the lessons learned from Darsee's case

'Once a crook, often always a crook'

Darsee was found to have had a long history of faking his results in different projects & in different settings

Lock S, Wells F, Farthing M. Fraud & misconduct in biomedical research. BMJ Publishing Group, London, 3rd Edition, 2001.

Existing tools to assess trial quality

- Several components grouped in

  Scales Each item scored numerically
  Overall quality score is generated

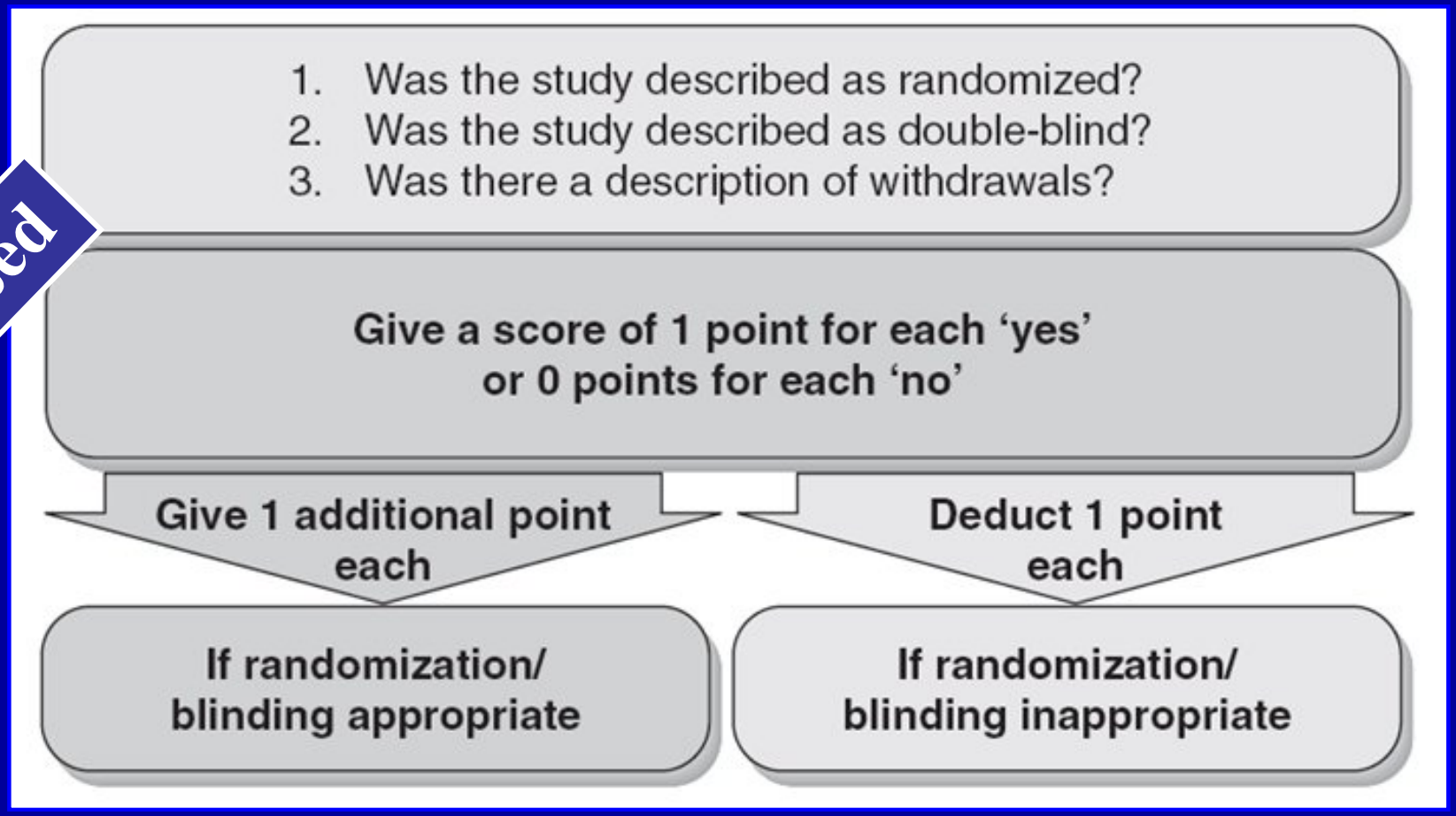
  Checklists Components evaluated separately
  No numerical scores

- Systematic search of literature in 1995 identified
  25 scales & **9 checklists** for assessing trial quality*

* Moher D et all. Controlled clinical trials 1995 ; 16 : 62 – 73.

The Jadad scale

Widely used



Scores: 0 - 5 points – Poor quality if ≤ 2 points

Jadad AR, Enkin MW. Randomized control trials.
Blackwell Publishing, 2nd Ed, 2007.

Appraising a RCT (checklist) – 1

Are the results valid?	
At start of trial	❶ Were the patients **randomized**? ❷ Was the randomization **concealed**? ❸ Similar prognostic factors in 2 groups?
During trial	❹ Was trial **blinded** & to what extent?
At end of trial	❺ Was **follow-up** complete? ❻ Was **ITT** principle applied? ❼ Was the trial **stopped early**?

Guyatt G, et al. User's guide to the medical literature.
Essentials of evidence based clinical practice. Mc Graw Hill, 2nd ed, 2008.

Appraising a RCT (checklist) – 2

What are the results?

8- How **large** was the treatment effect?

9- How **precise** was estimate of treatment effect (**CI**)?

How can I apply the results to patient care?

10- Were the study patients **similar** to my patient?

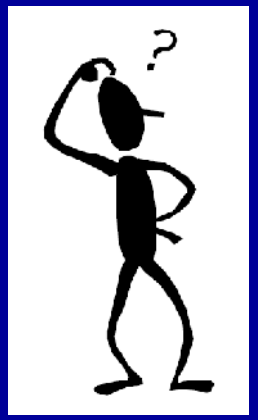
11- Were all patient-**important outcomes** considered?

12- Are the likely treatment benefits worth **harm & cost**?

Guyatt G, et al. User's guide to the medical literature.
Essentials of evidence based clinical practice. Mc Graw Hill, 2nd ed, 2008.

Scales or checklists?

No consensus on which is preferable



	Quality assessment in systematic reviews	
	Medical journals	**CDSR***
Number of SR	78 SR in 204 journals	36 SR
Checklists	20/78 (26%)	92 %
Scales	52/78 (67%)	None

•**CDSR**: **C**ochrane **D**atabase of **S**ystematic **R**eviews
Moher D et all. Health Technol Assess 1999 ; **3 (12).**

Improving quality of reports

RCTs	Meta-analysis	Diagnostic accuracy study
CONSORT*	**QUOROM****	**STARD*****
Consolidated **S**tandards **o**f **R**eporting **T**rials	**Qu**ality **o**f **R**eporting of **M**eta-analyses	**Sta**ndards for **R**eporting of **D**iagnostic Accuracy

* Altman DG et al. Ann Intern Med 2001 ; 134 : 663 - 94.

** Moher D et al. Lancet 1999 ; 354 : 1896 - 900.

*** Bossuyt PM et all. BMJ 2003; 326 : 41 – 44.

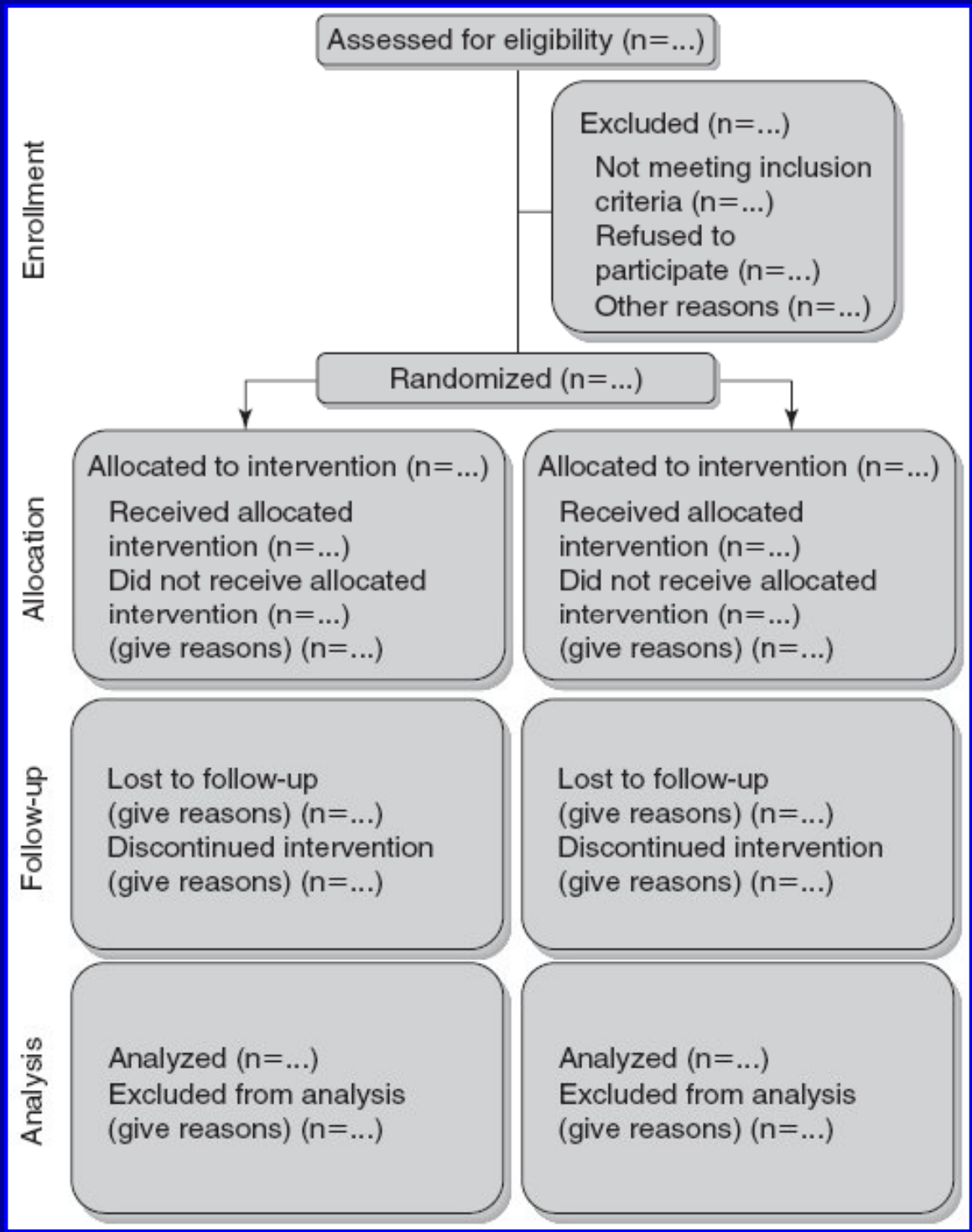
CONSORT statement

Targeted authors of trial reports rather than readers

- **Experts** Clinical epidemiologists, journal editors, & biostatisticians published CONSORT statement
- **Aim** Improve standard of written reports of RCTs
- **Results** Latest version of CONSORT statement includes[2]
  Flow diagram: Patients progress through a trial
  Checklist: 22 items

[1] Begg C, et all. JAMA 1996 ;276 (63): 7 – 9.
[2] Moher D, et al. CMAJ 2004 ; 171 : 349 – 350.

Flow diagram of a RCT



Ann Intern Med 2001 ; 134 : 657 – 662.

CONSORT statement

Paper Section & Topic		Item	Descriptor	Reported on Page No
Title & abstract		1	How participants allocated to interventions	
Introduction background		2	Scientific background	
Methods	Participants	3	Criteria for participants, settings, locations	
	Interventions	4	Details of interventions for each group	
	Objectives	5	Specific objectives & hypotheses	
	Outcomes	6	Defined **primary & secondary outcomes**	
	Sample size	7	How **sample size** was determined?	
	Randomization	8-9-10	**Allocation concealment**, implementation	
	Blinding (masking)	11	Whether or not blinding applied	
	Statistical methods	12	**Statistical methods** used	
Results	Participant flow	13	**Flow diagram** strongly recommended	
	Recruitment	14	Periods of recruitment & **follow-up**	
	Baseline data	15	**Baseline characteristics** of each group	
	Numbers analyzed	16	No of participants in each group	
	Outcomes, estimation	17	Summary of results with **95% CI**	
	Ancillary analyses	18	Subgroup & adjusted analyses	
	Adverse events	19	**All important adverse events**	
Comment	Interpretation	20	Interpretation of the results	
	Generalizability	21	**External validity** of trial findings	
	Overall evidence	22	General interpretation of results	

Ann Intern Med 2001 ; 134 : 657 - 662.

Reasons for doing RCTs

- Only study design that can prove causation
- Required by FDA (and others) for **new drugs** and some devices
- Most influential to clinical practice

Disadvantages of RCTs

- Expensive: typically in $ millions
- Time consuming: typically years
- Can only answer a single question
- May not apply to some patients in practice
- May not be practical
- Generally difficult to get funded
- Organizationally complex

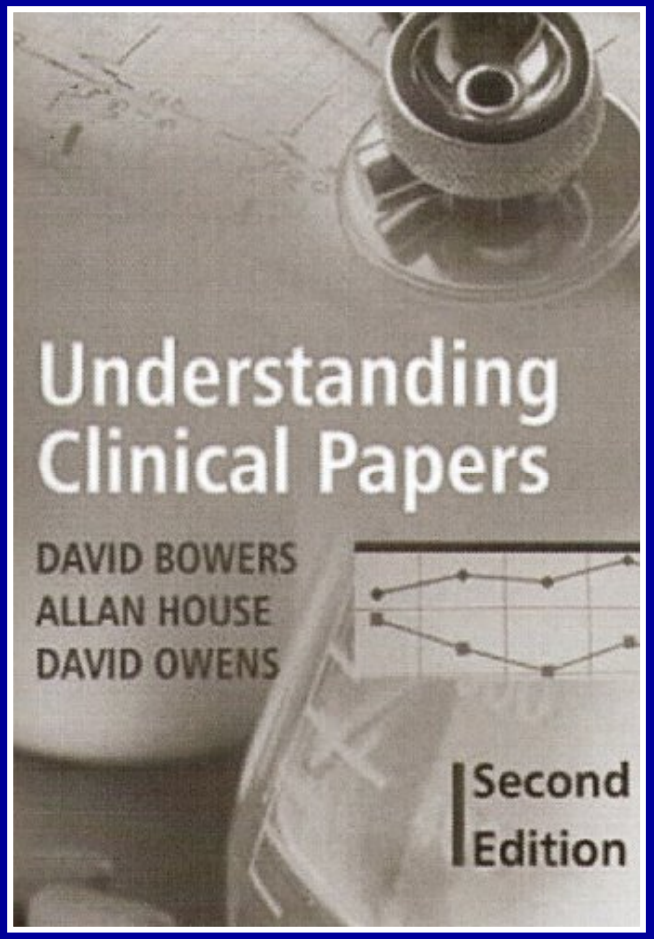
Carefully conducted observational studies may provide more evidence than poor RCTs*

Unfortunately, a perfect trial can only exist in our imagination**

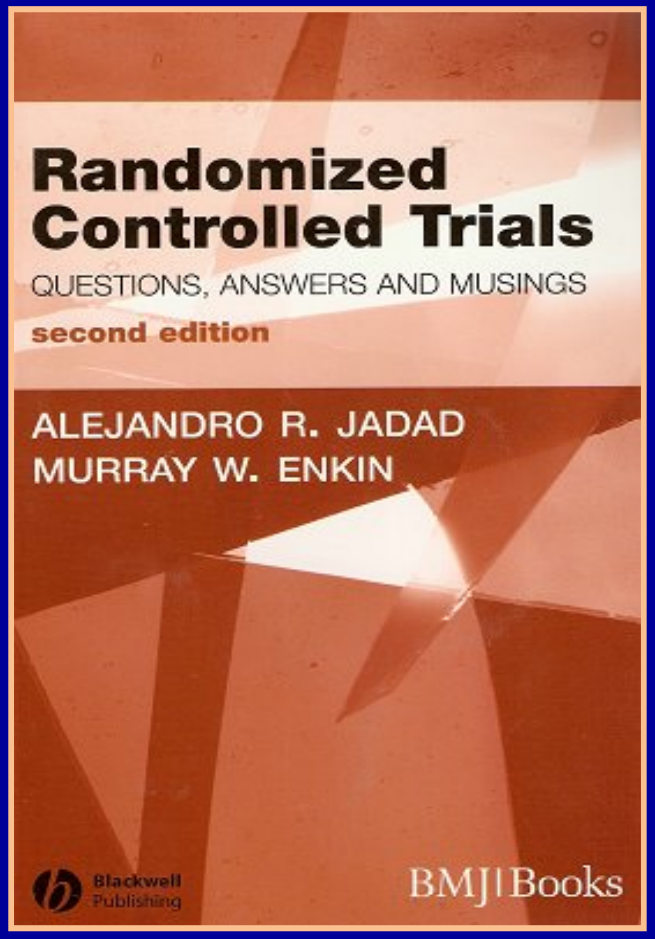
* Guyatt G, et al. User's guide to the medical literature. Essentials of evidence based clinical practice. Mc Graw Hill, 2nd edition, 2008.

** Jadad AR, Enkin MW. Randomized control trials. Blackwell Publishing, 2nd ed, 2007.

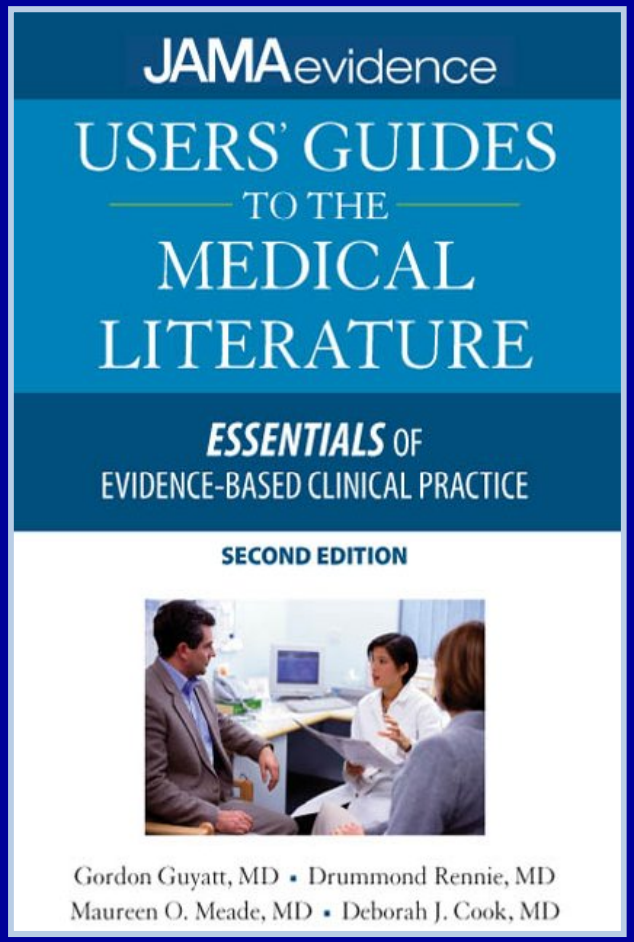
References



John Wiley & Sons
2006

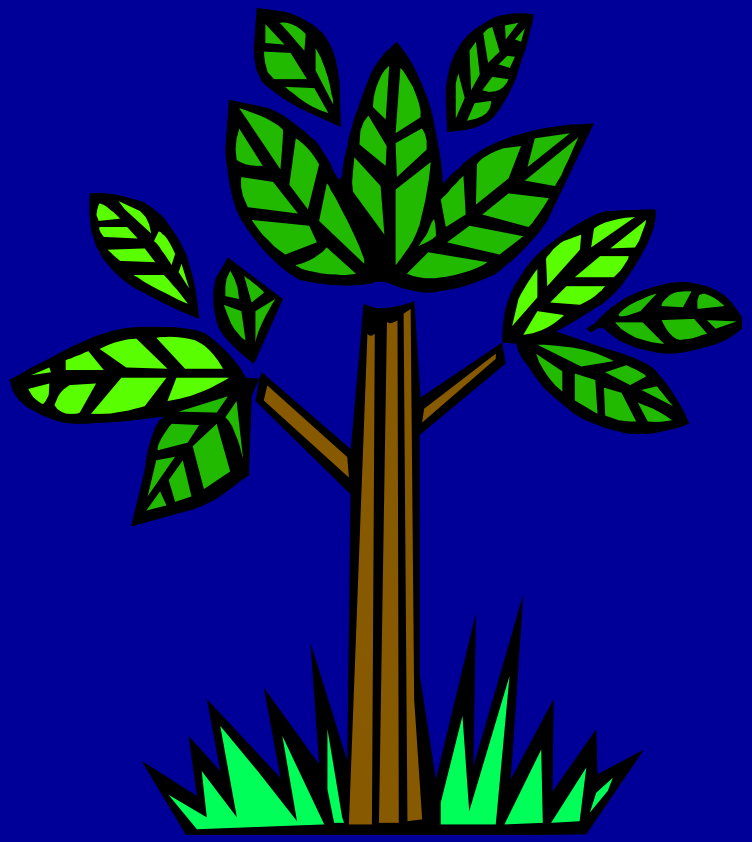


Blackwell Publishing
2007



Mc Graw Hill
2008

Thank You



Thank You

Thank You

Types of RCTs

RCTs	Types
RCTs according to how participants are exposed to the interventions	Parallel trials Factorial trials Cross-over trials
RCTs exploring different aspects of the interventions they evaluate	Efficacy & effectiveness trials Equivalence trials Phase III trial
RCTs by unit of analysis	Body part Individual Group
RCTs according to the number of participants	Fixed to variable sample size N-of-1 trials to mega-trials
RCTs according to whether investigators know which intervention is being assessed	Open trials Blinded trials
RCTs that take into account non-randomized individuals & participants' preferences	Zelen's design Comprehensive cohort design Wennberg's design

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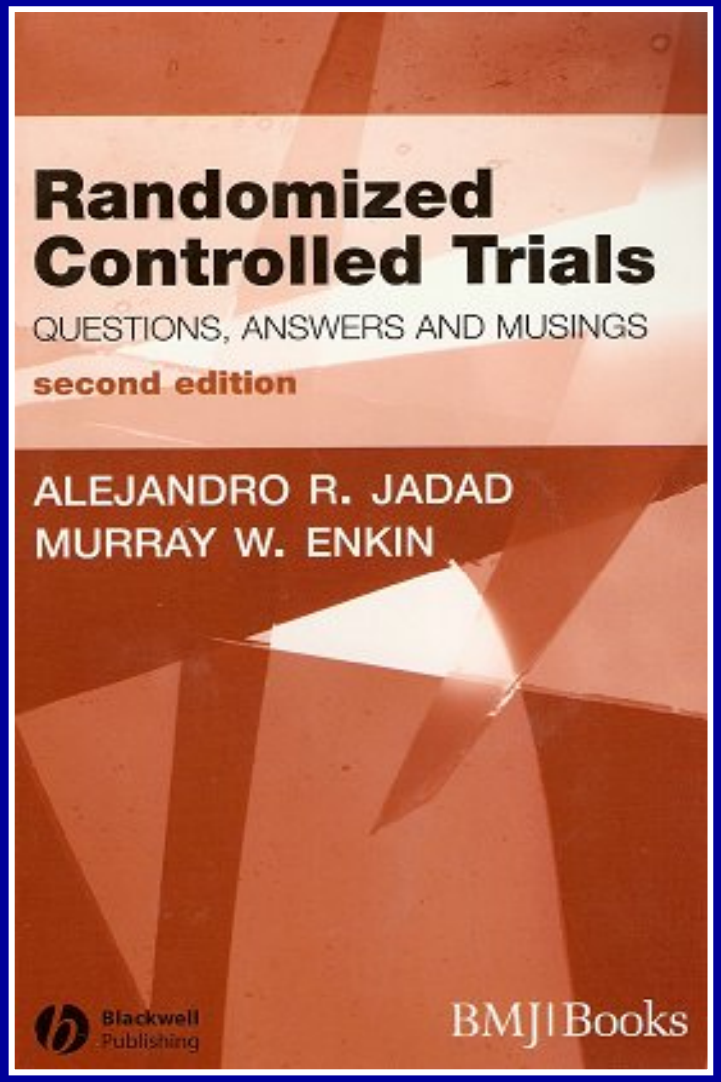
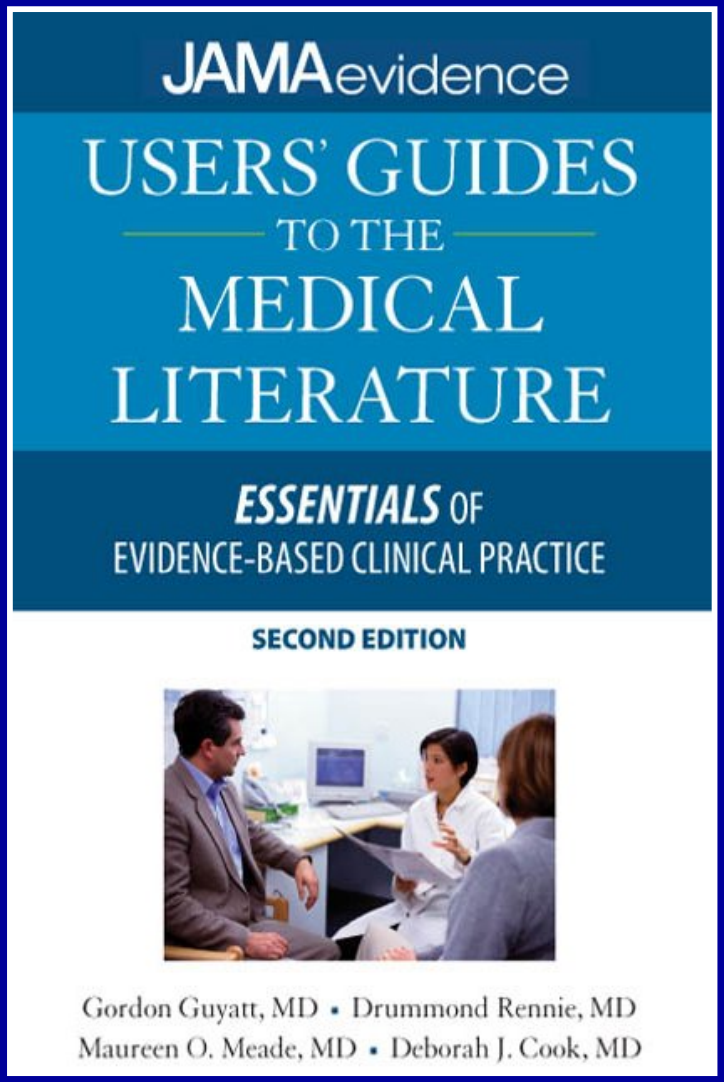
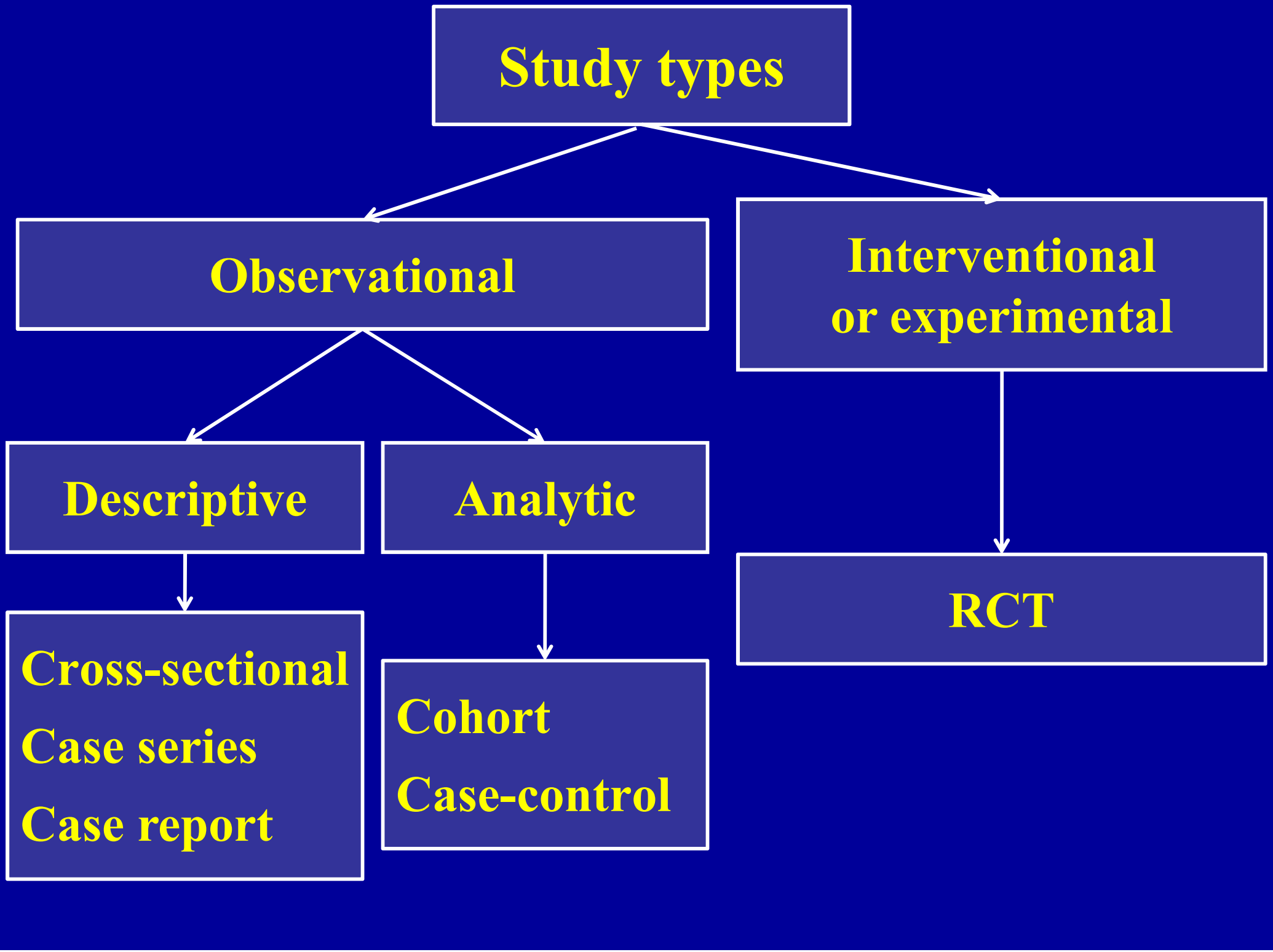


Blackwell Publishing
2007



Mc Graw Hill
2008


Study types
Observational
Interventional or experimental
Descriptive
Analytic
RCT
Cross-sectional
Case series
Case report
Cohort
Case-control

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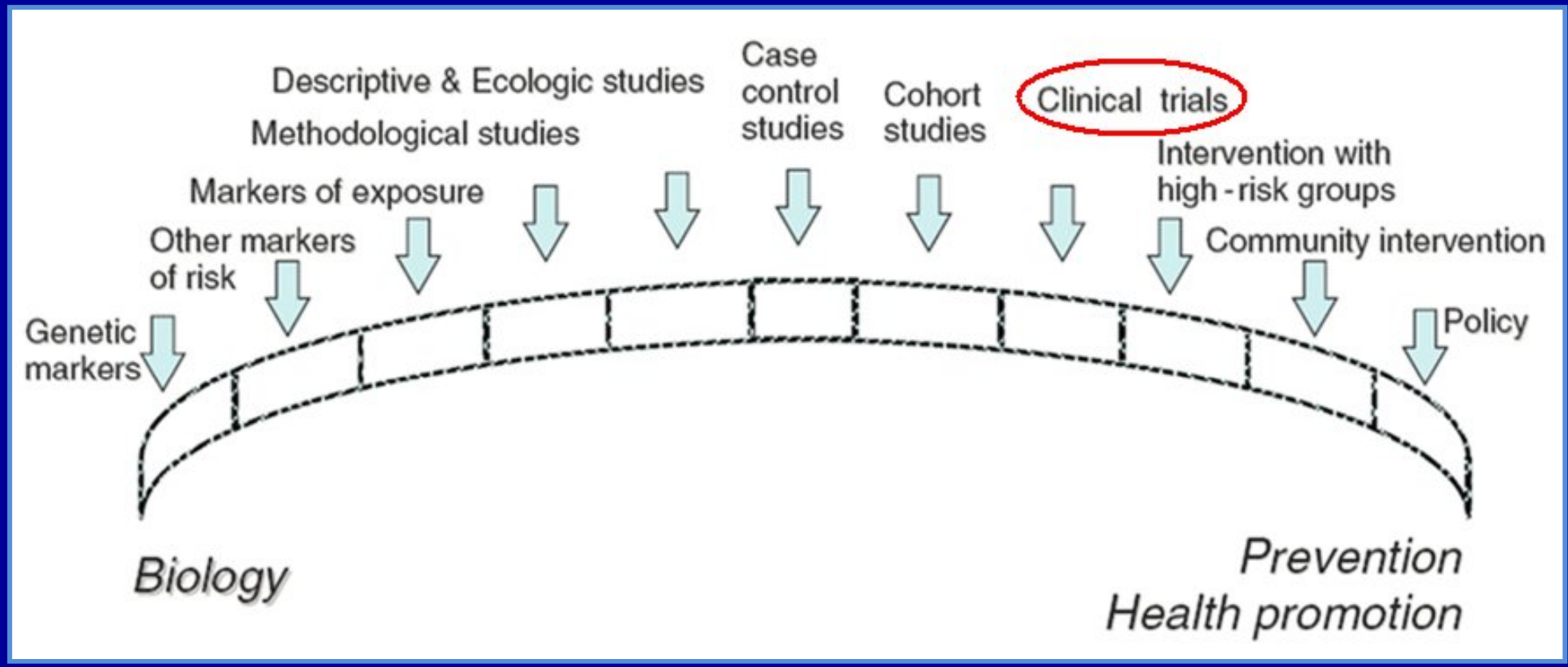
The clinical research bridge



The broad range that encompasses the term "clinical research"

Glasser SP. Essentials of clinical research. Springer, 1st edition, 2008

Table of Random Numbers

Table C4. 1000 Random Digits

07048	52841	54969	87057	30570	50494	29936	93967	10641	79871
09165	56926	17294	03803	31755	11321	33681	12997	17625	25954
35654	69761	83791	63371	28189	19944	04514	56533	89108	27861
79065	63956	39443	30373	55571	00919	15377	36851	28318	40846
27969	74368	77782	88616	06368	07345	00725	81221	78417	37992
47528	70548	25078	80729	27806	42877	80287	21759	61980	52447
65694	95760	64031	24046	77606	91163	51492	20958	18384	49840
24253	39427	80642	36718	92164	77732	69754	01291	53704	33054
34302	60309	27186	22418	59962	13934	67591	17476	21559	73437
76809	84341	74012	50947	83214	19967	44219	75929	13182	34858
85183	35958	04301	49628	91493	66103	65699	04241	82441	38112
27541	79187	99777	22894	83283	56218	86183	74497	21070	78935
74188	09083	54938	79920	27158	24864	31116	33173	43032	52000
13270	57457	30968	65978	67679	91216	47969	39204	46030	93954
89150	53922	40537	23169	46948	05519	72171	85417	31580	98102
49980	44551	99908	46115	92508	77184	44556	69725	42878	60298
26810	40280	15387	30976	15478	77703	34109	02682	52877	36755
35056	23942	42645	67063	44118	46433	83172	95689	60923	32769
09873	65959	77912	70059	07704	16015	57527	09818	84379	35903
40806	30051	54251	73489	47215	90651	90083	21019	63860	41369

Random number

Numbers usually have two or more digits

- Select **starting point in the table** (beginning, end, any point of table by a pencil dropped with the eyes closed)
- Select **direction of reading table** (upward - downward)
- Odd numbers: group A – even numbers: group B
  From 01 – 49: group A, from 50 – 99: group B
- Numbers with four digits
  Select position of numbers that determine allocation
  Choose last two digits, or first two, or first & third

Stratified randomization

- First,
  Identify prognostic factors (or 'strata') known to be related to outcome of the study
- Second,
  Produce separate block randomization lists for different combinations of prognostic factors

It is not practical to stratify on more than one or perhaps two variables

Chemotherapy of breast cancer

- **Important prognostic factors:**
  Number of metastatic LN: absent, < 4, ≥ 4
- **Set of blocks could be generated as follow:**
  Breast cancer & no metastatic LN
  Breast cancer & < 4 metastatic LN
  Breast cancer & ≥ 4 metastatic LN

⇩

Separate block randomization lists for different combinations of prognostic factors

Minimization Method - 1

3 stratification factors: sex (2), age (3), disease stage (3)

		Treatment A	Treatment B
Sex	Male	16	14
	Female	10	10
Age	< 40	13	12
	41 – 60	9	6
	> 60	4	6
Disease	Stage I	6	4
	Stage II	13	16
	Stage III	7	4
Total		26	24

50 patients enrolled

the 51st patient is male, age 63, & stage III

Minimization Method - 2

Consider lines from the precedent table for that patient's stratification levels only

	Treatment A	Treatment B	Sign of difference
Male	16	14	+
Age ≥ 60	4	6	–
Stage III	7	4	+
Total	27	24	2 A, 1 B –

Minimization Method - 3

2 possible criteria

Count only the sign of the difference in each category
Treatment t A is “ahead” in 2 categories out of 3
Assign patient to treatment B

Add the total overall categories (27 As vs 24 Bs)
Treatment A is “ahead,” assign patient to treatment B

Usually agree

Unequal randomization

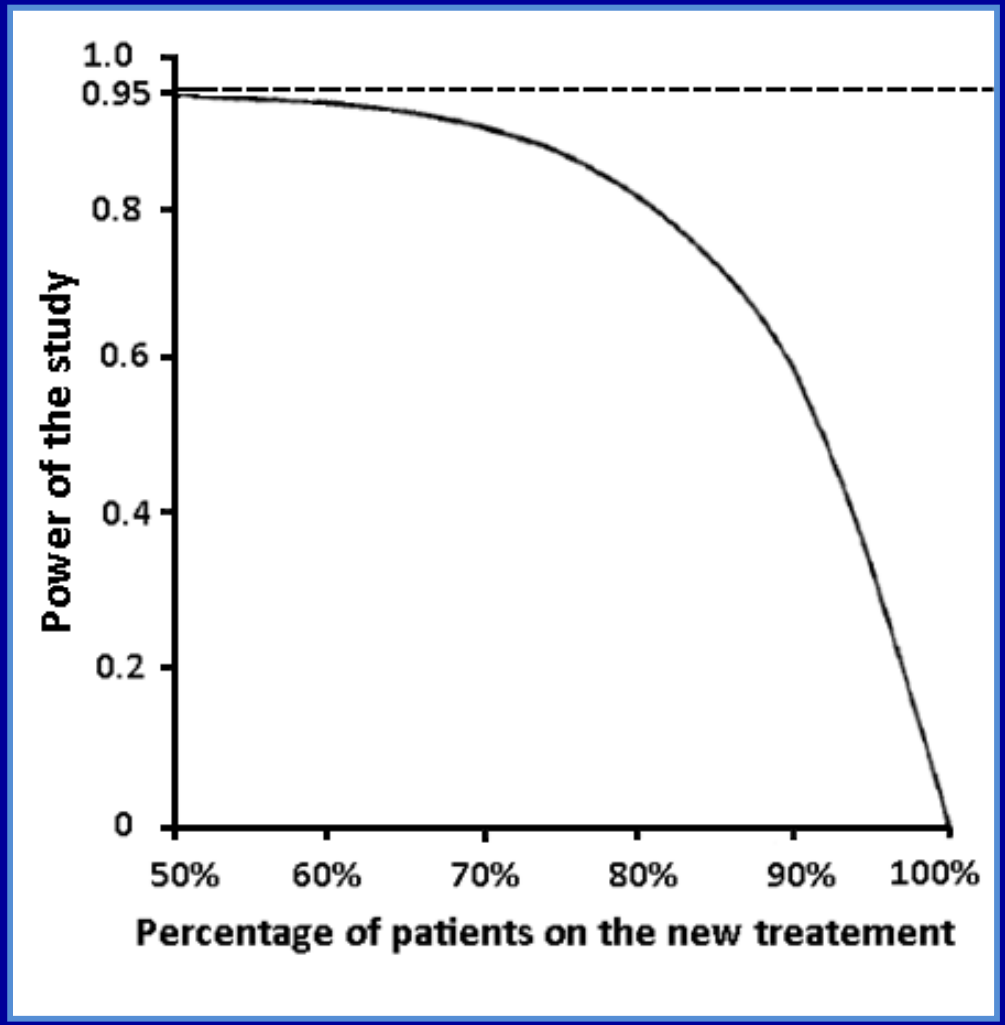
- Trial comparing a new treatment against a standard one
- Investigator more interested in obtaining information about the new treatment than for the old, where such characteristics are likely to be well known
- **Unbalanced design**

  Allocating larger number of patients to new treatment group

  Power decreases slowly as proportion of new tt increases

Everitt BS, Pickles A. Statistical aspects of the design & analysis of clinical trials. Imperial College Press, London, 2nd edition, 2004.

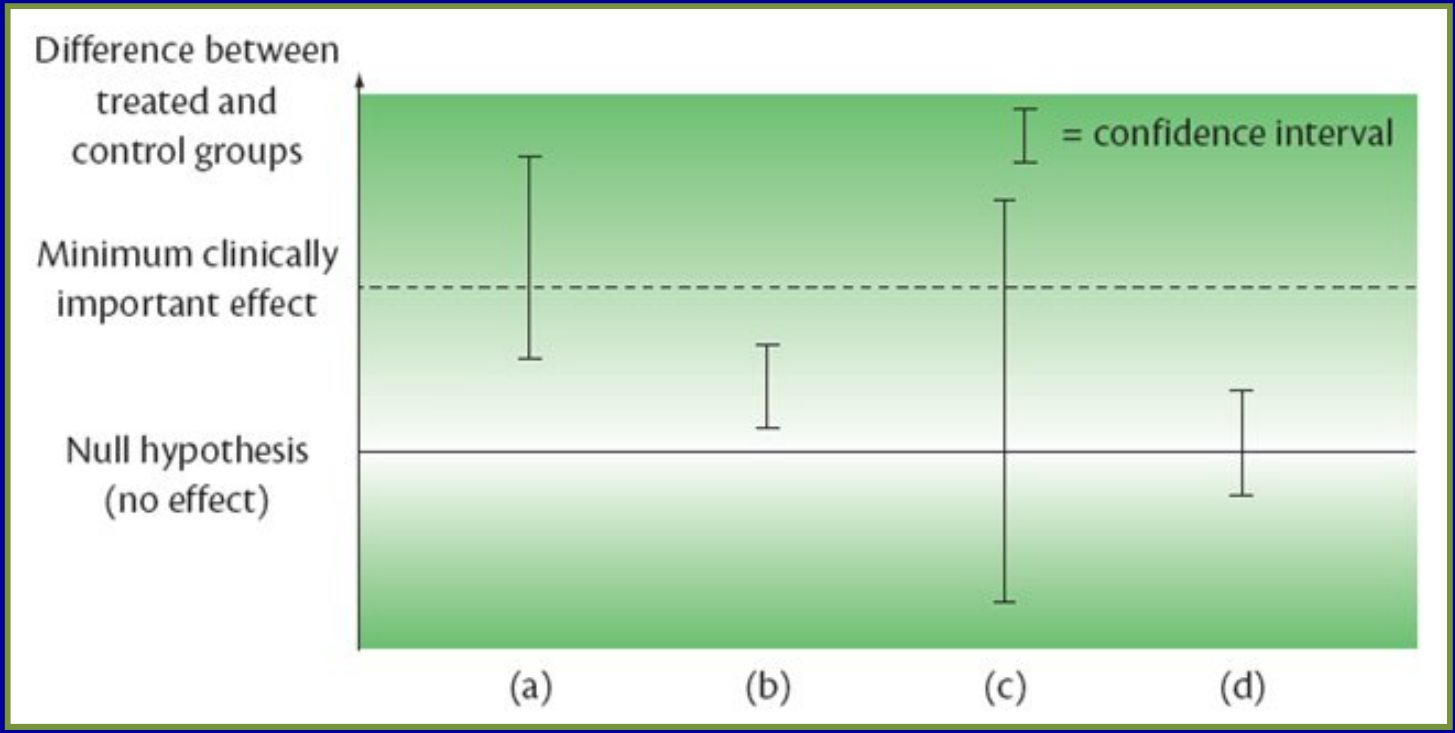
Unequal randomization & power



Reduction in power of a trial as proportion of new tt increased

Everitt BS, Pickles A. Statistical aspects of the design & analysis of clinical trials. Imperial College Press, London, 2nd edition, 2004.

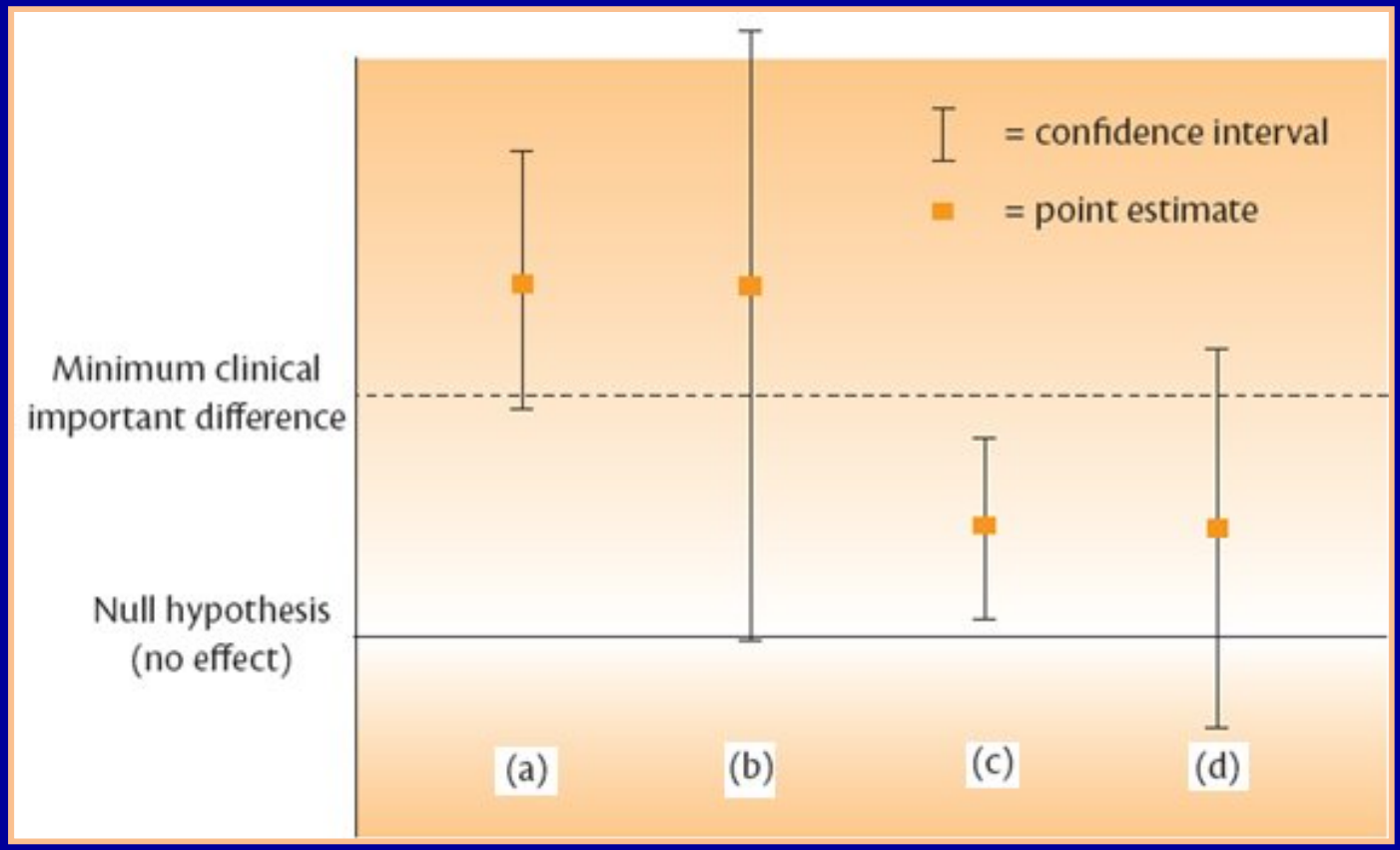
Statistical & clinical significance in CI



(a) Statistically significant – clinically important
(b) Statistically significant – not clinically important
(c) Not statistically significant – inconclusive
(d) Not statistically significant – true negative

Glasziou P, Del Mar C & Salisbury J. Evidence based medicine Workbook. BMJ Publishing Group, 1st edition, London, 2003.

Statistical & clinical significance of CI



(a) Statistically significant, clinically important
(b) Not statistically significant, clinically important
(c) Statistically significant, not clinically important
(d) Not statistically significant, not clinically important

Main types of biases in RCTs

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During the dissemination of a RCT	Publication bias Language bias Time lag bias

Jadad AR, Enkin MW. Randomized control trials.
Blackwell Publishing, 2nd ed, 2007.

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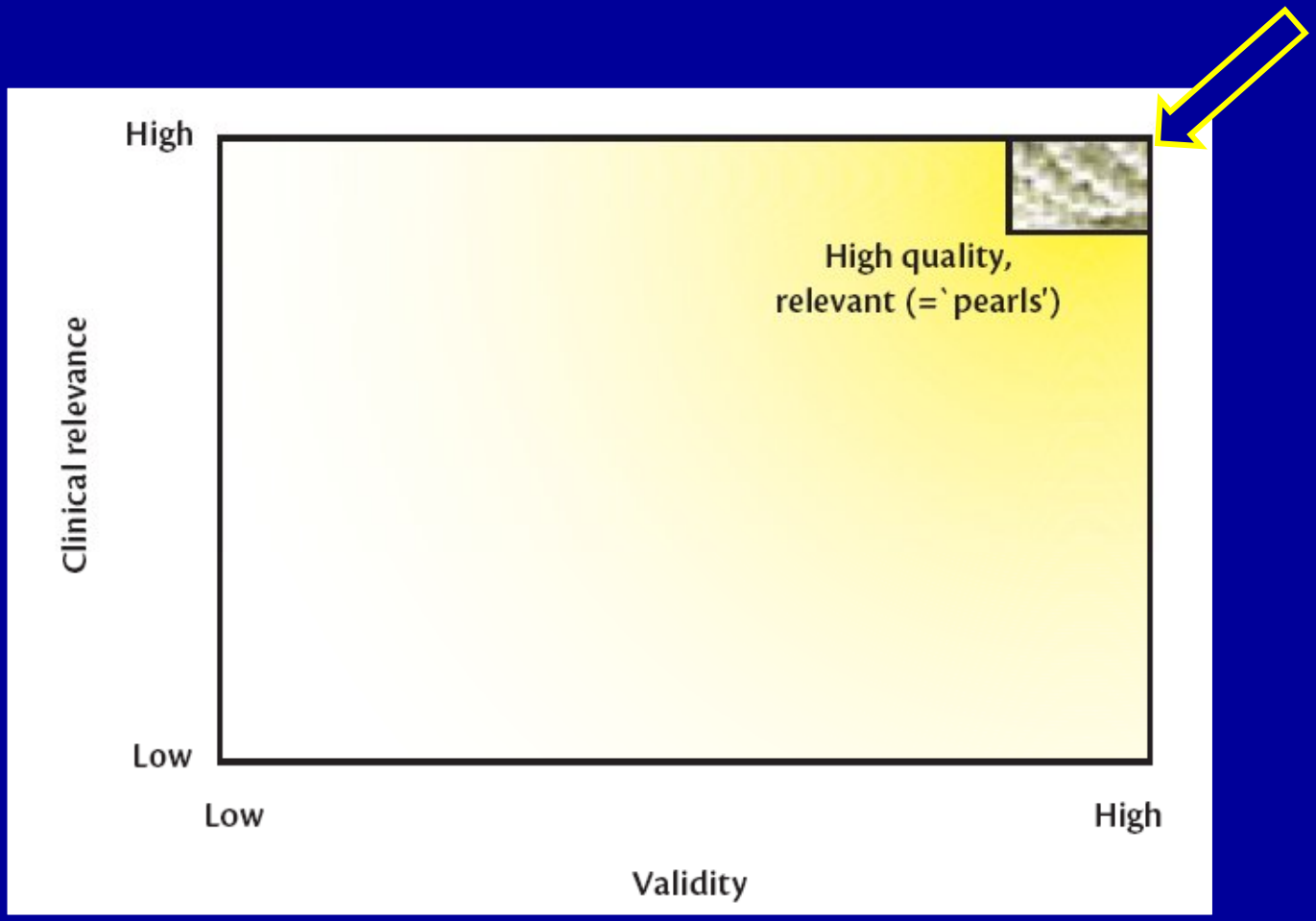
Trials of different phases in development of drug

Phase	Objective
I	Earliest types of studies Small numbers of healthy subjects Pharmacodynamics, pharmacokinetics & toxicity
II	Carried out in patients Find best dose of drug & to investigate safety
III	Major trials aimed at demonstrating efficacy Registration of a new product will be based on
IV	Carried out after registration of a product Marketing purposes Gain broader experience with using the new product

Day S. Dictionary for Clinical Trials. Chichester: John Wiley & Sons (1999).

High quality/relevant data – Pearls



Pearls selected from the rest of lower quality literature

Glasziou P, Del Mar C & Salisbury J. Evidence based medicine Workbook. BMJ Publishing Group, 1st ed, London, 2003.

Ways to reduce bias in studies of therapy

Source of Bias	Strategy to reduce Bias
❶Differences at the start of study	
Control & tt group differ in prognosis	Randomization ± stratification
❷Differences as study proceeds	
Placebo effects	Blinding of patients
Cointervention	Blinding of caregivers
Bias in outcome assessment	Blinding of outcome assessors
❸Differences at completion of study	
Loss to follow-up	Ensure complete follow-up
Stopping study early (large effect)	Complete study as inially planned
Patient not receiving assigned tt	Adhere to ITT principle

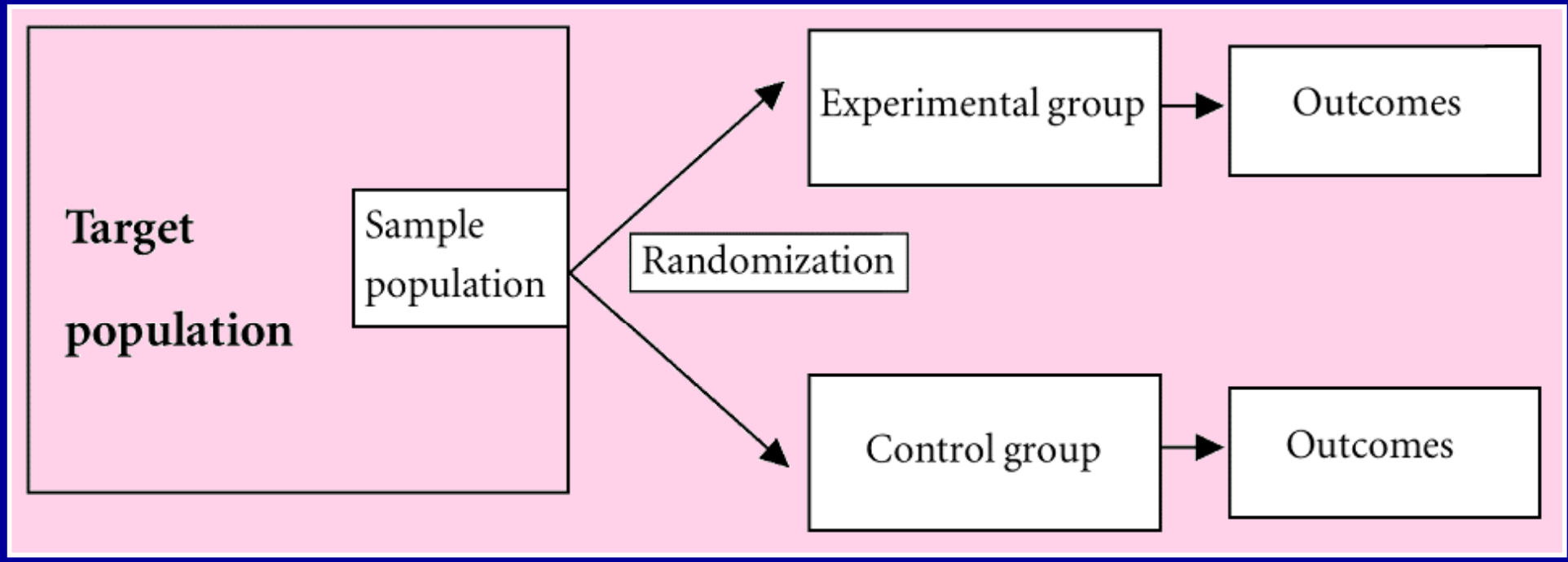
Some historical examples of treatments with dramatic effects

- Insulin for diabetes
- Blood transfusion for severe hemorrhagic shock
- Defibrillation for ventricular fibrillation
- Neostigmine for myasthenia gravis
- Tracheotomy for tracheal obstruction
- Drainage for pain associated with abscesses
- Pressure or suturing for arresting hemorrhage

Glasziou P et al. Br Med J 2007 ; 334 : 349 – 351.

Basic Structure of a RCT

Parallel Trial



Most frequently used design

McGovern D, Summerskill W, Valori R, Levi M. Key topics in EBM. BIOS Scientific Publishers, 1st Edition, Oxford, 2001.

Appraising a RCT (10 questions)

- Did the study ask a clearly focused question?
- Was the study an RCT and was it appropriately so?
- Were participants appropriately allocated to intervention and control groups?
- Were participants, staff, and study personnel blind to participants' study groups?
- Were all the participants who entered the trial accounted for at its conclusion?
- Were participants in all groups followed up and data collected in the same way?
- Did the study have enough participants to minimise the play of chance?
- How are the results presented and what are the main results?
- How precise are the results?
- Were all important outcomes considered and can the results be applied to your local population?

Critical Appraisal Skills Program. Appraisal tools. Oxford, UK, http://www.phru.nhs.uk/casp/rcts.htm (accessed 8 December 2004).

First RCT in the United States

1951

NIH started a study of adrenocorticotropic hormone (ACTH), cortisone & aspirin in the treatment of rheumatic heart disease*

* Rheumatic Fever Working Party. Circulation 1960 ; **22 :** 505 – 15.

Ethical principles of research

- All research should be approved by an **ethics committee**
- Study will justify any risk or inconvenience to the subjects
- Researchers are informed of study purpose & must have training to conduct the study with high degree of scientific integrity
- Subjects must be free to withdraw consent at any time & withdrawal must not influence their future treatment
- Subjects must be provided with information on purpose, demands of the protocol prior to their given **informed consent**

Nuremberg Code (1946 – 1947)
Declaration of Helsinki (World Medical Association 1964 → 2002)

Trials in the next 50 years

Much simpler & much larger

- **Large simple RCT**

  Moderate but worthwhile benefits will appear

  Randomize many thousands in breast & intestinal cancer

  Randomize tens of thousands in stroke & heart disease

- Design trials that are extremely **simple & flexible**

  Simplify entry criteria by use of **uncertainty principle**

  Simplify treatments

  Simplify enormously data requirements

Peto R, Baigent C. BMJ 1998 ; 317 : 1170 - 1.

The Uncertainty Principle

- A patient can be **entered** if, and only if, the responsible clinician is substantially uncertain which of the trial treatments would be most appropriate for that patient
- A patient **should not be entered** if responsible clinician or patient are, for any medical or non-medical reasons, reasonably certain that one of treatments that might be allocated would be inappropriate for this patient

Why a RCT?

- Main purpose is to prevent selection bias by distributing characteristics of patients that may influence the outcome randomly between the groups, so that any difference in outcome can be explained only by treatment
- Thus, there will be balancing of baseline differences between intervention groups that may affect outcome such
  - Age
  - Sex
  - Disease activity
  - Duration of disease

Patients not adhered to allocated management

- **Per protocol analysis**

  Excluding participants from analysis

  Those who adhere tend to do better than who do not

  Destroys comparison afforded by randomization

- **Intention-to treat bias**

  If effective treatment & substantial nonadherence underestimates magnitude of treatment effect

  Using protocol ensuring maximal adherence

  Run-in periods: exclude nonadherents before R

Blinding

Sometimes called masking

- **Single blind** Only patients or only investigators are ignorant of assigned treatment
- **Double blind** Patients & investigators are ignorant of assigned treatment
- **Triple blind** Patients, investigators & data evaluators are ignorant of assigned treatment

History of Streptomycin – 1

Nov 1943	Isolated by Albert Schatz – PhD student
	Pr Waksman – Rutgers University -NJ
	Developed by the American firm Merck
1945	Feldman showed effect on TB in guinea pigs
	Merck invested $3.5m in new plant
	10 other firms tried to produce the drug
July 1946	Feldman visited Britain at instigation of MRC
	Persuasive presentations in Oxford & London
	Ministry of Supply asked MRC to plan CT

Yoshioka A. BMJ 1998 ; 317 : 1220 – 3.

History of Streptomycin – 2

Oct 1946	Creation of SPM Clinical Trials Committee Marshall (chairman), Philip Hart (secretary) Bradford Hill (Statistician-Random allocation)
Nov 1946	50 kg to British government at $ 320.000 Only hope to obtain SPM through MRC BBC broadcast many emergency appeals Black market emerged
1948	BMJ report Pains to defend use of untreated control group

Yoshioka A. BMJ 1998 ; 317 : 1220 – 3.

Why is blinding/masking so important

- Vitamin C trial for prevention & treatment of common cold
- Conducted among employees at NIH
- Many of enrollees could not resist temptation to analyze the content of their blinded study medications
- Among participants who did not break the blind, mean duration of colds was similar in the two groups
- Among participants who knew they were taking vit C reported shorter cold durations than those who knew they took placebo

Furberg BD & Furberg CD. Evaluating clinical research.
Springer Science & Business Media – First Edition – New York – 2007.

Treatment Allocation by Minimization

Different principle from randomization

- First described by Taves in 1974*
- First participant is allocated at random

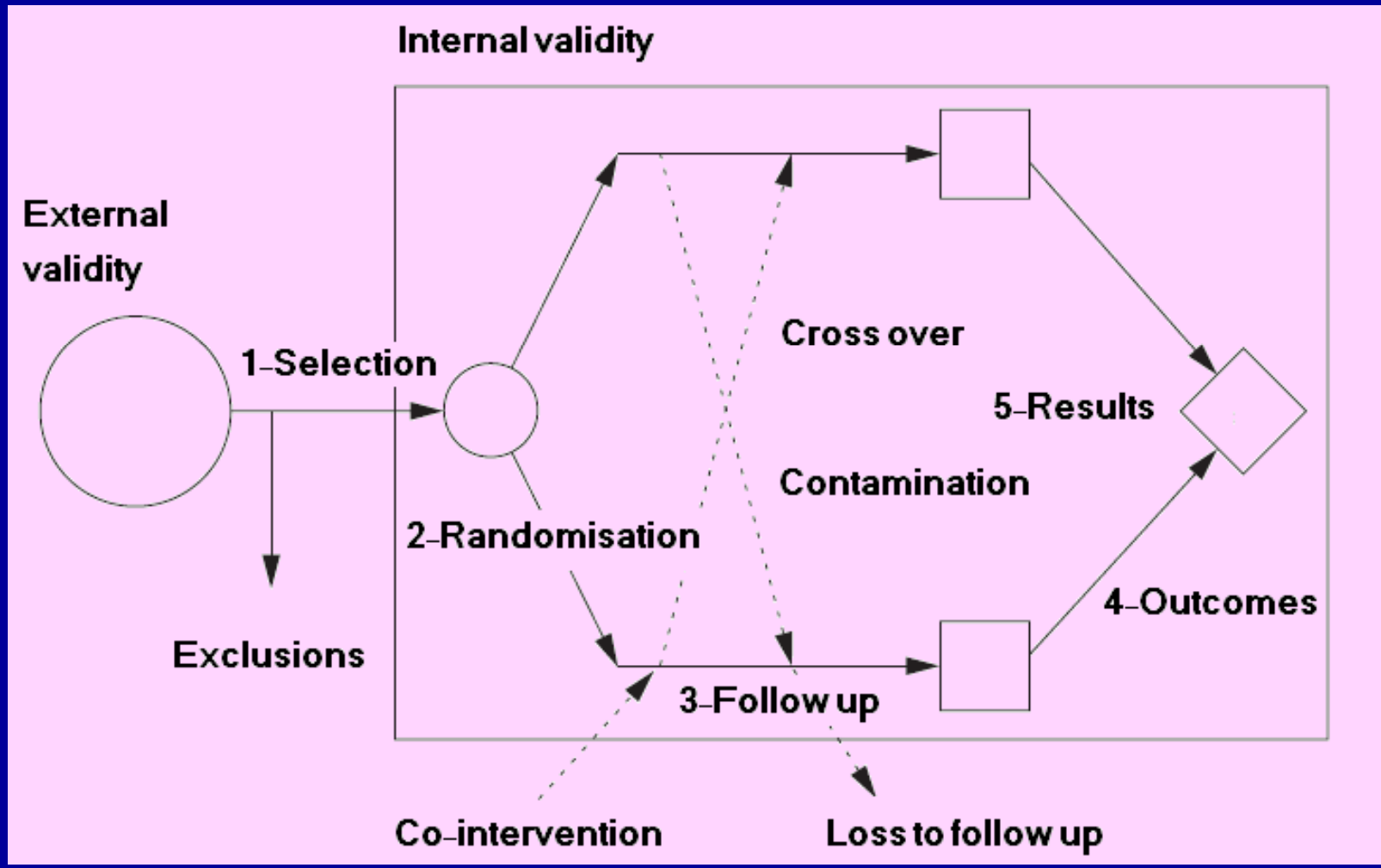
  For each subsequent participant, we determine which treatment lead to better balance between groups
- Ensure excellent balance between groups for several prognostic factors even in small samples
- Possible by hand or software (minim**, free program)

---

* Taves DR. Clin Pharmacol Therap 1974; 15 : 443 - 453

** http://www-users.york.ac.uk/zmb55/guide/minim.htm

Sources of Bias in RCTs



Wrong or Unreliable Therapeutic Answers

Wrong therapeutic answers are generated by:

- Nonrandomized "outcomes research"
- Small randomized studies
- Small meta-analyses
- Statistically inappropriate analyses
- Large scale randomized evidence
  Selective emphasis on particular trials or subgroups

Patients not adhered to allocated management

- **Per protocol analysis**

  Excluding participants from analysis

  Those who adhere tend to do better than who do not

  Destroys comparison afforded by randomization

- **Intention-to treat bias**

  If effective treatment & substantial nonadherence underestimates magnitude of treatment effect

  Using protocol ensuring maximal adherence

  Run-in periods: exclude nonadherents before R

Blinding

Sometimes called masking

- **Single blind** Participants don't know details of tt Researchers do
- **Double blind** Both participants & data collectors are ignorant of assigned treatment
- **Triple blind** Participants, data collectors, & data evaluators are all blinded

Production of streptomycin

was technically difficult

Porter RW. Chemical Engineering 1946 (Oct).

History of streptomycin

- **Nov 1943**
  Developed by American firm Merck
- **1945**
  10 other firms tried to produce SPM
- **1946**
  50 kg to British government at $ 320.000
  Only hope to obtain SPM through MRC
  BBC broadcast many emergency appeals
  Black market emerged

Porter RW. Chemical Engineering 1946 (Oct).

Treatment Allocation by Minimization

Different principle from randomization

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  For each subsequent participant, we determine which treatment lead to better balance between groups
- Ensure excellent balance between groups for several prognostic factors even in small samples
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** http://www-users.york.ac.uk/zmb55/guide/minim.htm

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- **Intention-to treat bias**

  If effective treatment & substantial nonadherence

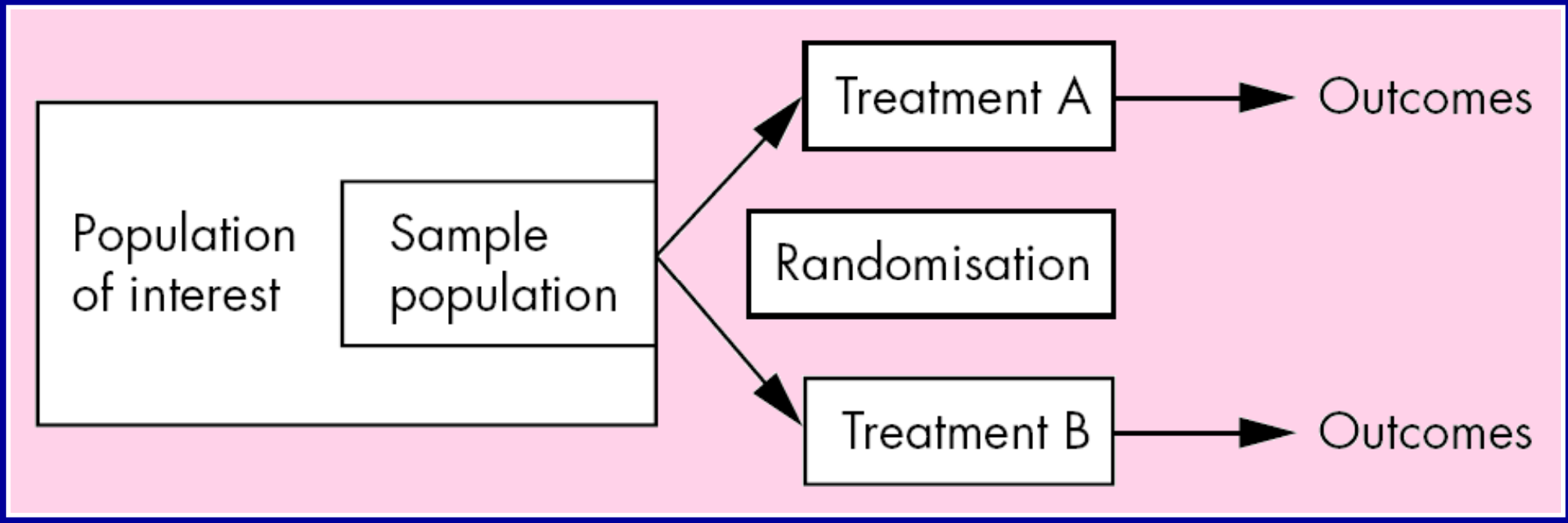
  Underestimates magnitude of treatment effect

  Using protocol ensuring maximal adherence

  Run-in periods: exclude nonadherents before randomization

Basic Structure of a RCT

Parallel Trial



Each group exposed only to one of study interventions

Most frequently used design

Akobeng AK. Arch Dis Child 2005 ; 90 : 840 - 844.

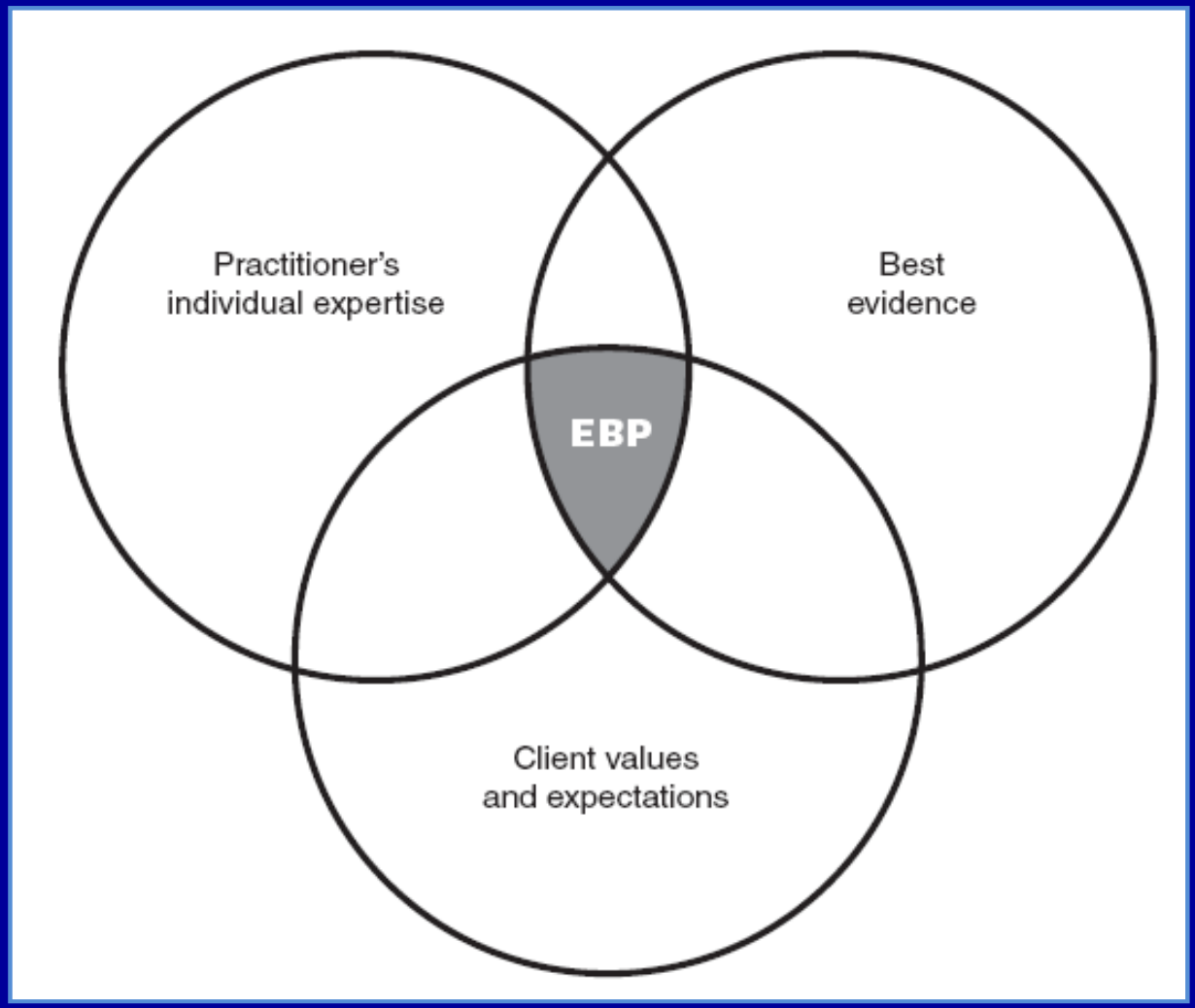
Ways to reduce bias in studies of therapy

Differences at the start of trial		
Difference in prognostic factors		Randomization & stratification

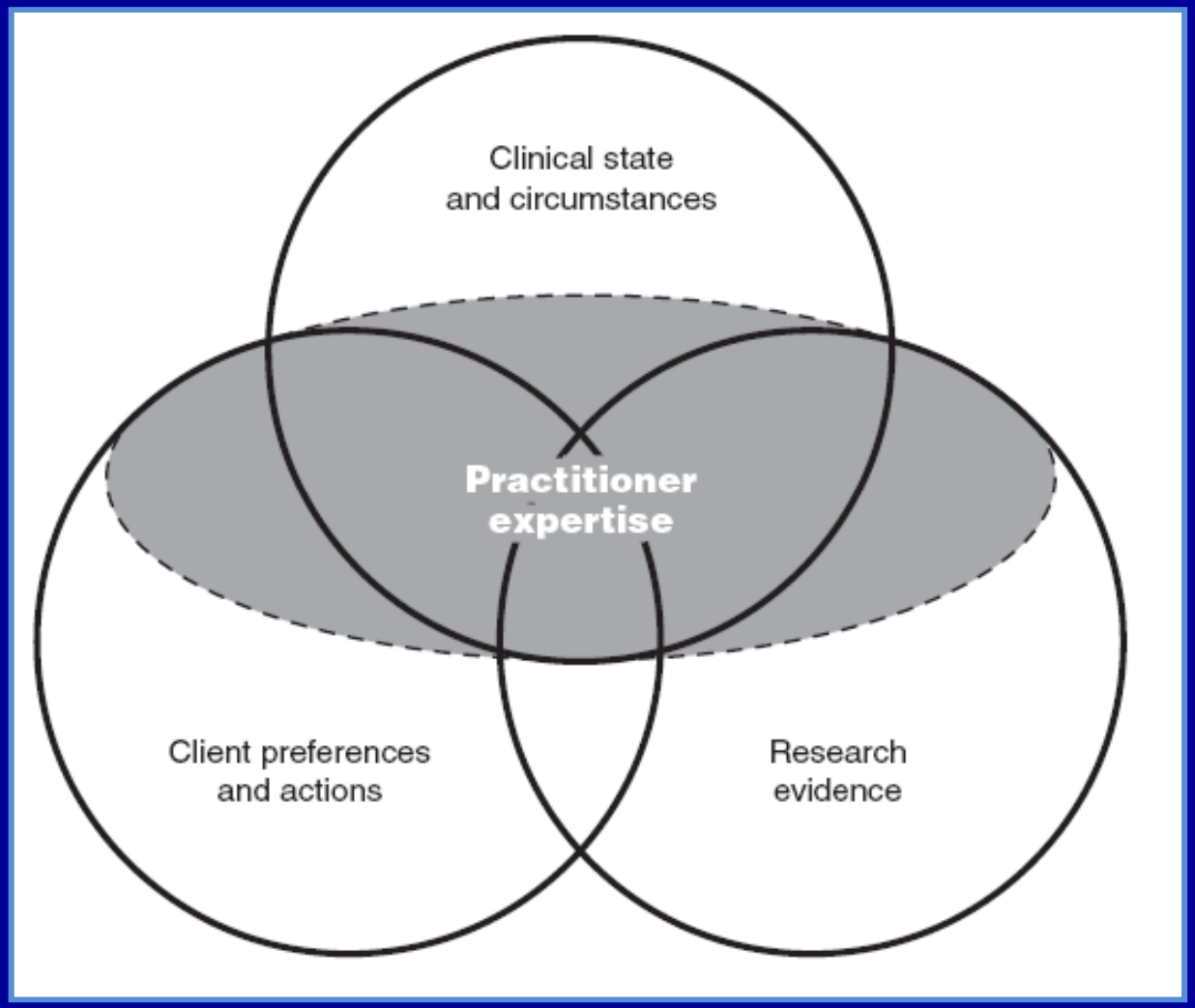
Differences as trial proceeds		
Placebo effects	→	Blinding of patients
Cointervention	→	Blinding of caregivers
Bias in outcome assessment	→	Blinding of outcome assessors

Differences at end of the trial		
Loss to follow-up	→	Ensure complete follow-up
Stopping study early	→	Complete study as planned
Pts not receiving assigned tt	→	ITT principle

Original EBP model

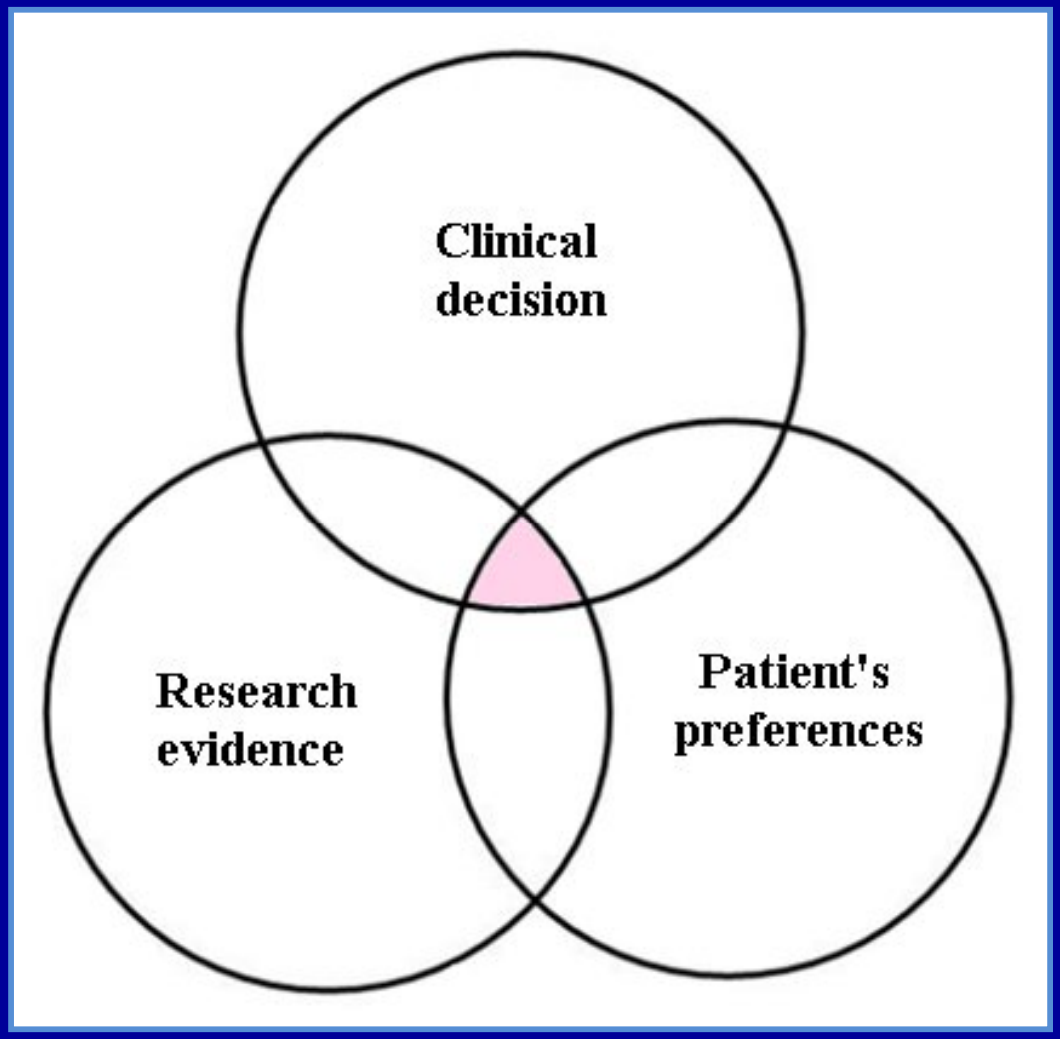


Newer EBP model



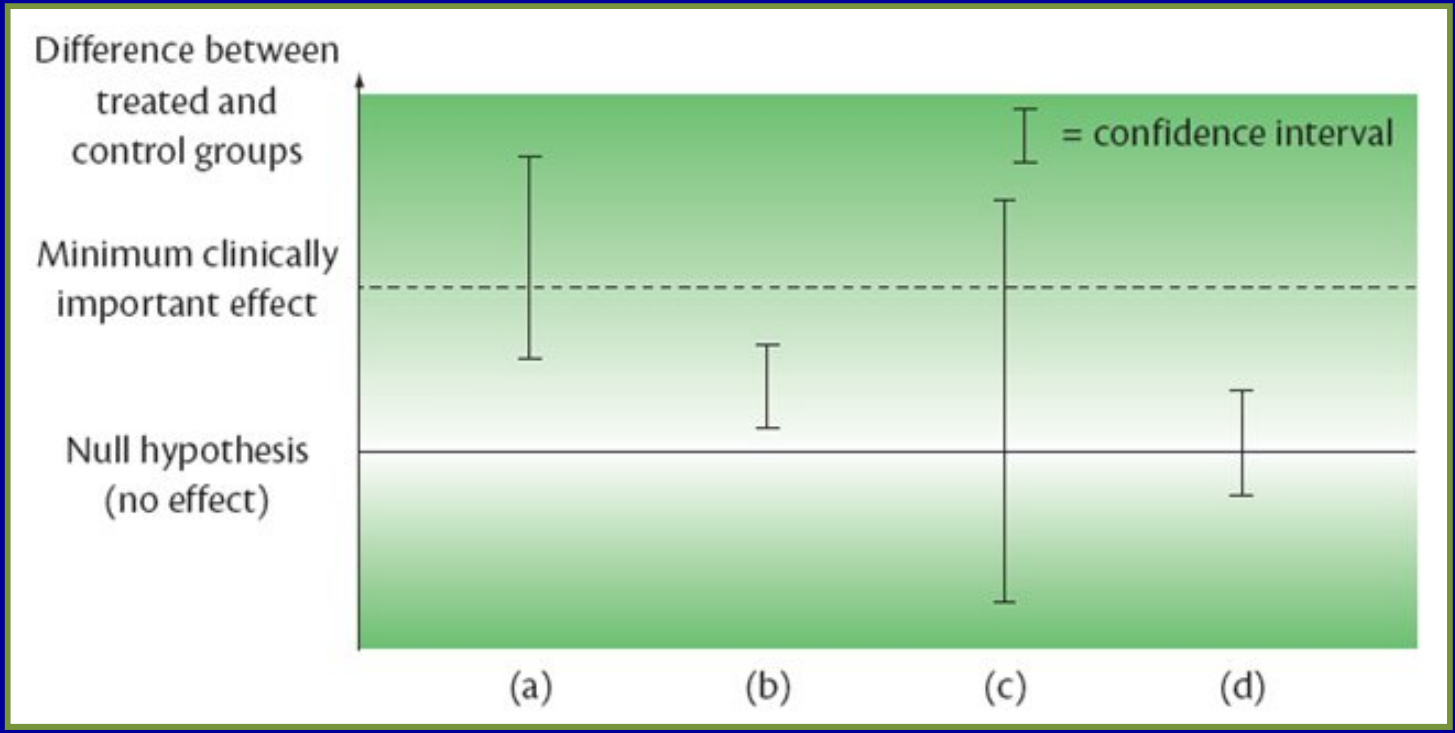
Haynes R t al. British Medical Journal, 2002 ; 324 : 1350.

Basic elements of clinical decision making



BMC Health Services Research 2002, 2:3

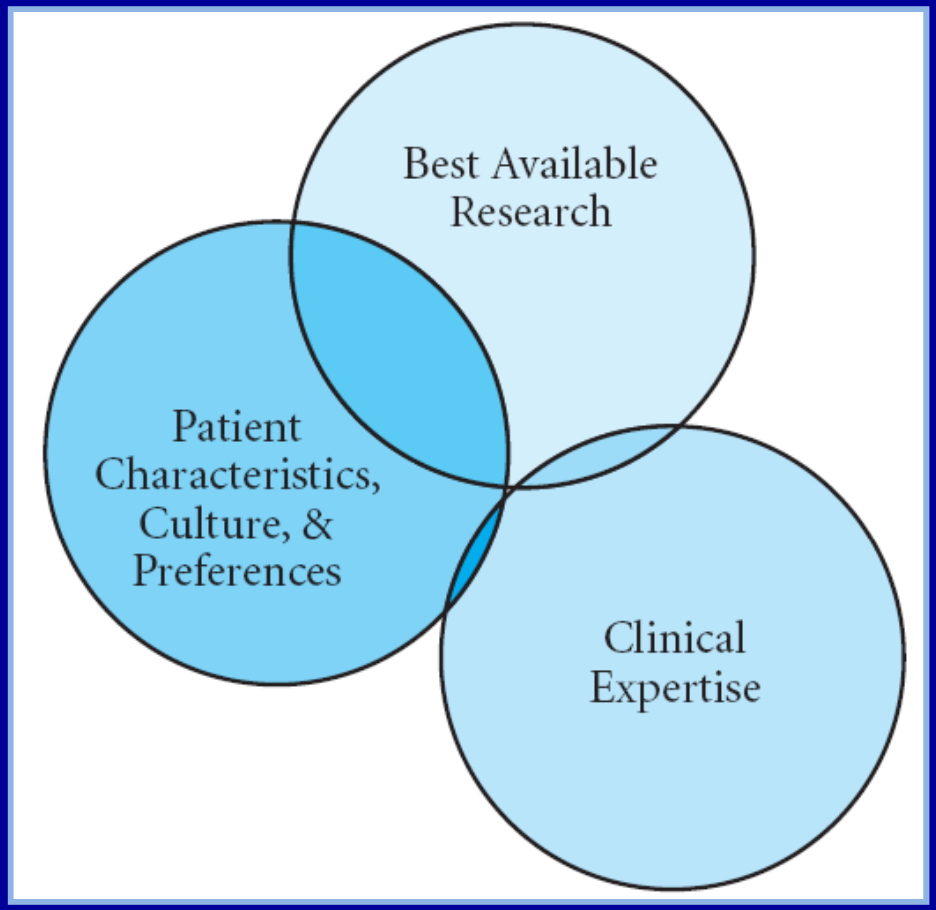
Statistical & clinical significance in CI



(a) Statistically significant – clinically important
(b) Statistically significant – not clinically important
(c) Not statistically significant – inconclusive
(d) Not statistically significant – true negative

Glasziou P, Del Mar C & Salisbury J. Evidence based medicine Workbook. BMJ Publishing Group, 1st edition, London, 2003.

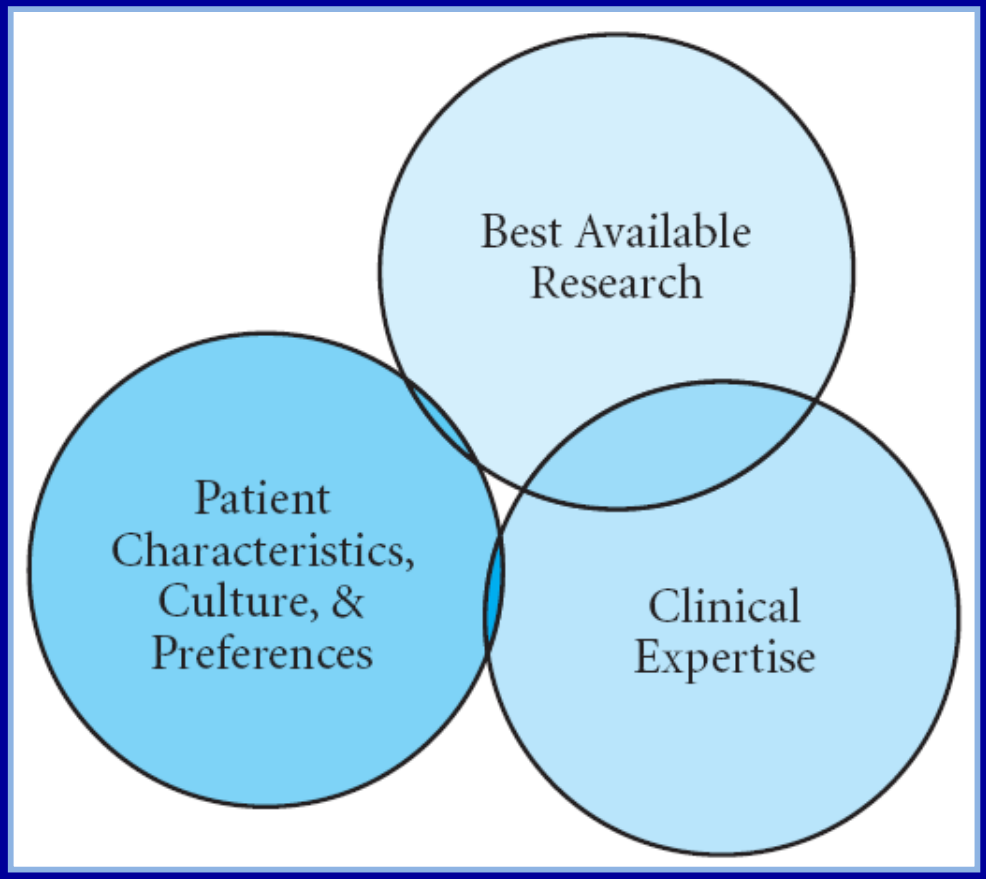
The 3 EBP components



Minimal overlap with clinical expertise

Clinician's guide to evidence-based practices.
Norcross JC et al. Oxford University Press, New York, 2008.

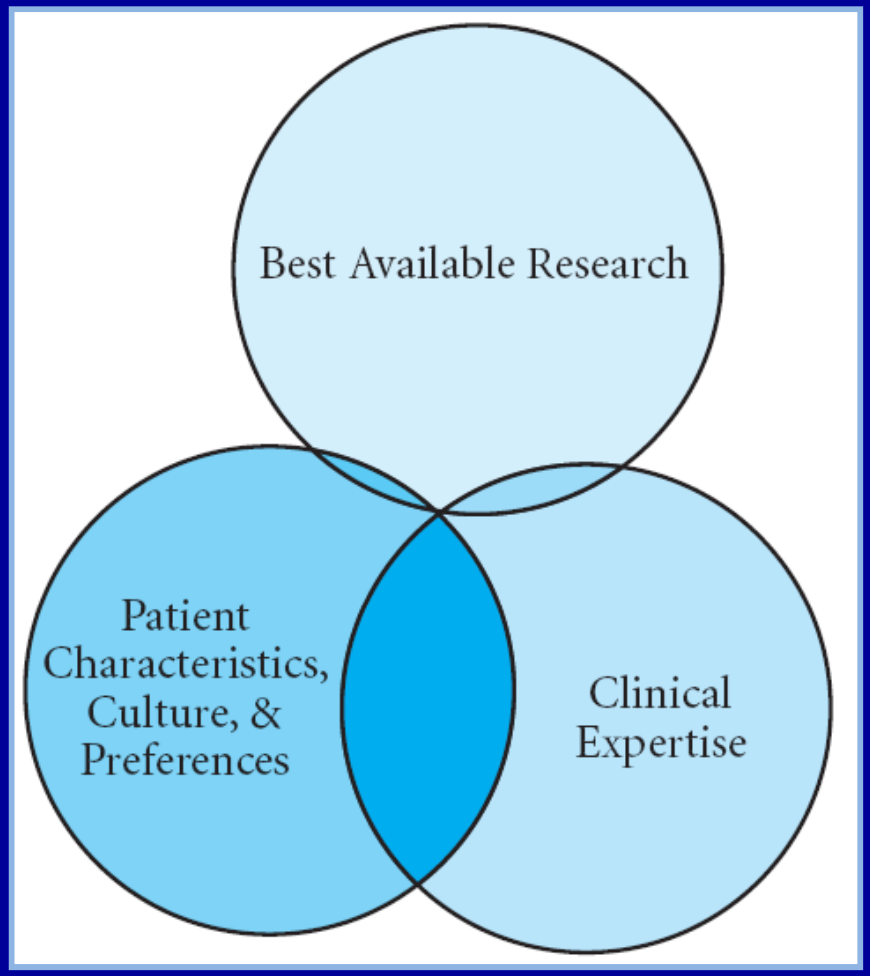
The 3 EBP components



Minimal overlap with patient preferences & culture

Clinician's guide to evidence-based practices.
Norcross JC et al. Oxford University Press, New York, 2008.

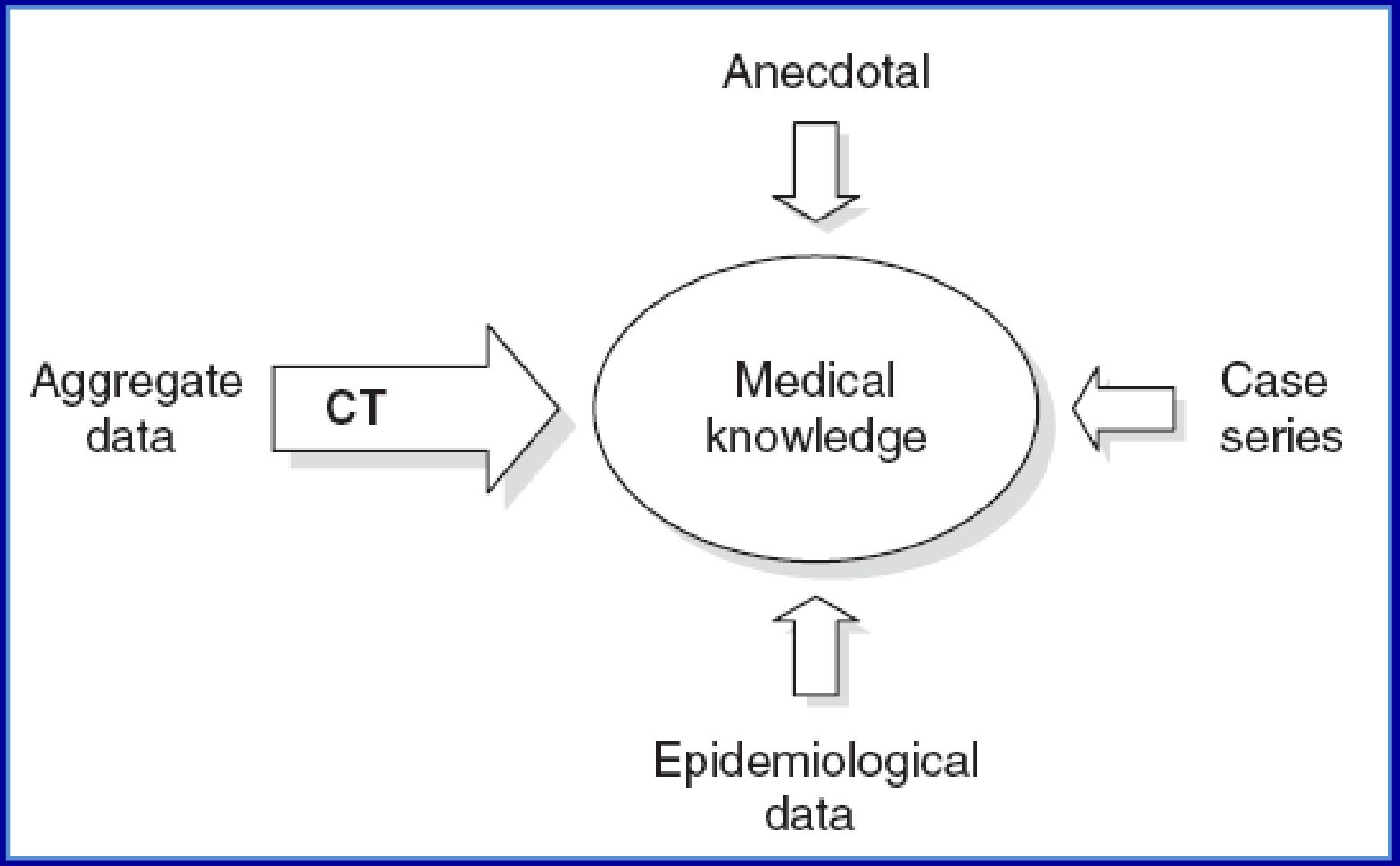
The 3 EBP components



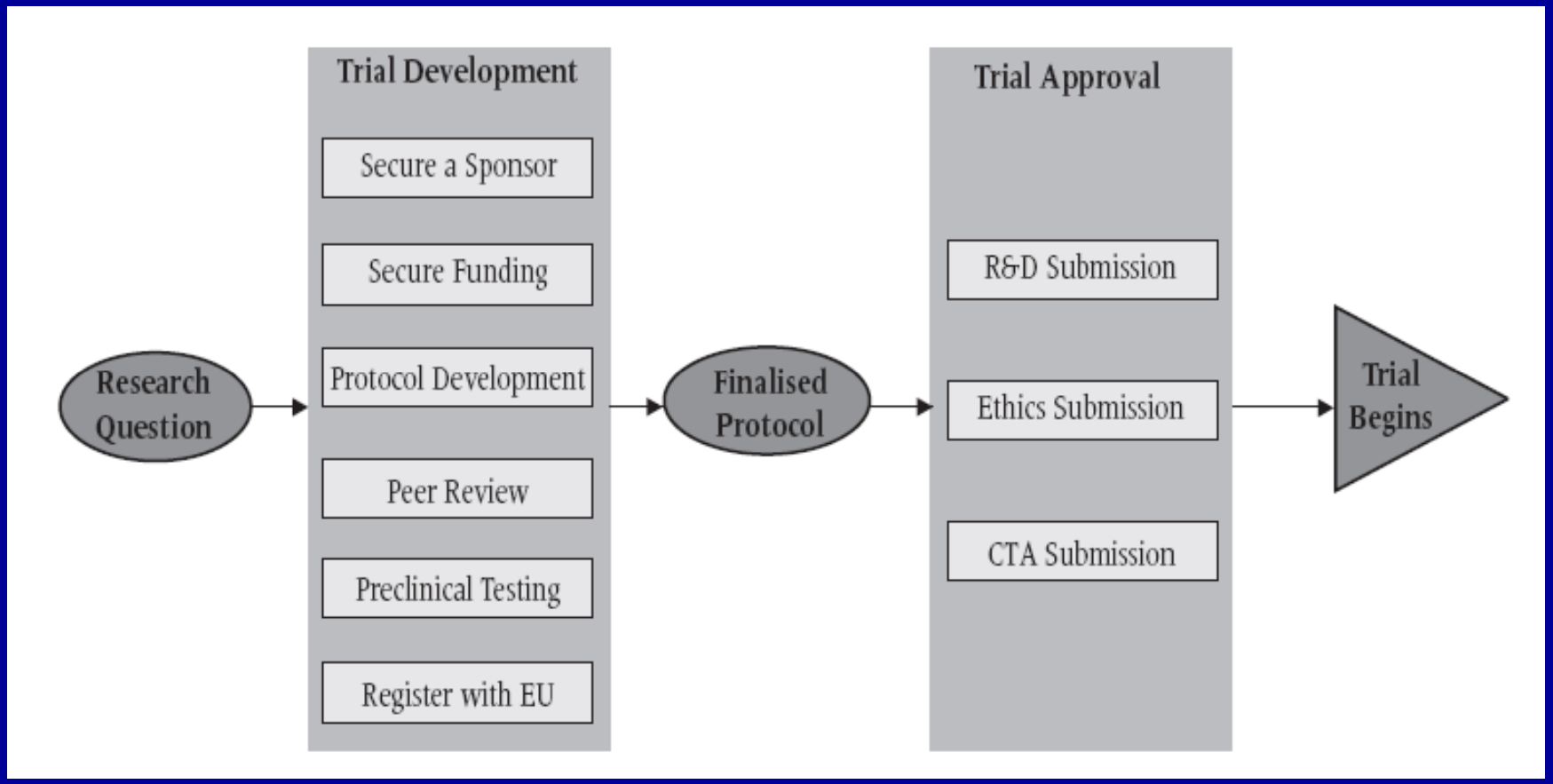
Minimal overlap with available research

Clinician's guide to evidence-based practices.
Norcross JC et al. Oxford University Press, New York, 2008.

Sources of medical knowledge



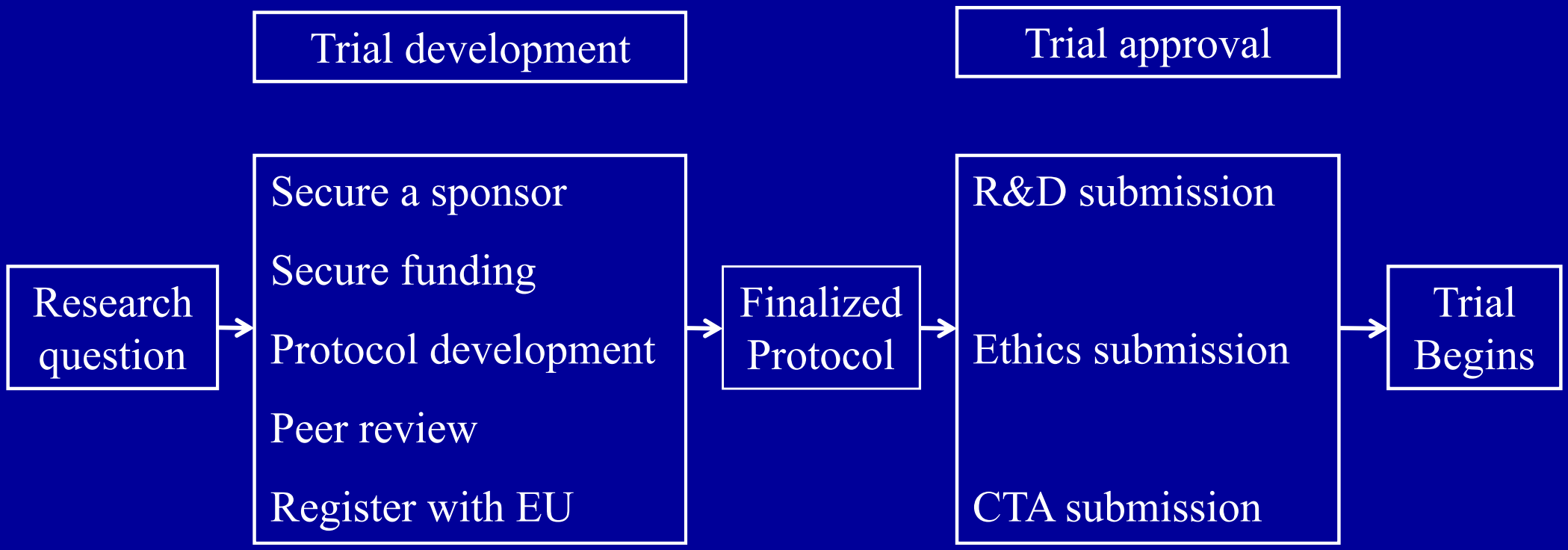
Chin R, Lee BY. Principal & practice of clinical trial medicine. AP



R & D: Research & Development Committee

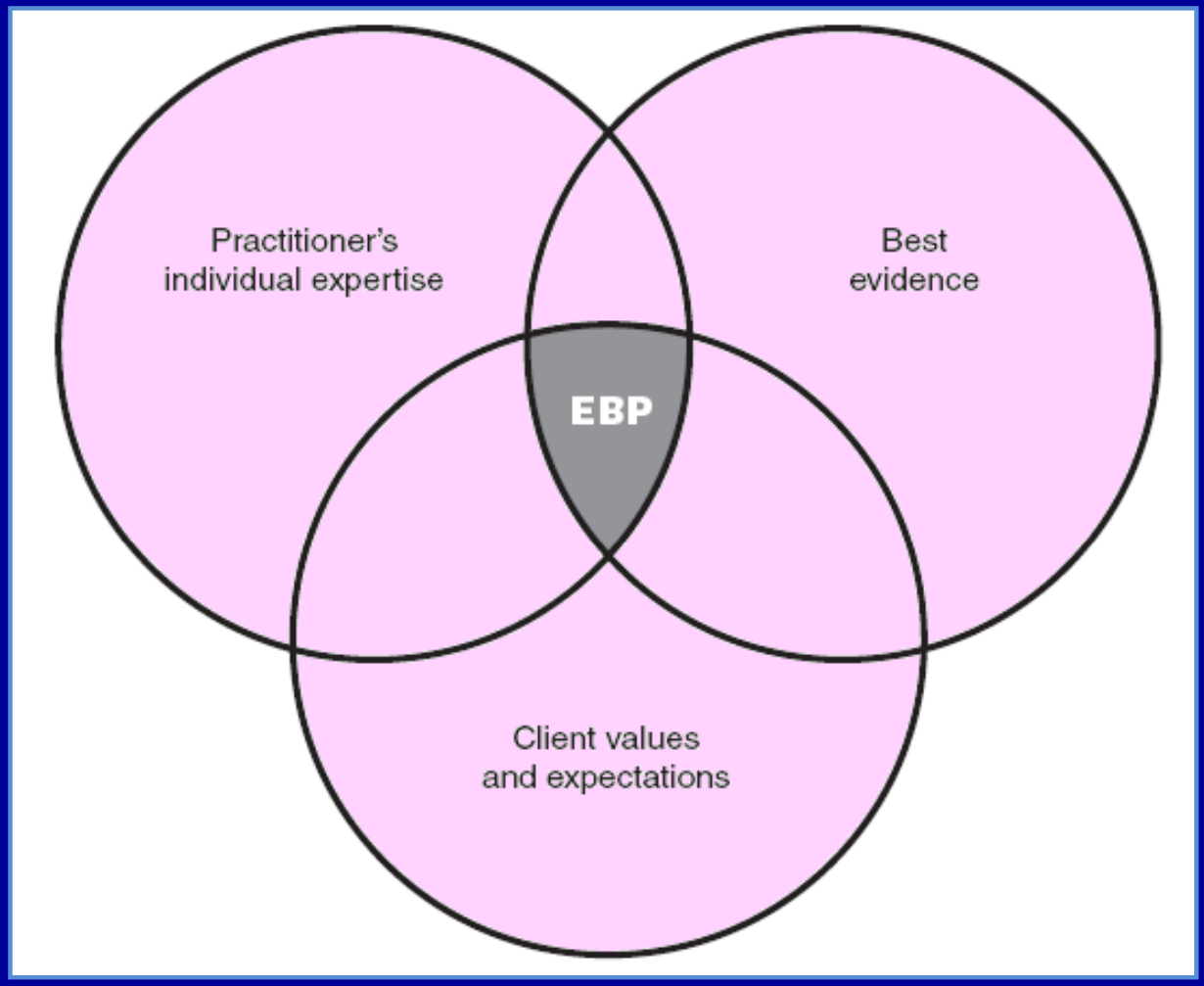
Kerr DJ et al. Clinical trials explained. Blackwell Publishing, Oxford, 2006

Development & approval of clinical trials



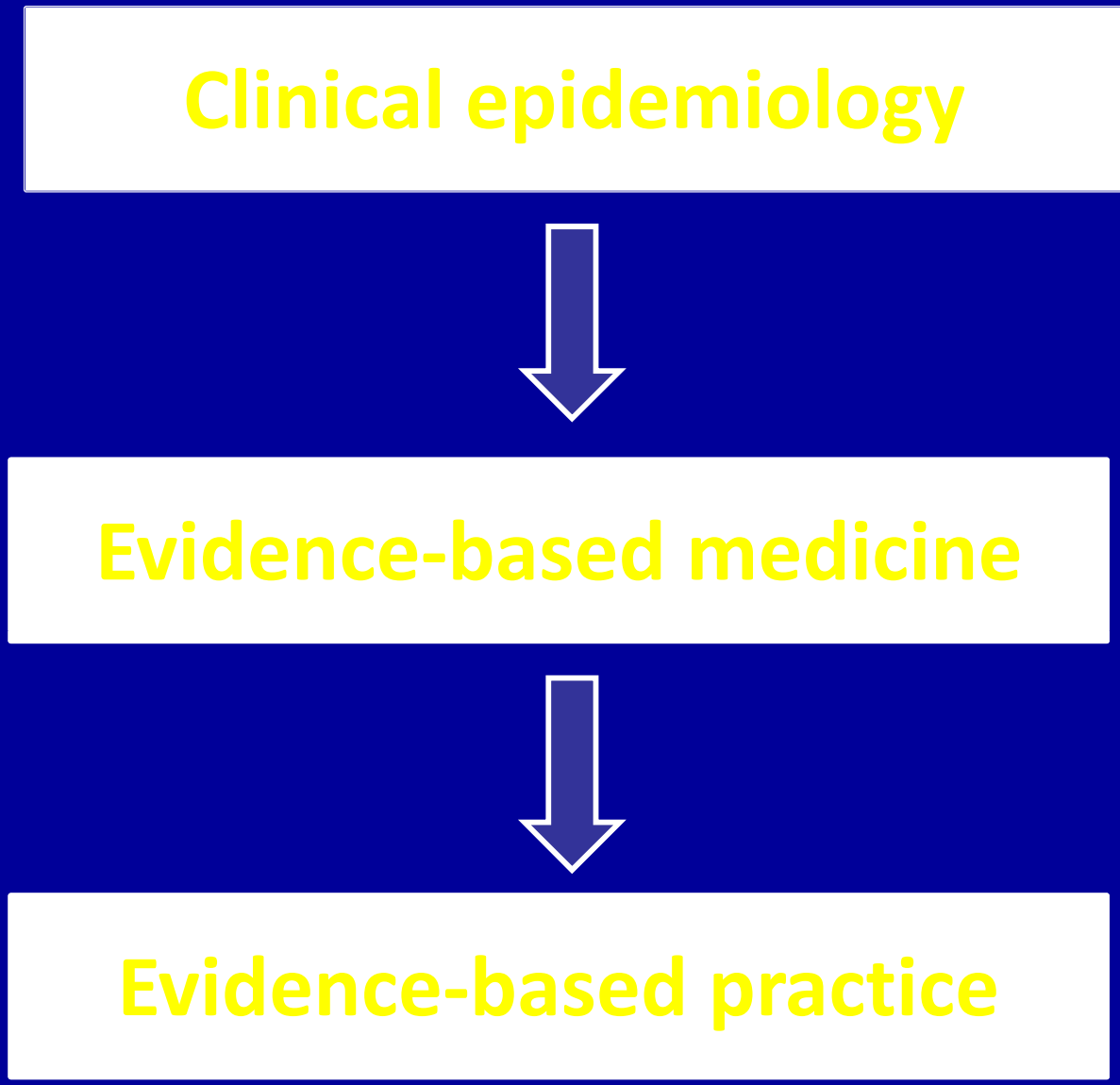
Kerr DJ et al. Clinical trials explained. Blackwell Publishing, Oxford, 2006

The 3 EBP components



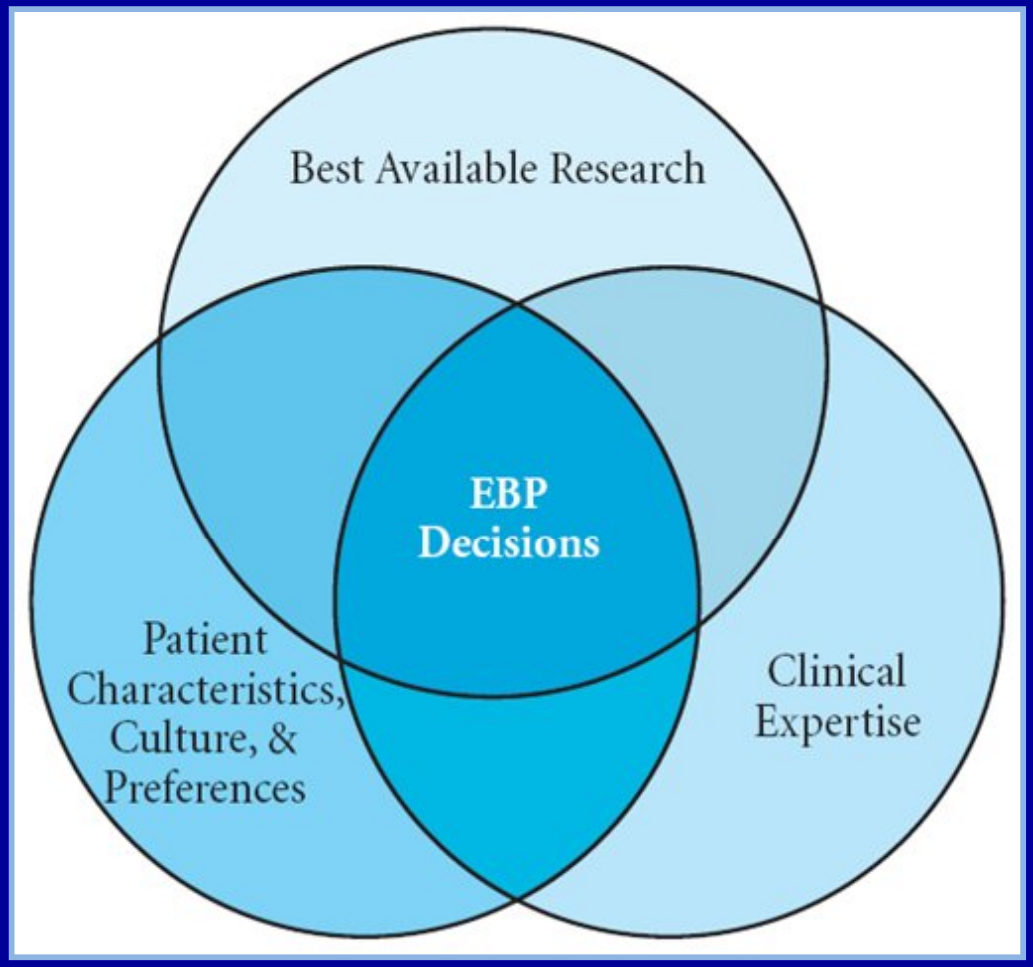
Major convergence between the 3 components

Rubin A. Practitioner's guide to using research for EB practice.
John Wiley & Sons, 2007



Glasziou P, Del Mar C & Salisbury J. Evidence based medicine Workbook. BMJ Publishing Group – First edition – London – 2003.

The 3 EBP components



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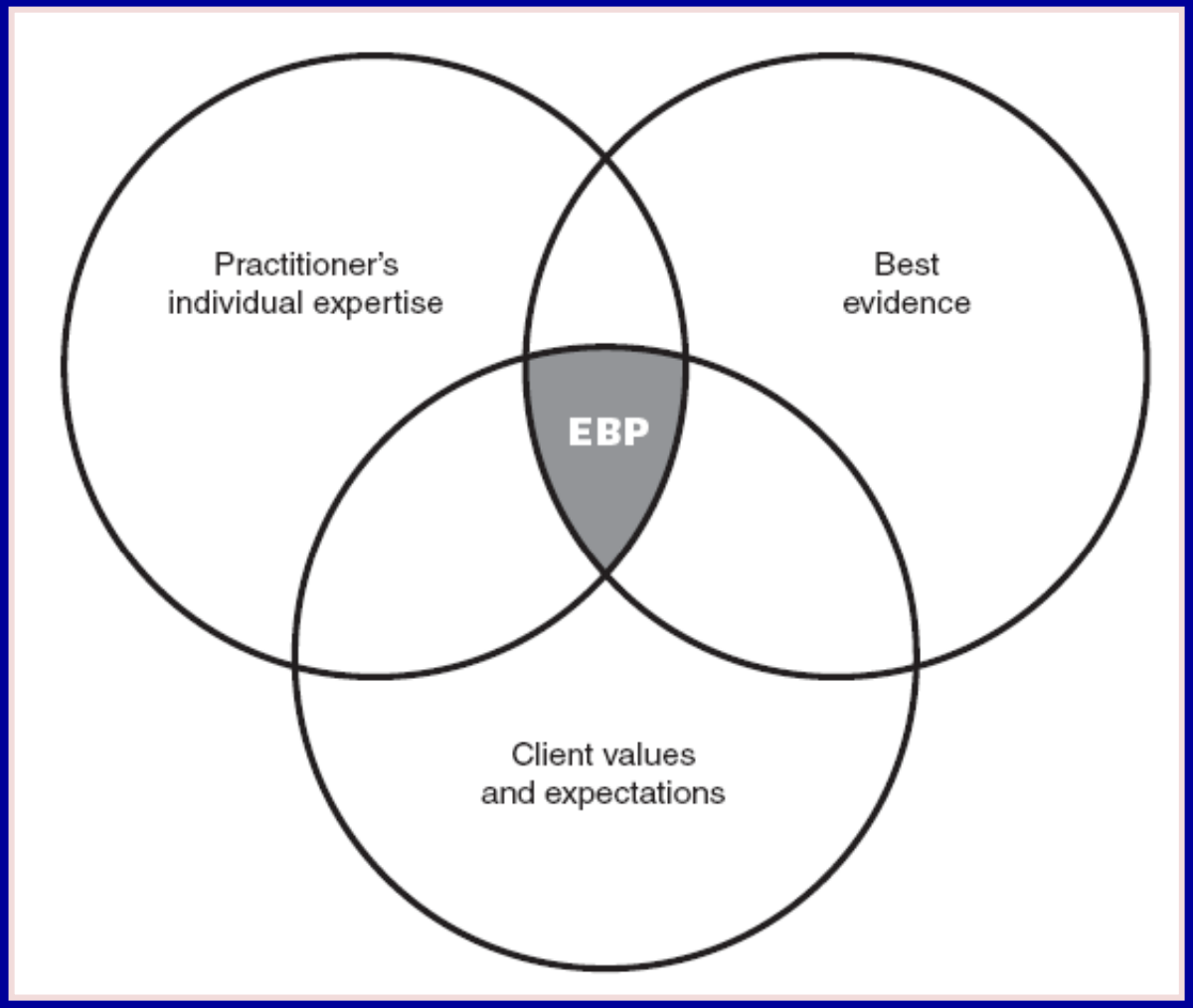
Norcross JC et al. Oxford University Press, New York, 2008.

The 3 EBP components



Major convergence between the 3 components

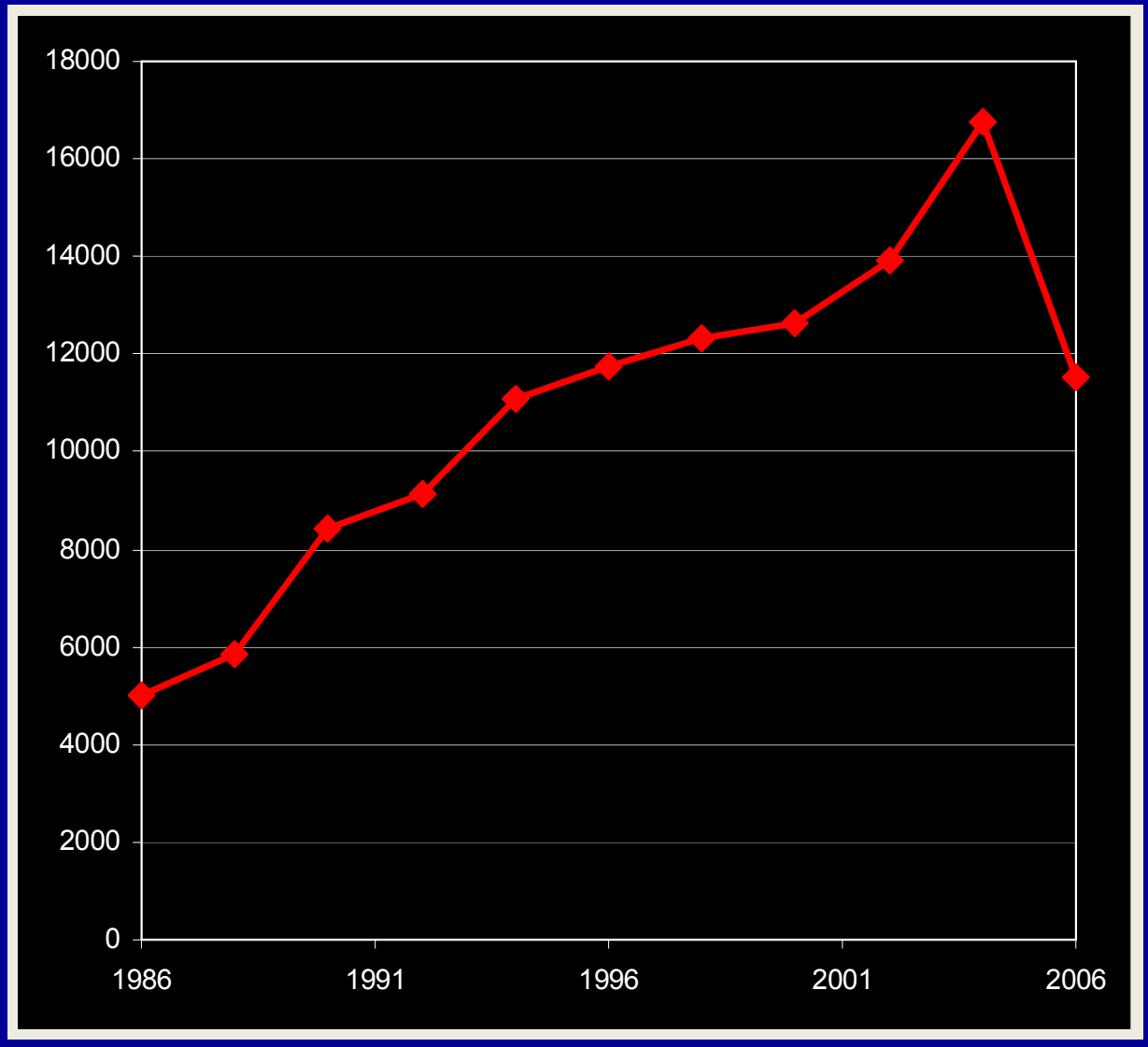
Rubin A. Practitioner's guide to using research for EB practice.
John Wiley & Sons, 2007

Trial design

- **Systematic review**
- **Meta-analysis**
- **Randomized controlled trial**
- **Cohort study**
- **Case control study**
- **Cross-sectional study**
- **Case series & case report**

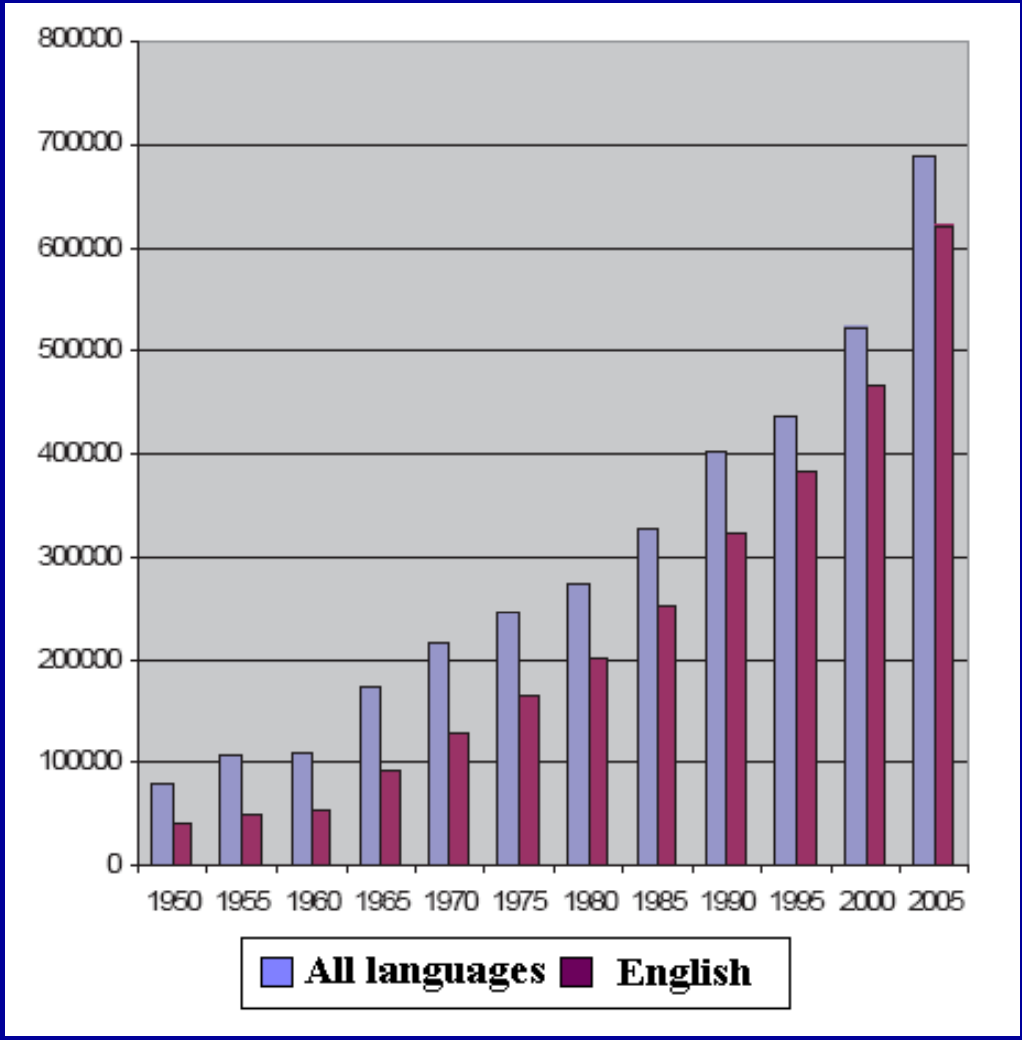
Based on RCTs

Number of randomized trials published*



* Based on Medline search restricted to "Randomized clinical trials"

Annual addition of articles to PubMed



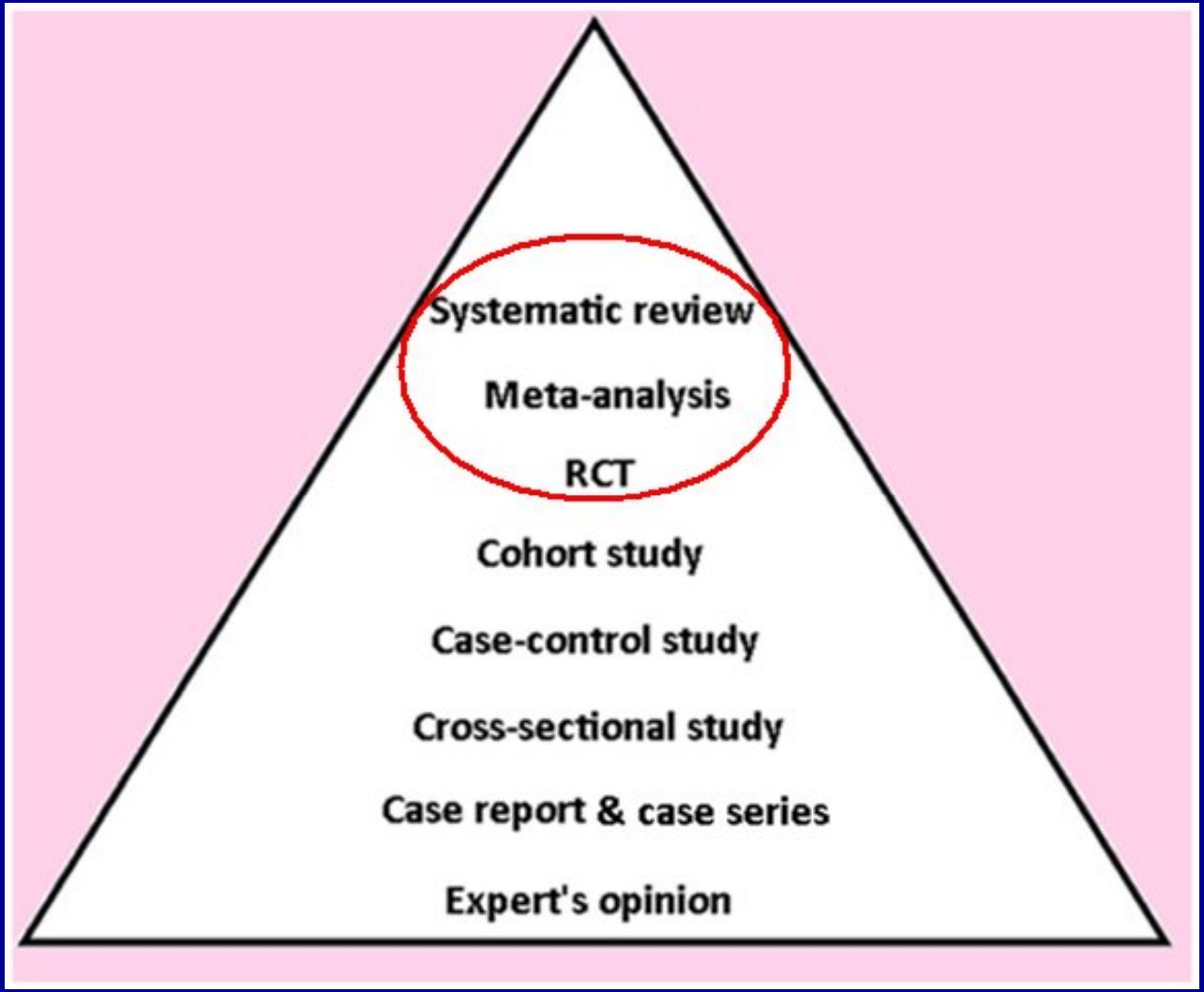
50 years ago: majority of articles published in non-English

Currently: 90% of articles published in English

De Brún C et all. Searching skills toolkit: Finding the evidence. John Wiley & Sons, West Sussex, 1st edition, 2009.

Sealed opaque envelope

Hierarchy of evidence in quantitative studies



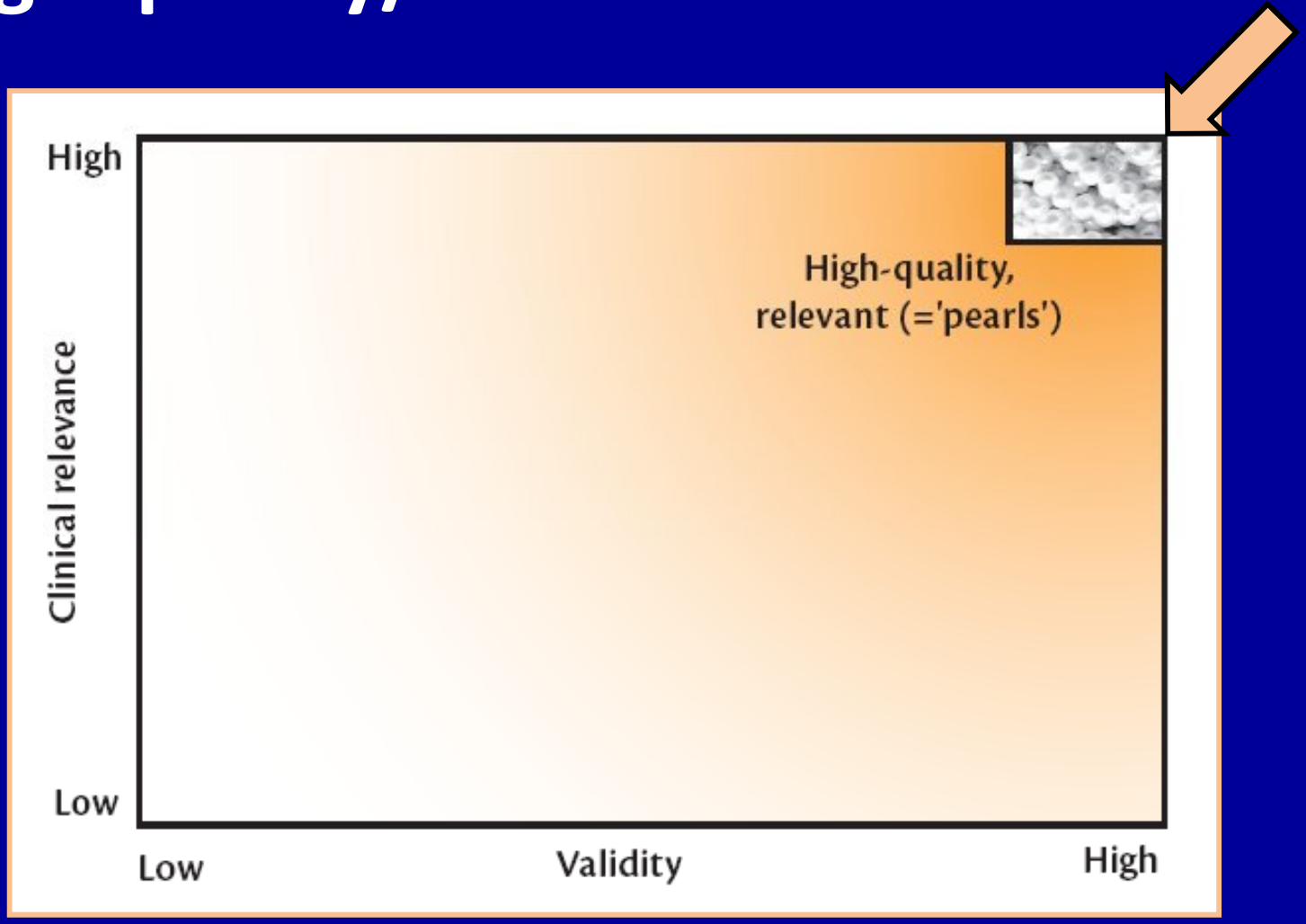
McGovern D, Summerskill W, Valori R, Levi M. Key topics in EBM. BIOS Scientific Publishers, 1st Edition, Oxford, 2001.

What is bias?

- **Tendency of an estimate to deviate in one direction from a true value** (underestimation or overestimation)
- More commonly **unintentional**, & often **unrecognized** even by researchers themselves

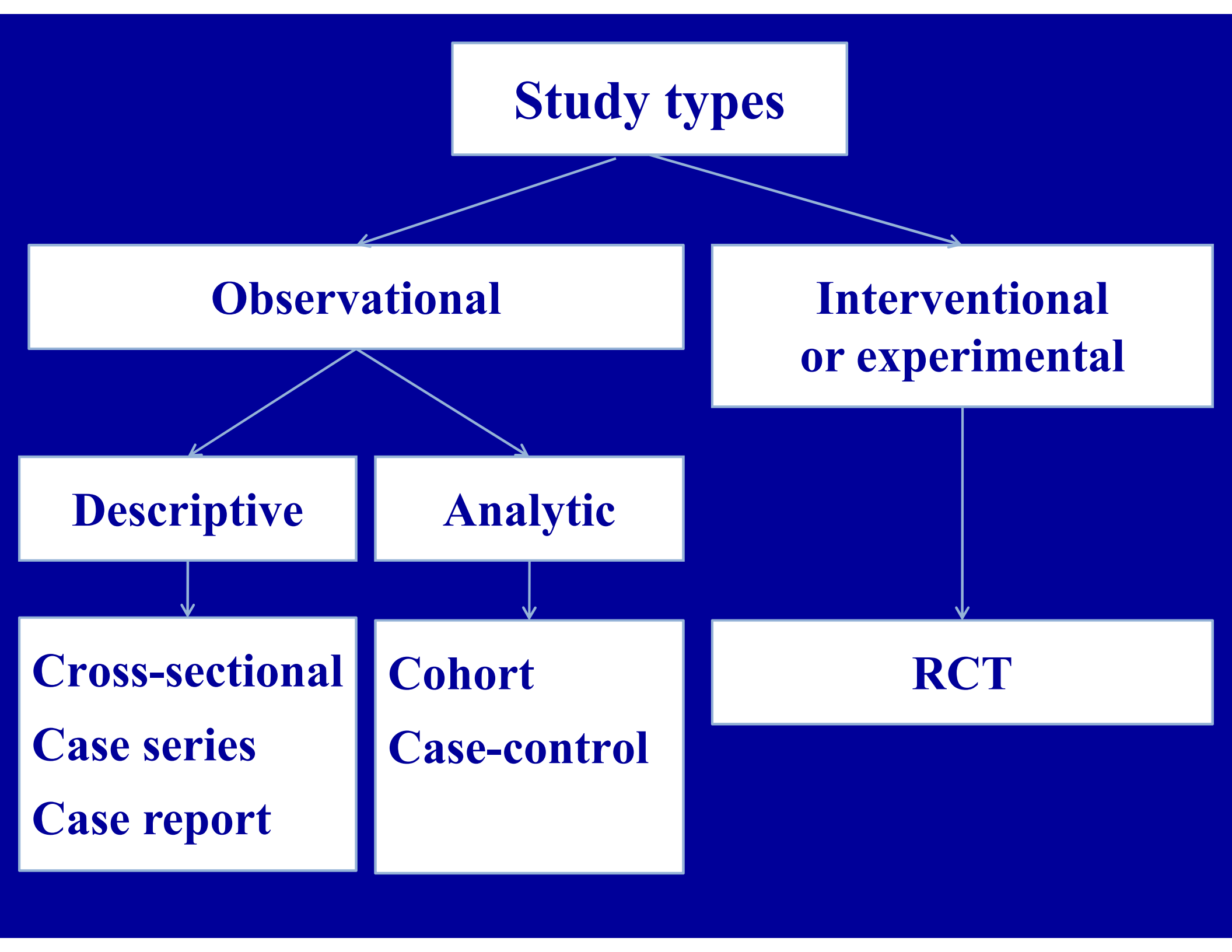
Jadad AR, Enkin MW. Randomized control trials.
Blackwell Publishing, 2nd ed, 2007.

High quality/relevant data – Pearls

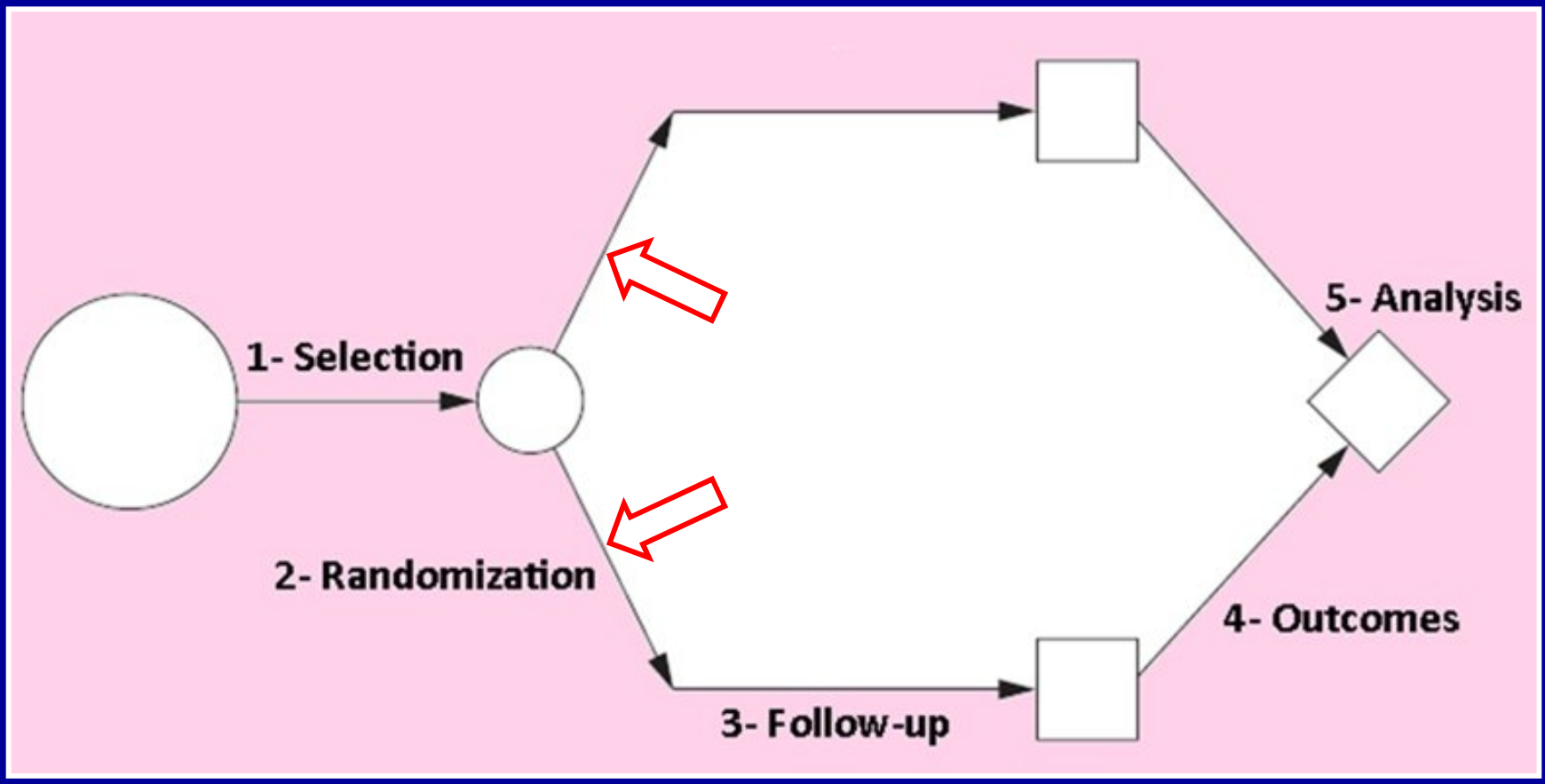


Finding high-quality evidence is like searching for ‘rare pearls’

Glasziou P, Del Mar C. Evidence based practice workbook.
Blackwell Publishing, 2nd edition, 2007.


Study types
Observational
Interventional or experimental
Descriptive
Analytic
Cross-sectional
Case series
Case report
Cohort
Case-control
RCT

Randomization in RCTs



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 – 69.

Sir Austin Bradford Hill

- Studied medicine when World War 1 intervened
- Pilot in the World War 1
- Contracted TB: 2 years hospital -2 years convalescence
- Took a degree of Economics by correspondence

- **1922** Attended statistical lectures by Karl Pearson
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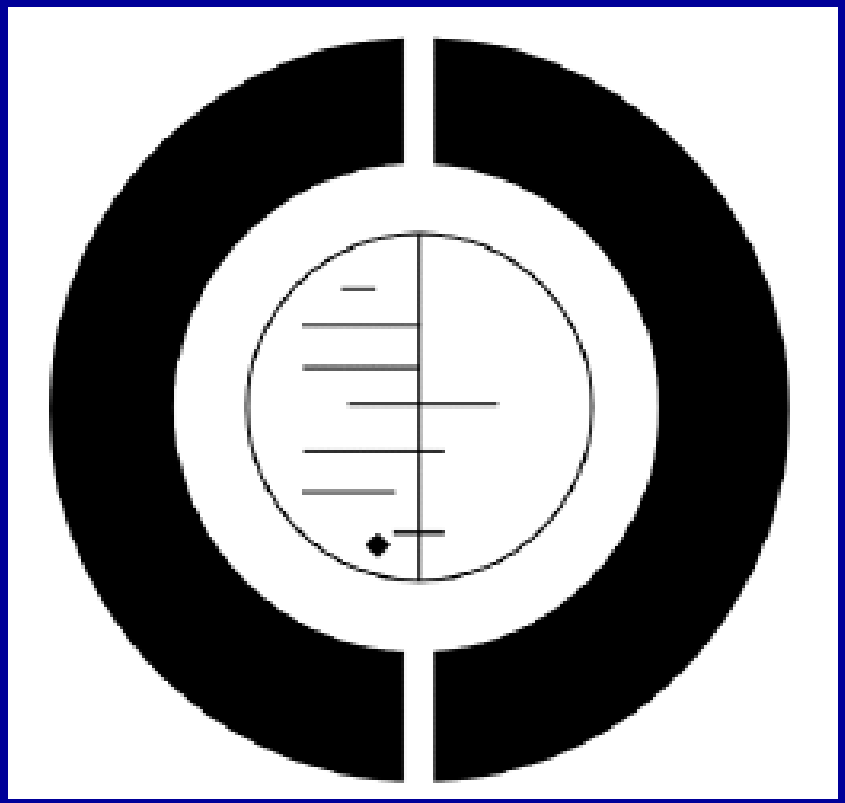
- **1947** Professor of Medical Statistics
- **1950-52** President of the Royal Statistical Society



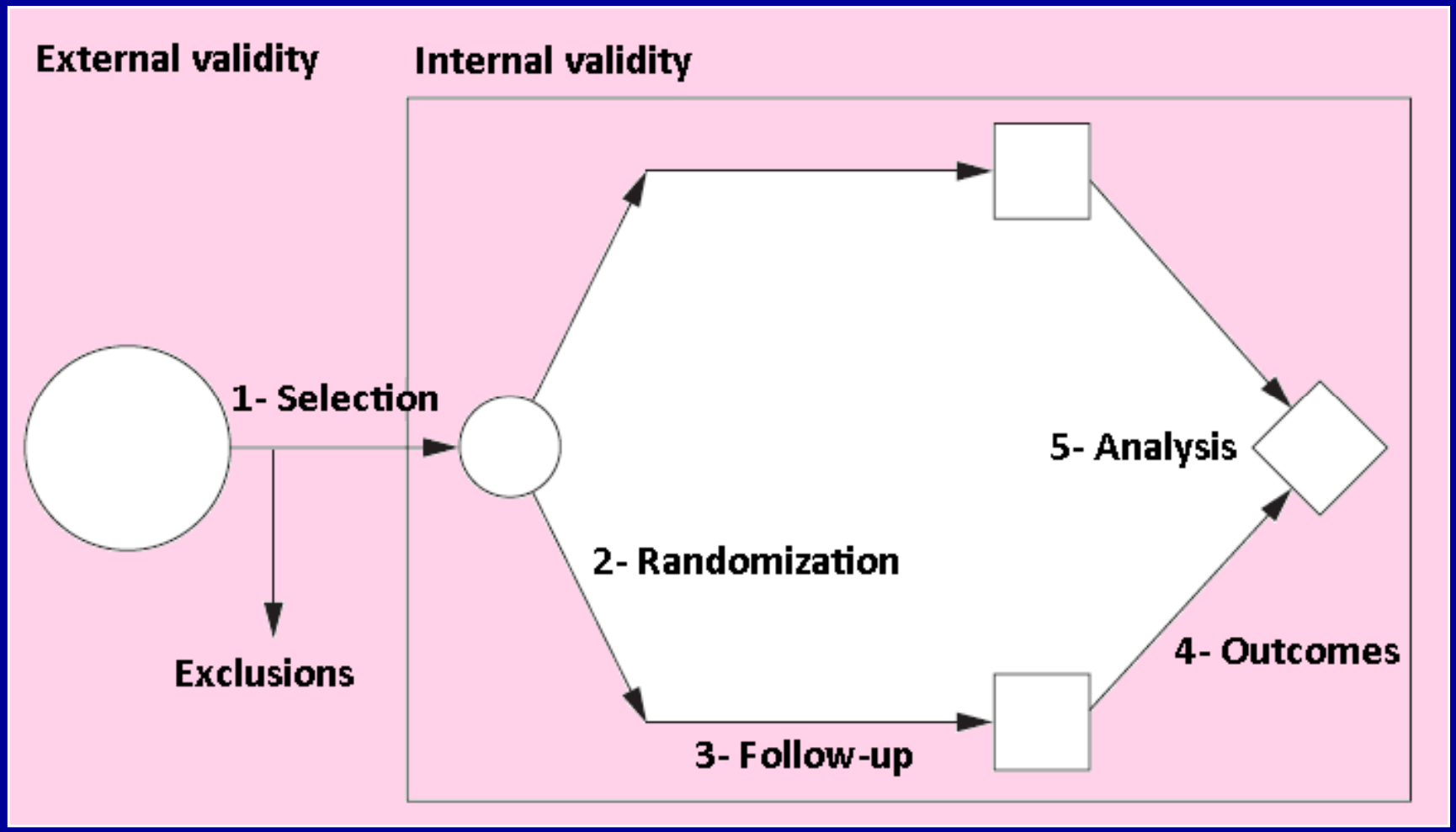
High quality/relevant data
Pearls

If it is not valid → **It is of no value**

If it is not relevant → **It is of no value**

- If the study wasn’t randomized, we’d suggest that you stop reading it and go on to the next article in your search

Internal & external validity of a RCT



Attia J & Page J. Evid Based Med 2001 ; 6 : 68 - 69.

ISIS-2 trial

Streptokinase &/or aspirin on AMI mortality

Post-hoc analysis

Zodiac signs of Gemini & Libra

5% higher mortality on aspirin compared to placebo

Other Zodiac signs

30% lower mortality on aspirin compared to placebo

Furberg B. Evaluating clinical research. Springer, NY, USA, 2007.

Steps of EBM

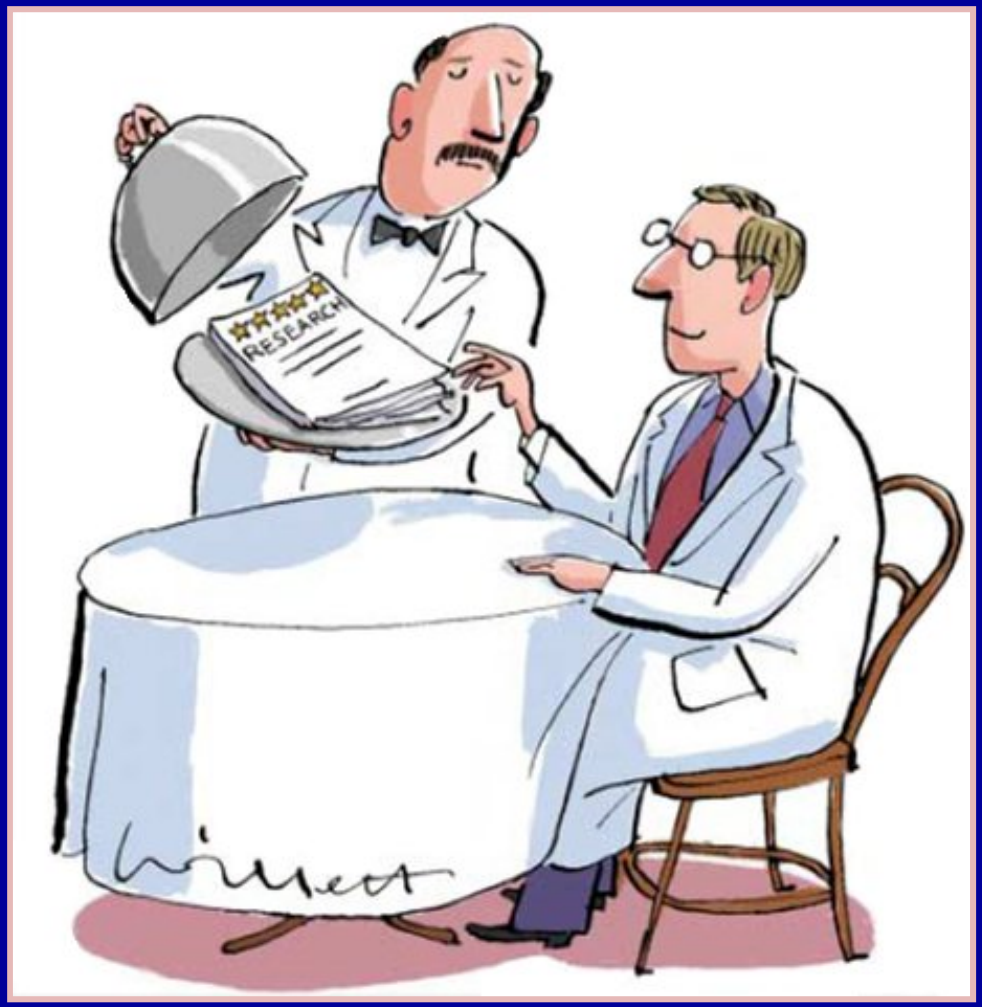
Steps of EBM

❷Acquire

Steps of EBM

❸ Appraise

Critical appraisal of a RCT



Glasziou P et al. BMJ 2004 ; 328 : 39 - 41.

Steps of EBM

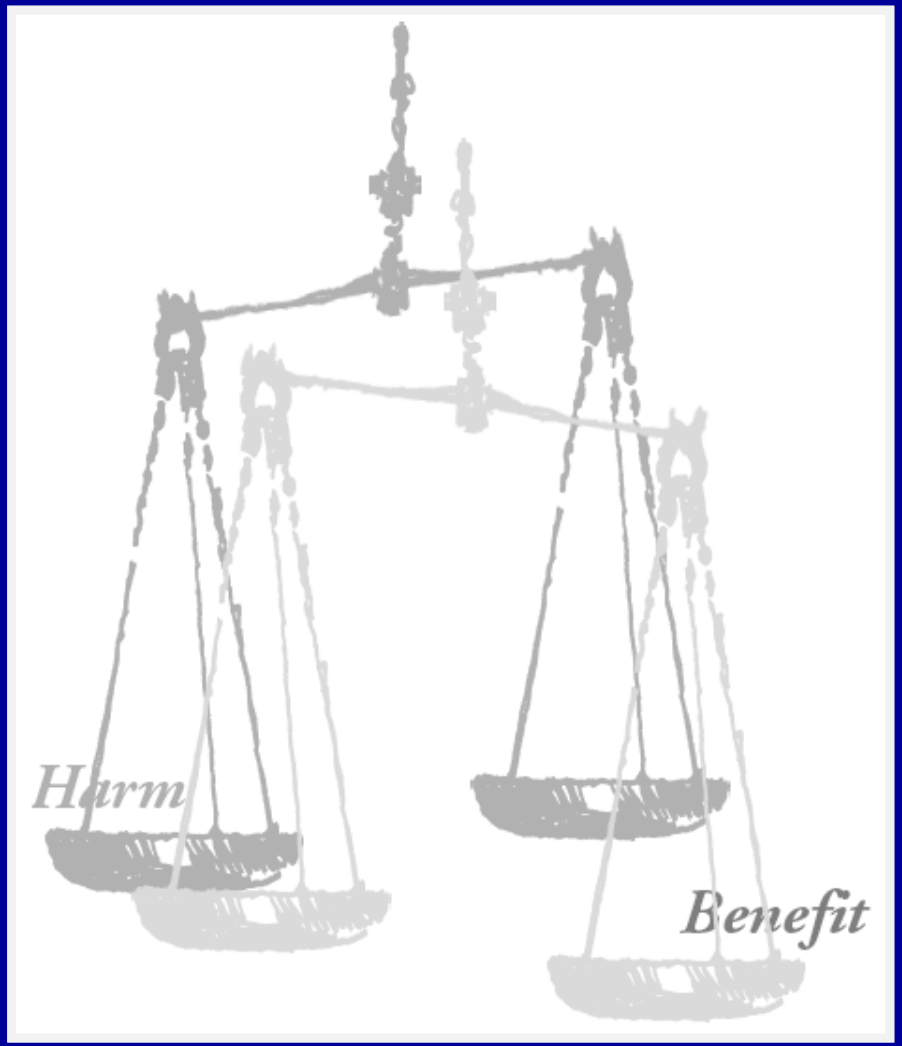
❹ Apply

Benefit versus harm

"All that glisters is not gold"

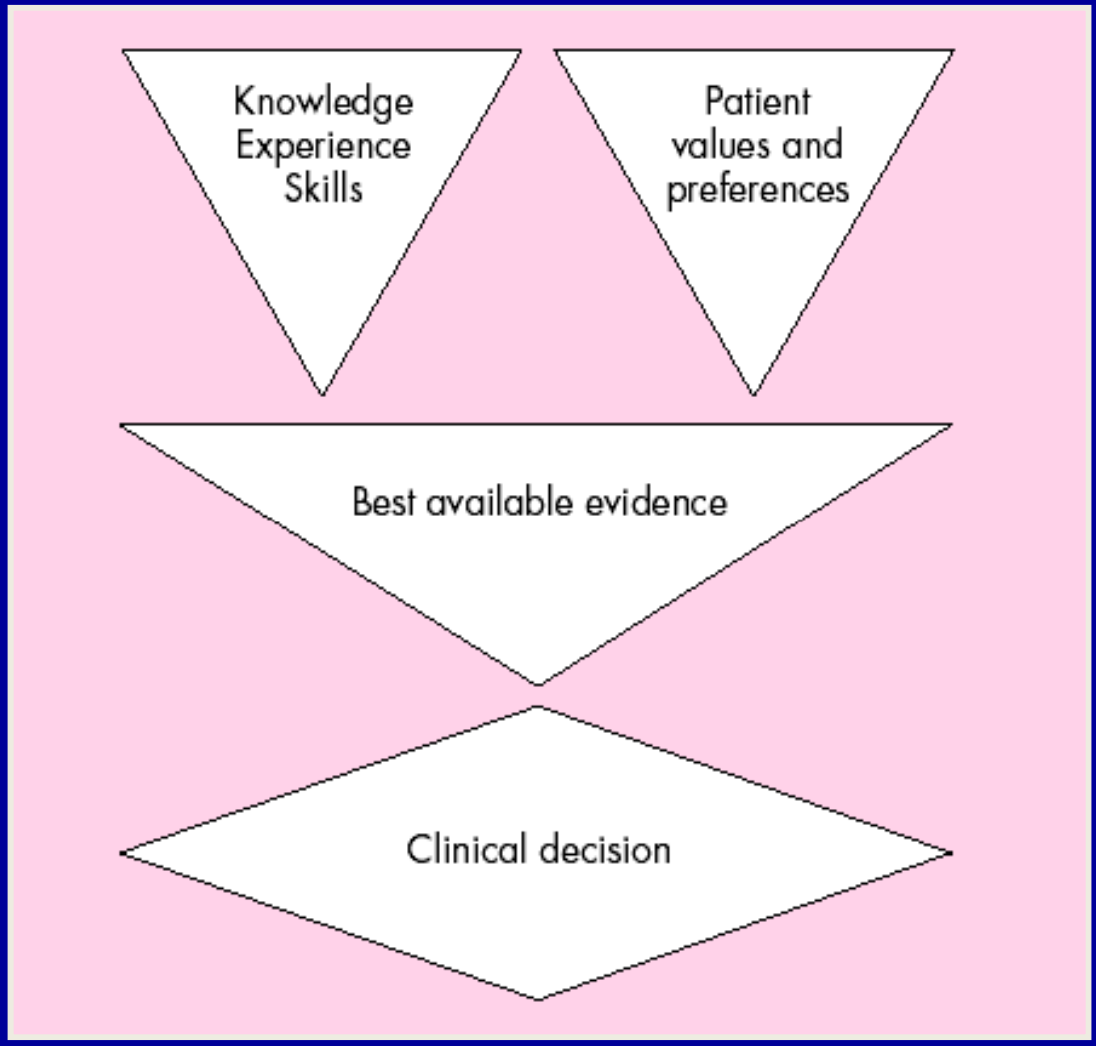
W. Shakespeare

In "The Merchant of Venice"



Furberg BD & Furberg CD. Evaluating clinical research.
Springer Science & Business Media – First Edition – New York – 2007.

Flow chart of evidence based practice



Akobeng AK. Arch Dis Child 2005 ; 90 : 840 – 844.

This so-called Hawthorne effect refers to tendency of people to alter their behavior when they are subject to special attention in a research setting

Sir Austin Bradford Hill

- Studied medicine when World War 1 intervened
- Pilot in the World War 1
- Contracted TB: 2 years hospital -2 years convalescence
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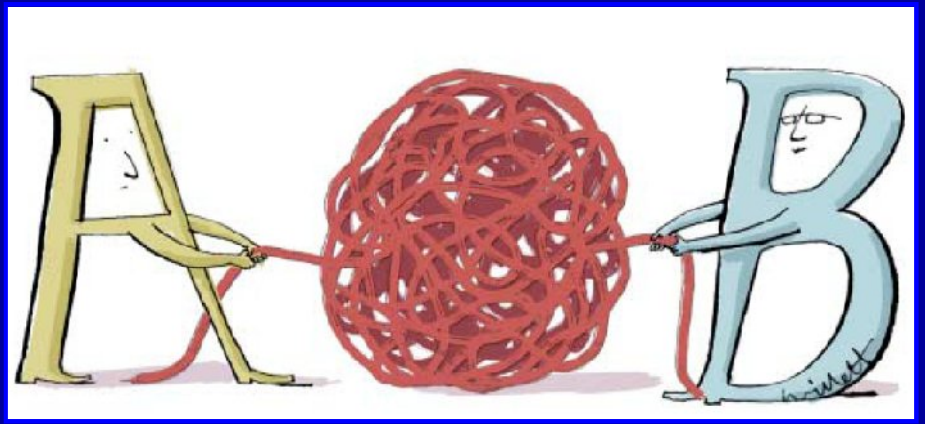
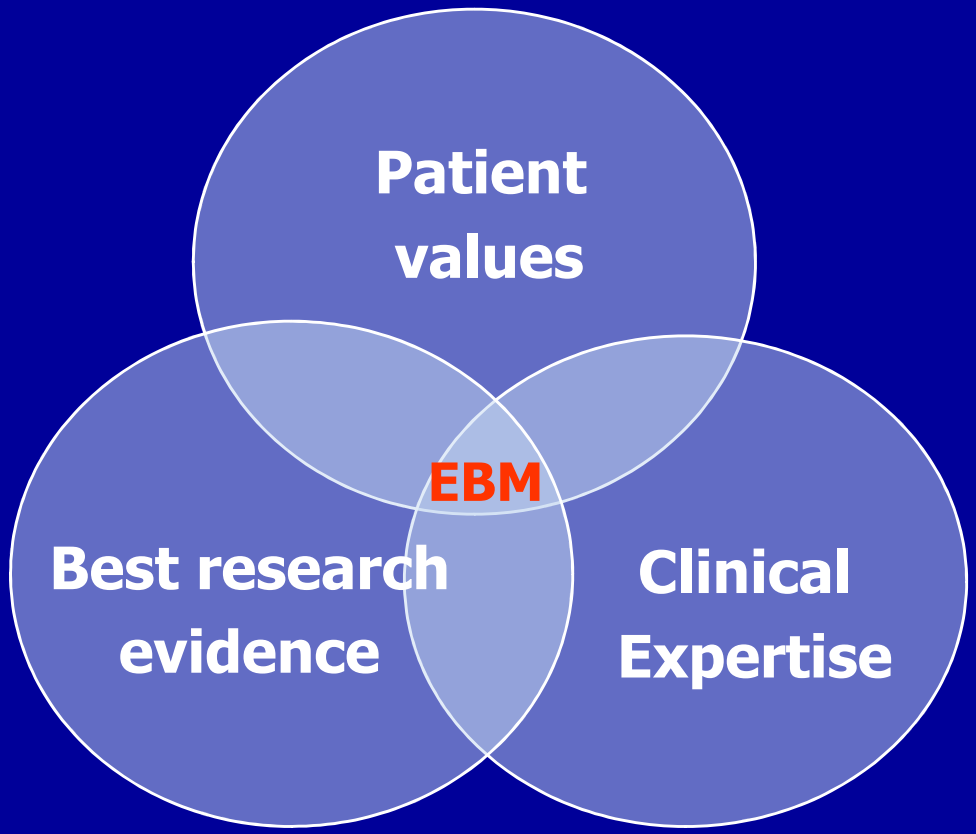
Randomization

- Simple randomization
- Random table
- Block randomization

- Stratified randomization
- Minimization method
- Unequal randomization
- Allocation concealment

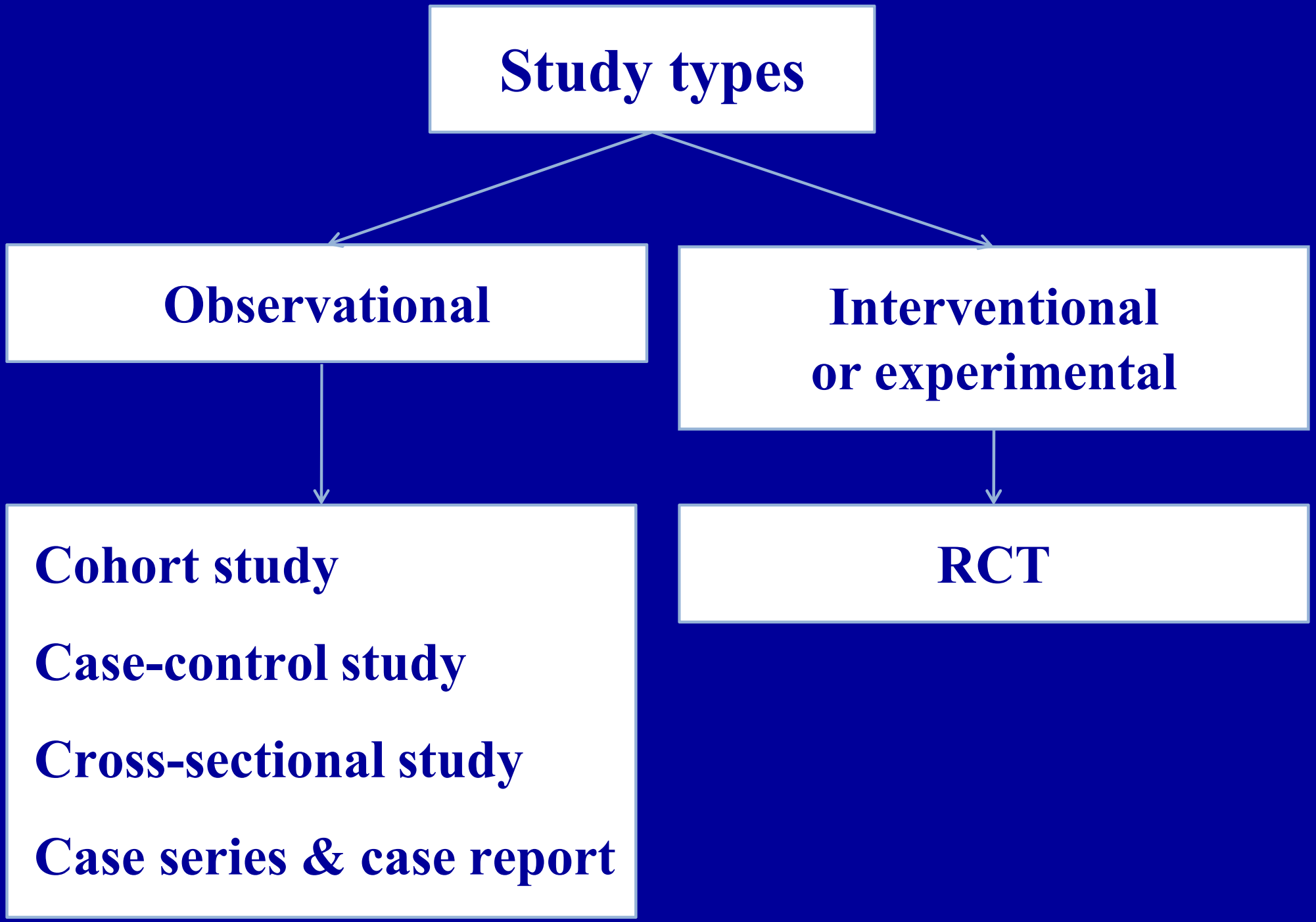


The 3 components of EBP



"EBM is the integration of best research evidence with clinical expertise & patient values"

- *David Sackett*


Study types
Observational
Interventional or experimental
Cohort study
Case-control study
Cross-sectional study
Case series & case report
RCT

Trial designs

- Systematic review
- Meta-analysis

Secondary research

- Randomized clinical trial
- Cohort study
- Case control study
- Cross-sectional study
- Case series & case report

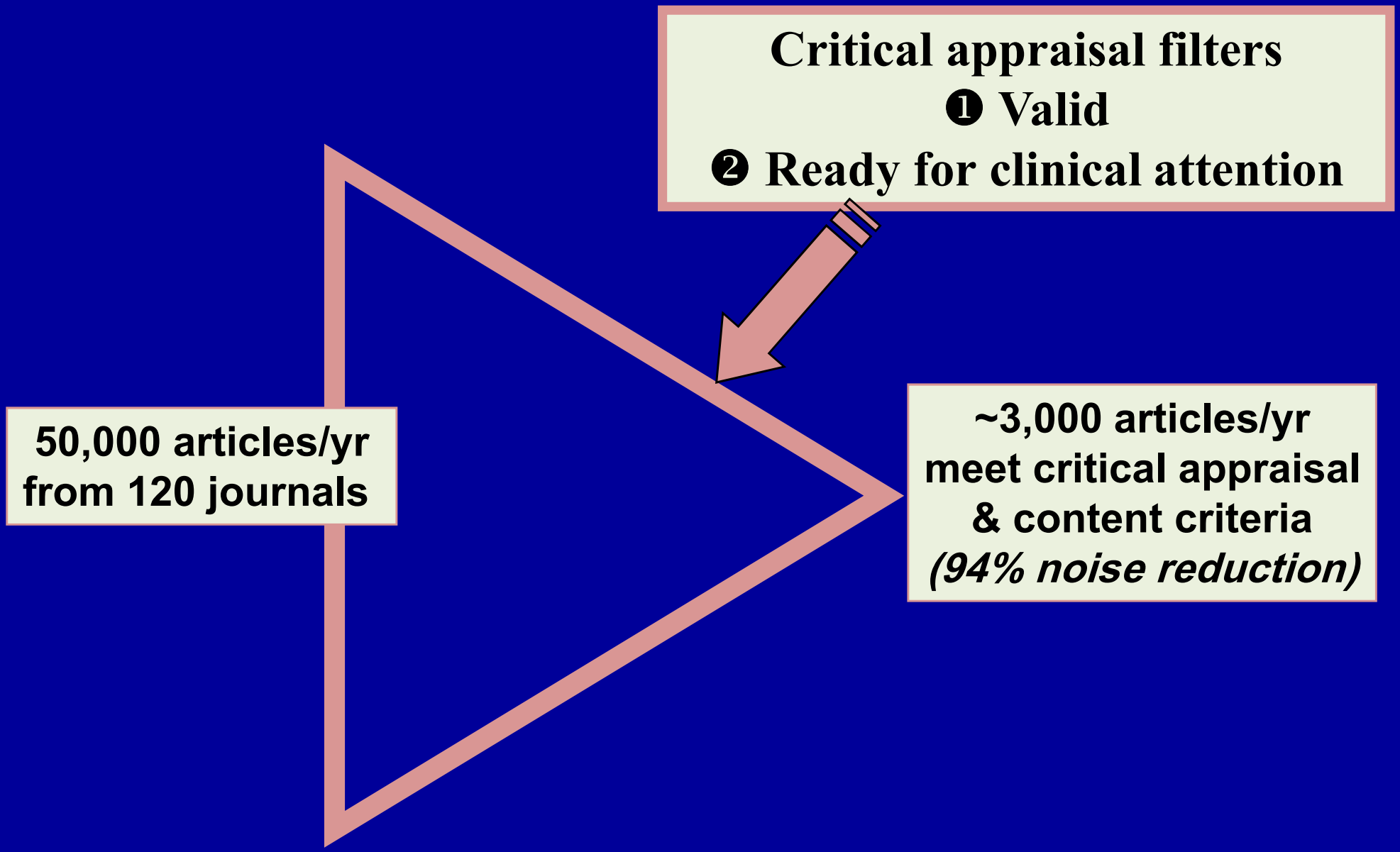
Primary research

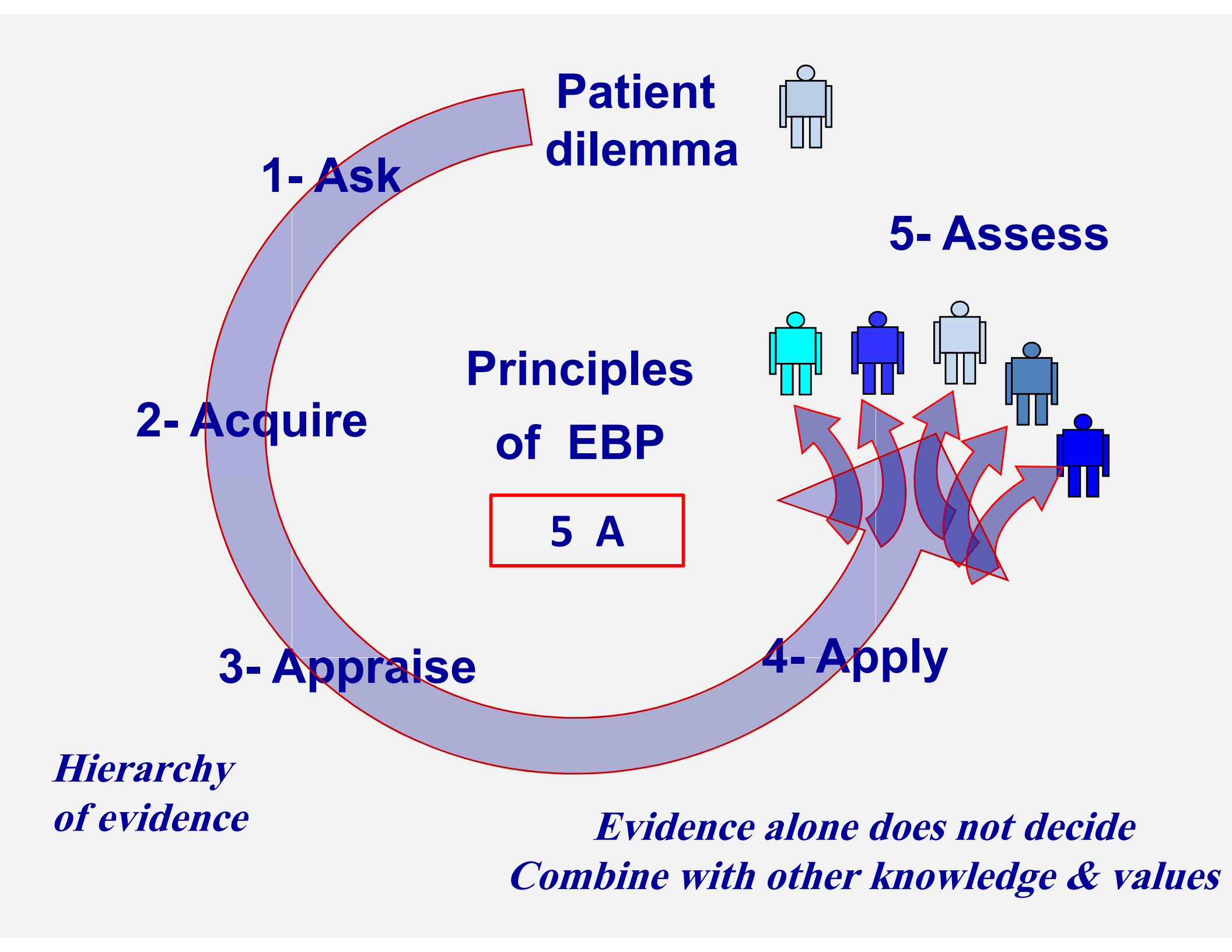
History of randomization

Sir Austin Bradford Hill

- Desirability to use randomization in clinical medicine when he published articles on medical statistics in **1937**
- He didn't recommend randomization of individuals, because he might scared doctors off any use of concurrent controls
- In **1946**, when he judged the time was right, he recommended randomization of individual patients & this rapidly gained acceptance among medical scientists

McMaster PLUS project – First level




Patient dilemma
1- Ask
5- Assess
Principles of EBP
5 A
2- Acquire
3- Appraise
4- Apply
Hierarchy of evidence
Evidence alone does not decide
Combine with other knowledge & values

RCTs as the subject of research

- Important research efforts have used RCTs as the subject rather than the tool of research

- These studies aim to improve the design, reporting, dissemination, & the use of RCTs in health care

Jadad AR, Rennie D. JAMA 1998 ; 279 : 319 – 320.

Sample size formula for binary outcomes

($\alpha = 0.05$, $\beta = 0.10$, equal number in each group)

$$N = \frac{10{\cdot}51\,[(R + 1) - p2\,(R^2 + 1)]}{p2\,(1 - R)^2}$$

N	Sample size in each of the groups
p1	Event rate in treatment group (not in formula)
p2	Event rate in control group
R	Risk ratio (p1/p2)

If	p1 = 6% p2 = 10% R = 6% / 10% = 0.60

⇒ N = 962

Variable in the sample size formula

α (Type I error)	Power (1 – β)		
	0.80	0.90	0.95
0.05	7.58	10.51	13.00
0.01	11.68	14.88	47.82

Schulz KF, Grimes DA. Lancet 2005 ; 365 : 1348 – 53.

Being a statistician means never having to say you are certain

Anon

Hand DJ. Statistics: a very short introduction.
Oxford University Press, Oxford, 1st edition, 2008.

High quality/relevant data

Pearls

If not valid → No value

If not relevant → No value

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First properly RCTs

	Immunisation against whooping cough *	Streptomycin for pulmonary TB **
Authors	MRC	MRC (D'arcy Hart)
Statistician		Bradford Hill
Started	Months before Nov1946	Nov 1946
Reported	1951	Oct 1948
Journal	BMJ	BMJ

* Medical Research Council Whooping-Cough Immunization Committee. The prevention of whooping cough by vaccination. BMJ 1951 ; i : 1463 - 71.

** Medical Research Council Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment for pulmonary tuberculosis. BMJ 1948 ; ii : 769 - 82.

Hawthorne effect

- Employees of Hawthorne Works of Western Electric Company in Chicago participated in a study to evaluate effect of **light levels on work performance**
- Surprisingly, work **performance increased**, regardless of whether level of light at workplace was increased, kept constant, or decreased.
- **Special attention** given to workers participated in the study explains improvement in overall performance