Con il Patrocinio di

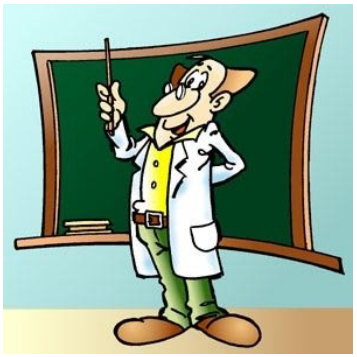
AIOM

STUDI CLINICI: CRITICITA' INTERPRETATIVE

Coordinatore:
Dr.ssa Stefania Gori

Evento ECM MODULO 2
(formazione avanzata)
"Confidence, directness, relevance"

NEGRAR
5-6 Febbraio 2016
Centro Formazione
Ospedale Sacro Cuore
Don Calabria



+

WHAT?

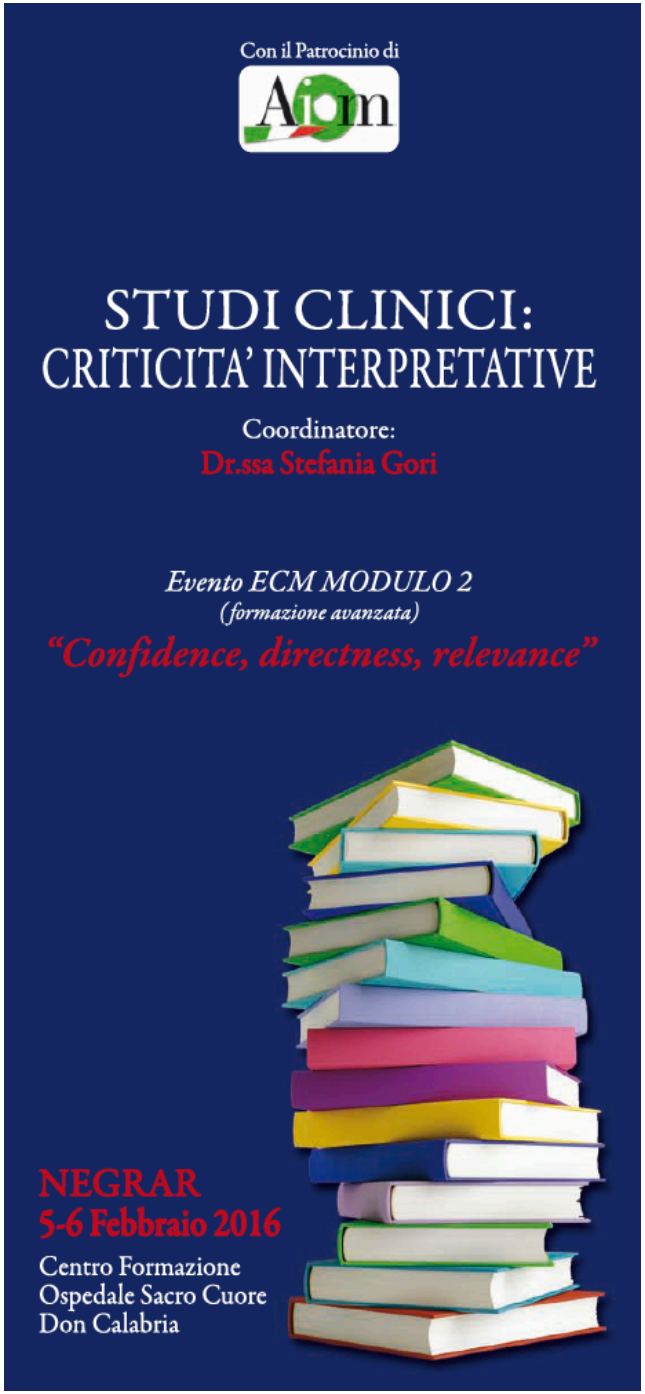
Cosa è emerso di particolarmente saliente e rilevante?
(indicare almeno 2 risposte condivise)

SO WHAT?

Perché le cose emerse sono così rilevanti?
(indicare almeno 2 risposte condivise)

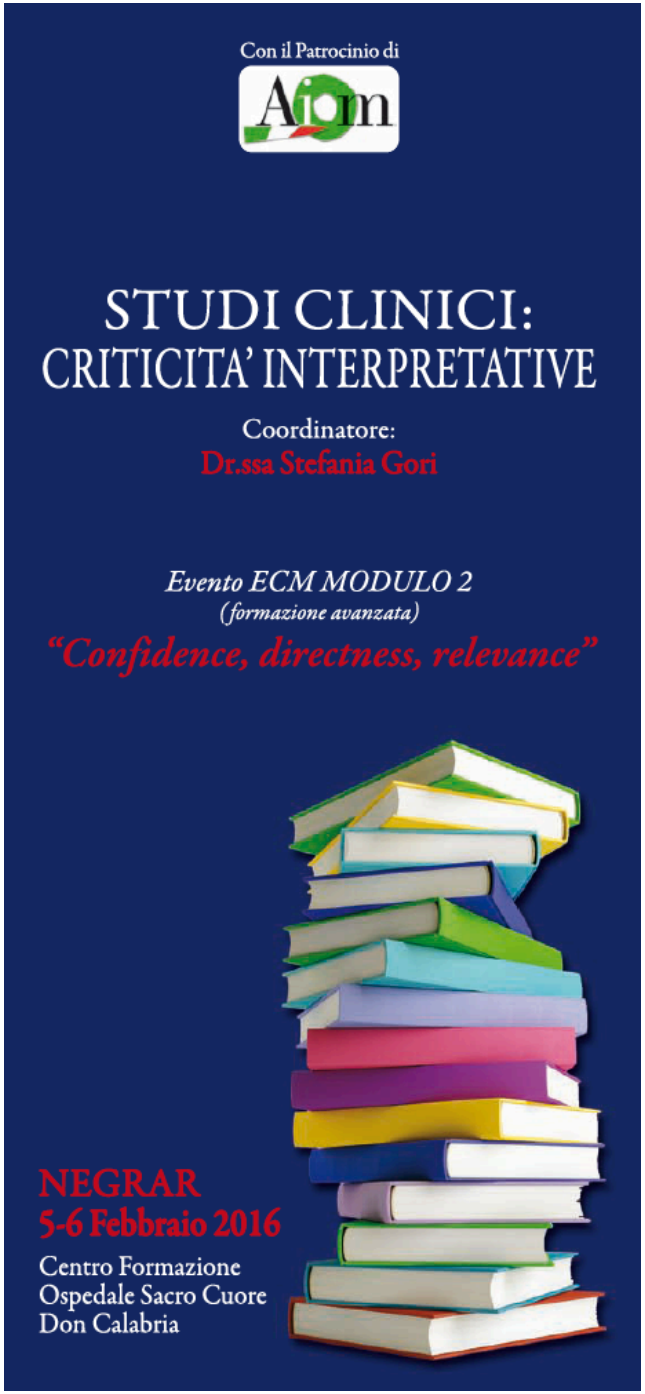
NOW WHAT?

Quali ricadute nell'immediato per la mia professione?
(indicare almeno 2 risposte condivise)



Venerdì 5 febbraio 2016

- Il quesito clinico come *primum movens* di ogni decisione terapeutica
- *Confidence*
  - ✓ rischio di bias
  - ✓ analisi per sottogruppi
  - ✓ imprecisione delle stime
  - ✓ eterogeneità delle evidenze
- *Directness*
  - ✓ adeguatezza delle evidenze al quesito P.I.C.O.
  - ✓ confronti indiretti, *network meta-analysis*
- *Relevance*
  - ✓ il *target* di rilevanza clinica



Venerdì 5 febbraio 2016

- **Il quesito clinico come *primum movens* di ogni decisione terapeutica**

- *Confidence*
  - ✓ rischio di bias
  - ✓ analisi per sottogruppi

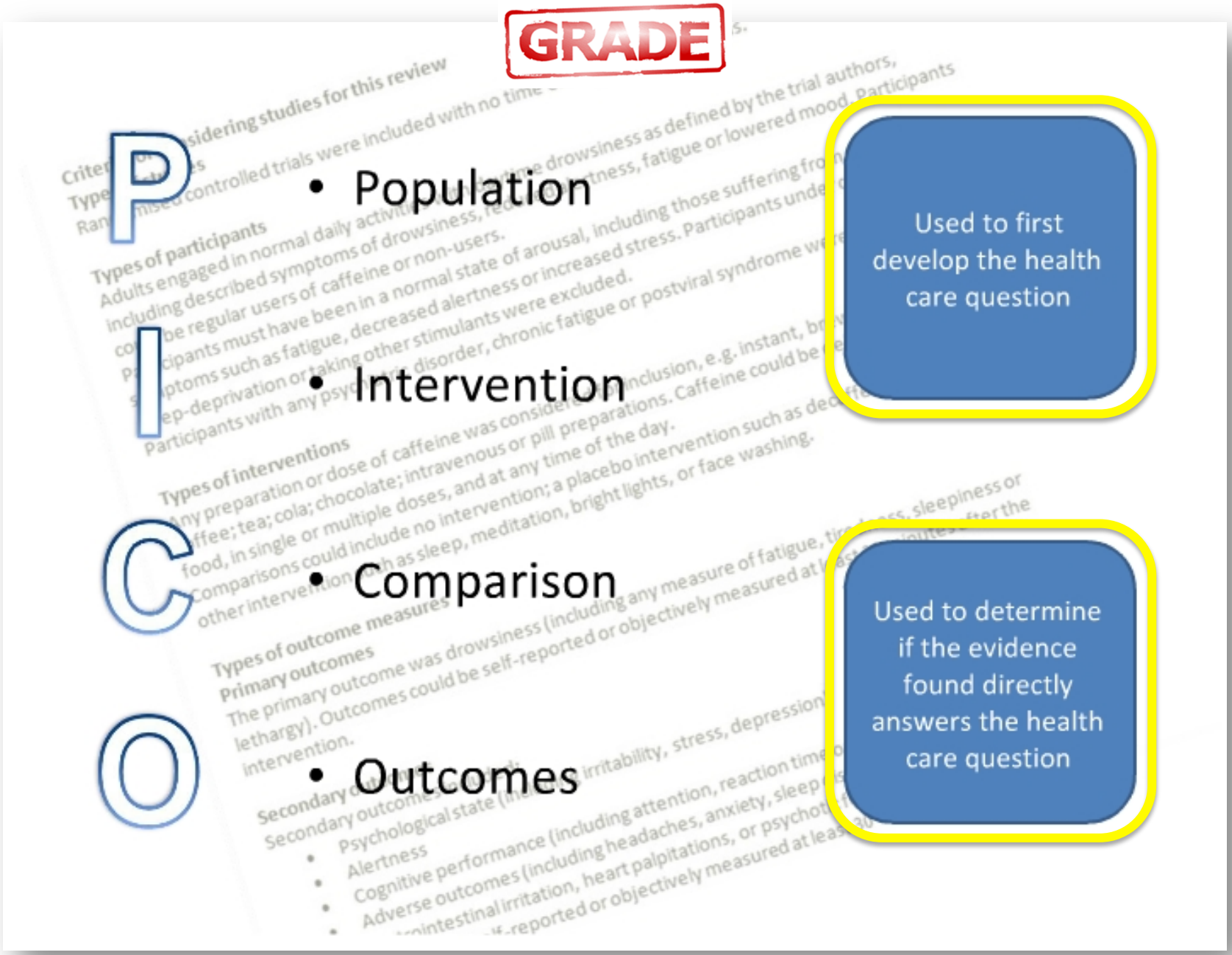
  - ✓ imprecisione delle stime
  - ✓ eterogeneità delle evidenze

- *Directness*
  - ✓ adeguatezza delle evidenze al quesito P.I.C.O.
  - ✓ confronti indiretti, *network meta-analysis*

- *Relevance*
  - ✓ il *target* di rilevanza clinica

Important Questions

Should be
from practice
NOT
evidence driven


GRADE
P
I
C
O
• Population
• Intervention
• Comparison
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

Strutturazione del Quesito Clinico sec. modello P.I.C.O.

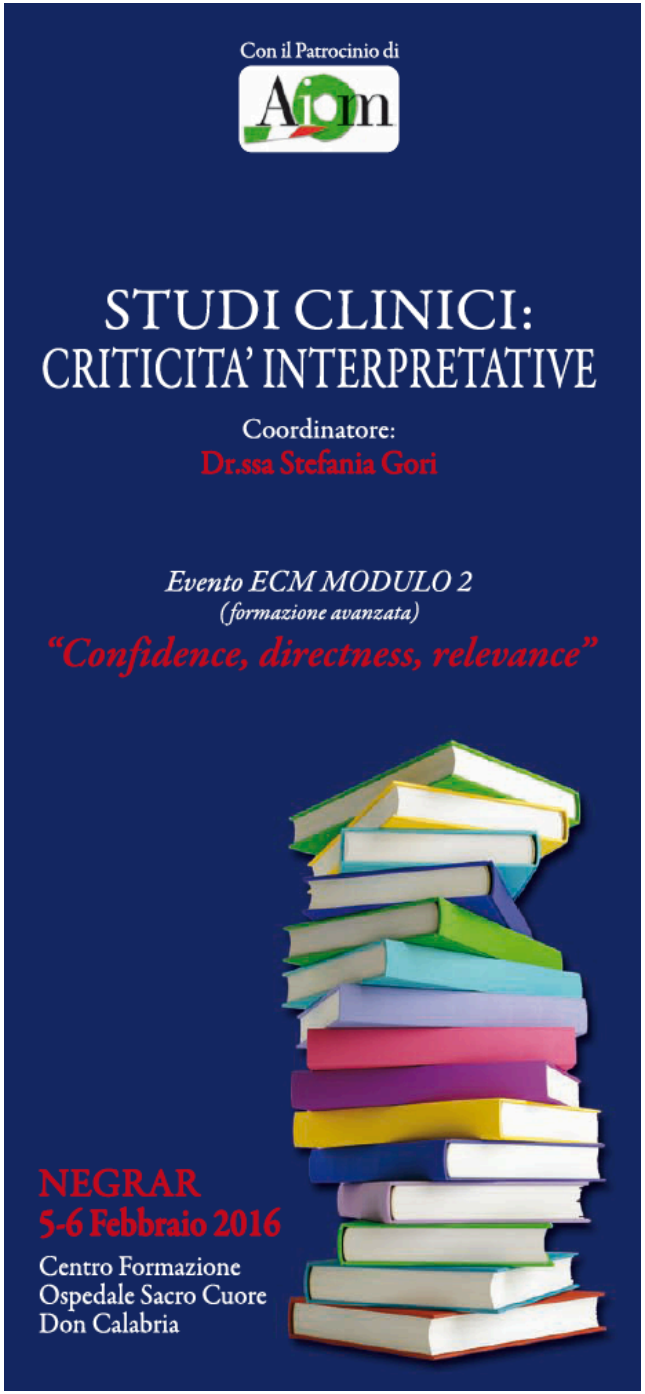
P	Nei **P**azienti con…	Specifiche caratteristiche di malattia (stadio, classe di rischio, ecc.)
I	l'**I**ntervento…	Intervento terapeutico oggetto del quesito clinico
C	(è suscettibile di impiego) in **C**onfronto con…	Trattamento altrimenti considerabile in alternativa all'intervento in esame
O	riguardo agli **O**utcome di beneficio/danno…	Parametri clinico-laboratoristici ritenuti essenziali per la decisione terapeutica

Outcomes

Should be
importance driven
NOT
evidence driven

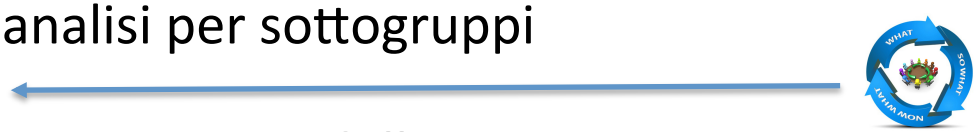
Il percorso verso la decisione terapeutica…

- Una volta definito con chiarezza il quesito clinico (e acquisita la Letteratura inerente)…
- sarà necessario verificare:
  - l'affidabilità delle evidenze (*confidence*)
  - la diretta (o meno) trasferibilità delle evidenze disponibili alla tipologia di paziente oggetto del quesito clinico (*directness*)
  - la rilevanza clinica degli effetti osservati (*relevance*)

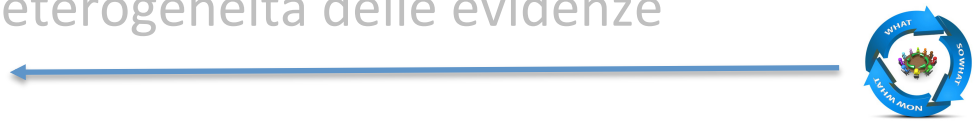


Venerdì 5 febbraio 2016

- Il quesito clinico come *primum movens* di ogni decisione terapeutica
- *Confidence*
  - ✓ rischio di bias
  - ✓ analisi per sottogruppi

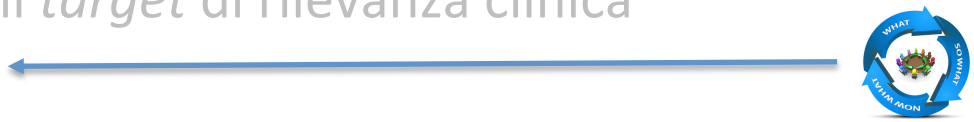


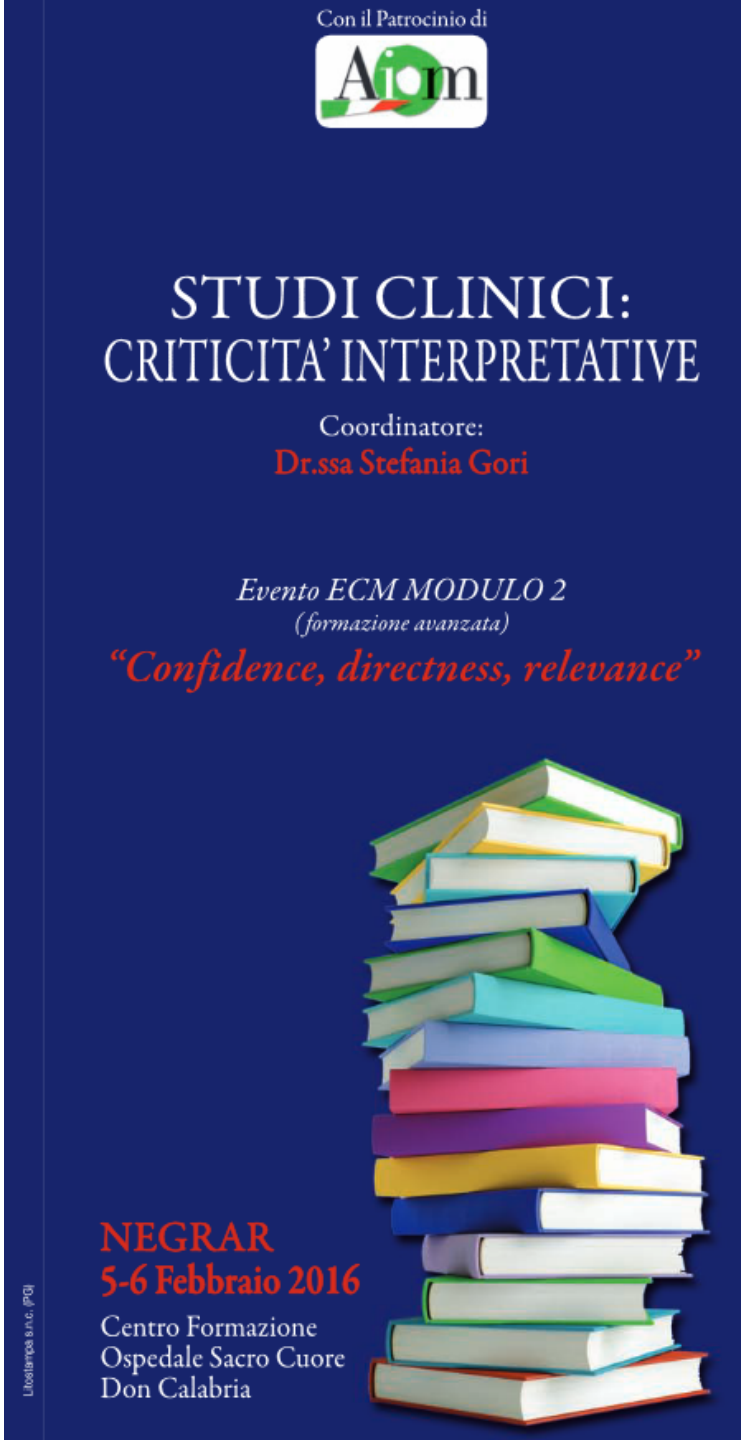
  - ✓ imprecisione delle stime
  - ✓ eterogeneità delle evidenze



- *Directness*
  - ✓ adeguatezza delle evidenze al quesito P.I.C.O.
  - ✓ confronti indiretti, *network meta-analysis*

- *Relevance*
  - ✓ il *target* di rilevanza clinica





Rischio di bias

Ivan Moschetti

ERRORE CASUALE

Errore che si verifica per effetto del caso

Replicazioni multiple della stessa misurazione producono differenti risultati in tutte le direzioni per variazioni casuali ma la media dà il risultato corretto

ERRORE SISTEMATICO

Errore che si verifica per la presenza di un fattore che distorce sistematicamente le osservazioni nella stessa direzione

Replicazioni multiple della stessa misurazione producono risultati sempre nella stessa direzione e “sbagliati”

Bias is not the same as

Imprecision

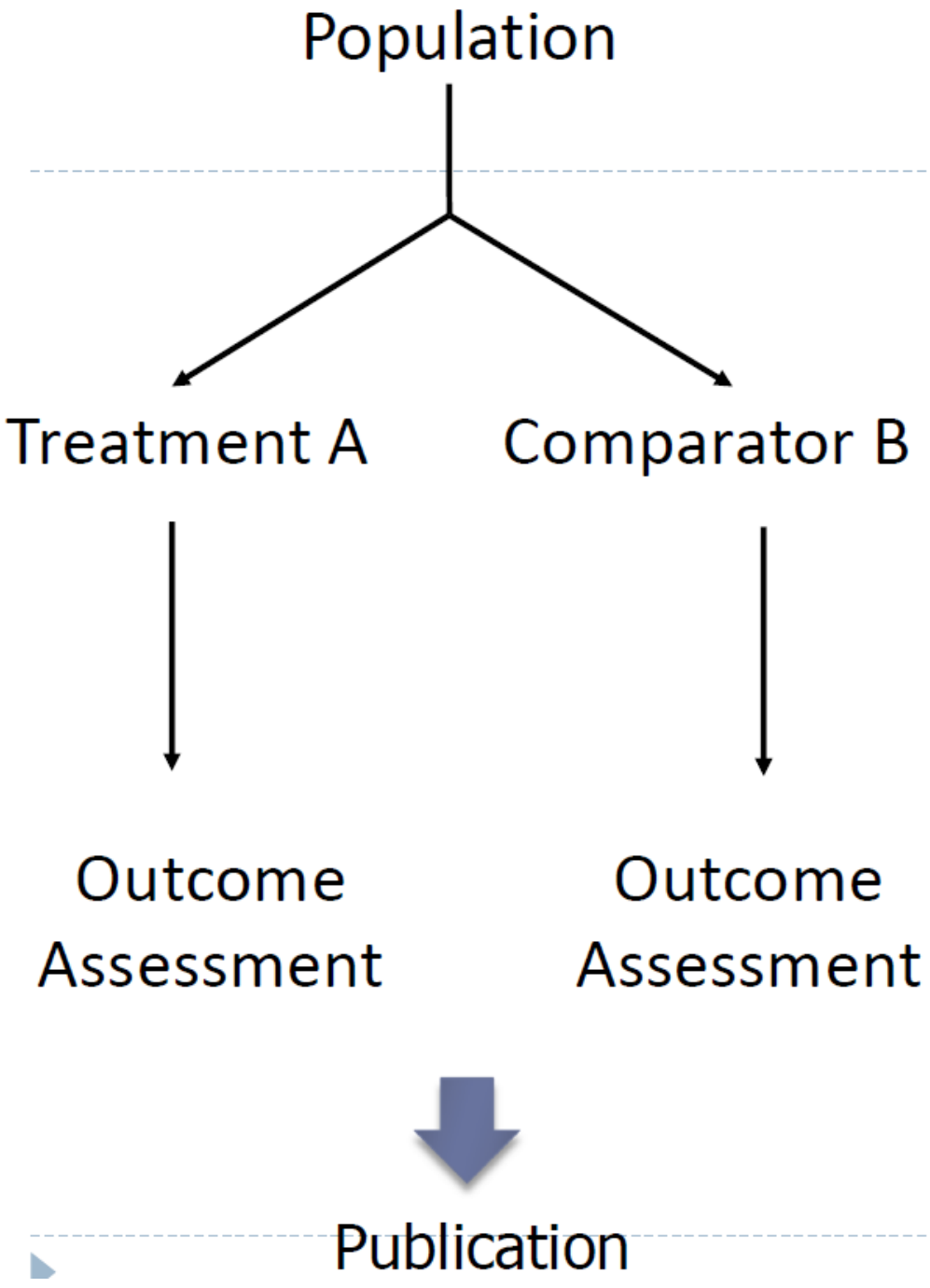
- random error due to sampling variation
- reflected in the confidence interval

Quality

- bias can occur in well-conducted studies
- not all methodological flaws introduce bias

Reporting

- good methods may have been used but not well reported



Bias

Selection bias

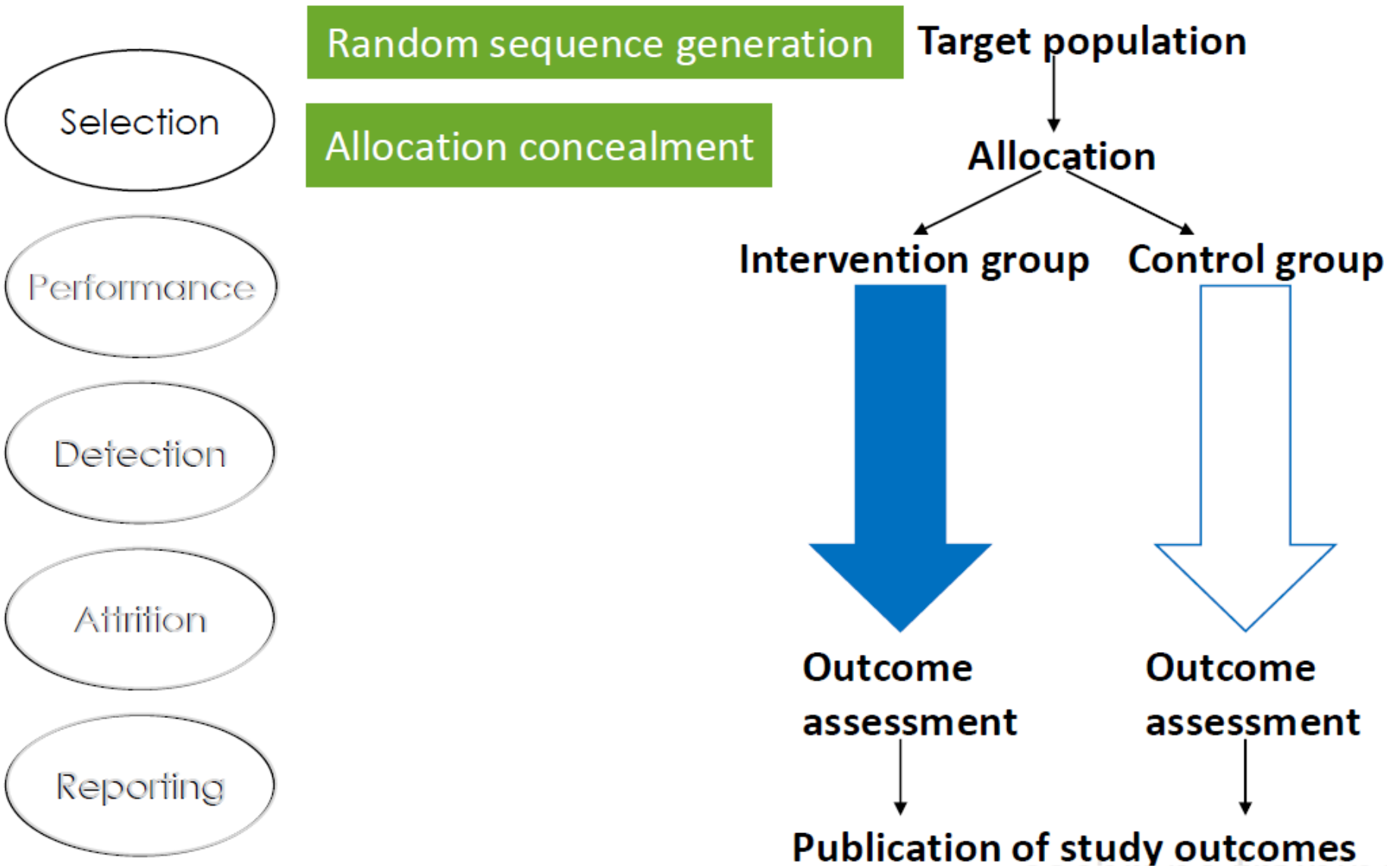
Performance bias

Detection bias

Attrition bias

Reporting bias

Sources of bias



Randomizzazione

Why randomise?

End of a clinical trial

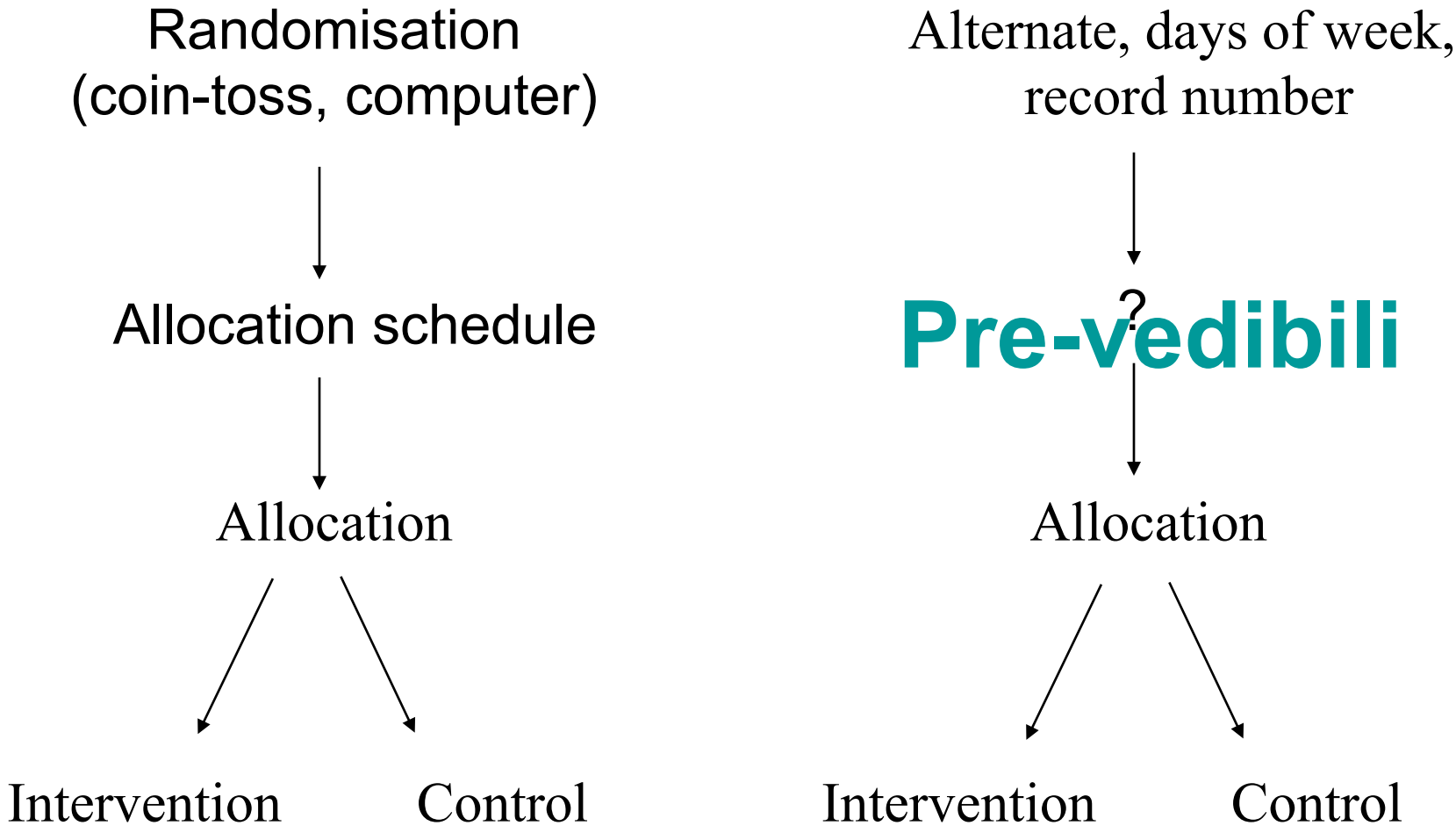
- We find a difference in outcomes between intervention and control groups
- Possible explanations:
  - the intervention exhibits a real effect
  - the outcome difference is due to chance
  - there is a systematic difference (or bias) between the groups due to factors other than the intervention
- Randomisation prevents the third possibility

Randomisation ensures similar levels of all risk factors
(known and unknown)

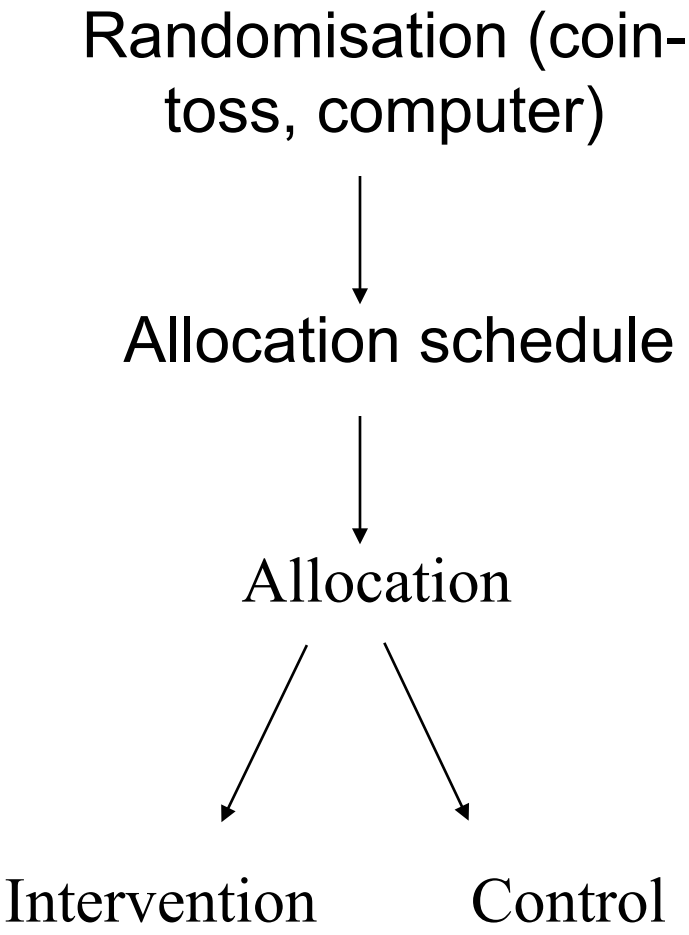
RANDOMIZATION COMPONENTS

Item	Descriptor
Sequence generation	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification)
Allocation concealment	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
Implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups

RANDOMIZATION BIAS



RANDOMIZATION BIAS



- **Recruiting selected individuals due to knowledge of the next allocation**
- **Manipulating allocations of people based on personal believing**
- **Exclusion of certain patients based on their prognosis**

Sequence generation

Criteria for a judgment of 'YES' (i.e. low risk of bias)

The investigators describe a random component in the sequence generation process such as:

- -referring to a random number table;
- -using a computer random number generator;
- -coin tossing;
- -shuffling card or envelopes;
- -throwing dice;
- -drawing of lots;
- -minimization

Criteria for a judgment of 'NO' (i.e. high risk of bias)

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach such as:

- -sequence generated by odd or even date of birth;
- -sequence generated by some rule based on date (or day) of admission;
- -sequence generated by some rule based on hospital or clinical record number.

Other non-random approaches involve judgment or some non-random classification of participants:

- -allocation by judgment of the clinician;
- -allocation by preference of the participant;
- -allocation based on the result of a laboratory test;
- -allocation by availability of the intervention.

Criteria for a judgment of 'UNCLEAR' (uncertain risk of bias)

Insufficient information about the sequence generation process to permit judgment of "Yes" and "No"

Allocation Concealment

Criteria for a judgment of 'YES' (i.e. low risk of bias)

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomization);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

Criteria for a judgment of 'NO' (i.e. high risk of bias)

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

- Using an open random allocation schedule (e.g. a list of random numbers);
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);
- Alternation or rotation;
- Date of birth;
- Case record number;
- Any other explicitly unconcealed procedure.

Criteria for a judgment of 'UNCLEAR' (uncertain risk of bias)

Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described but it remains unclear whether envelopes were sequentially numbered, opaque and sealed

Assessing methods can be tough

- “Randomisations were generated by a computer algorithm at Neose Technologies. The drug and placebo looked similar and were randomly assigned labels 1-10.
- “The randomisation list, provided by the manufacturer, had patient numbers one to 550 randomly linked in blocks of ten to the ten drug la[illegible]ts.”

E. *RANDOMIZZAZIONE*

E’ stata generata al computer una lista di numeri casuali in modo da assegnare ognuno degli 11 spazzolini ad un settore della bocca, lasciando un settore non spazzolato che servisse da controllo. La randomizzazione è stata di tipo “bloccato”, in maniera da non generare sbilanciamenti nei rapporti tra gli spazzolini e i settori della bocca nei quali erano utilizzati.

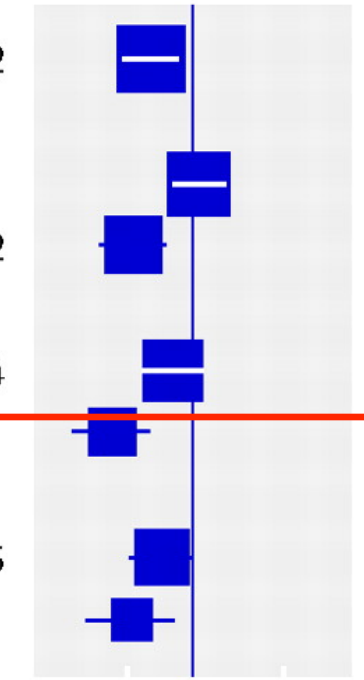
F. *ALLOCATION CONCEALMENT*

L’*allocation concealment* è stato ottenuto attraverso l’approntamento di buste chiuse contenenti, ognuna per ciascun soggetto che partecipava allo studio, la lista di assegnazione dei differenti spazzolini ai differenti settori della bocca. L’apertura di ogni busta e l’assegnazione dei trattamenti è stata effettuata sempre immediatamente prima che il paziente spazzolasse i denti.

?

Ratios of odds ratios comparing estimates of intervention effects 532 trials with inadequate or unclear allocation concealment versus 272 trials with adequate concealment

Comparison (No of meta-analyses)	No of trials*	Ratio of odds ratios	Ratio of odds ratios (95% CI)	P value of test of interaction	Variability in bias† (P value)
Overall (102)	532 *v* 272		0.83 (0.74 to 0.93)	–	0.11 (<0.001)
All cause mortality (23)	119 *v* 90		1.01 (0.90 to 1.15)	0.002	0.02 (0.24)
Other outcomes (79)	415 *v* 182		0.76 (0.66 to 0.87)		0.14 (<0.001)
Objective outcomes (62)	310 *v* 174		0.91 (0.80 to 1.03)	0.009	0.11 (<0.001)
Subjective outcomes (40)	222 *v* 98		0.69 (0.59 to 0.82)		0.07 (0.011)
Drug intervention (65)	411 *v* 205		0.87 (0.76 to 1.00)	0.27	0.09 (<0.001)
Other intervention (37)	121 *v* 67		0.77 (0.64 to 0.93)		0.16 (<0.001)



* Inadequately or unclearly concealed *v* adequately concealed

† Between-meta-analysis heterogeneity variance

Wood, L. et al. BMJ 2008;336:601-605

Allocation concealment

≠

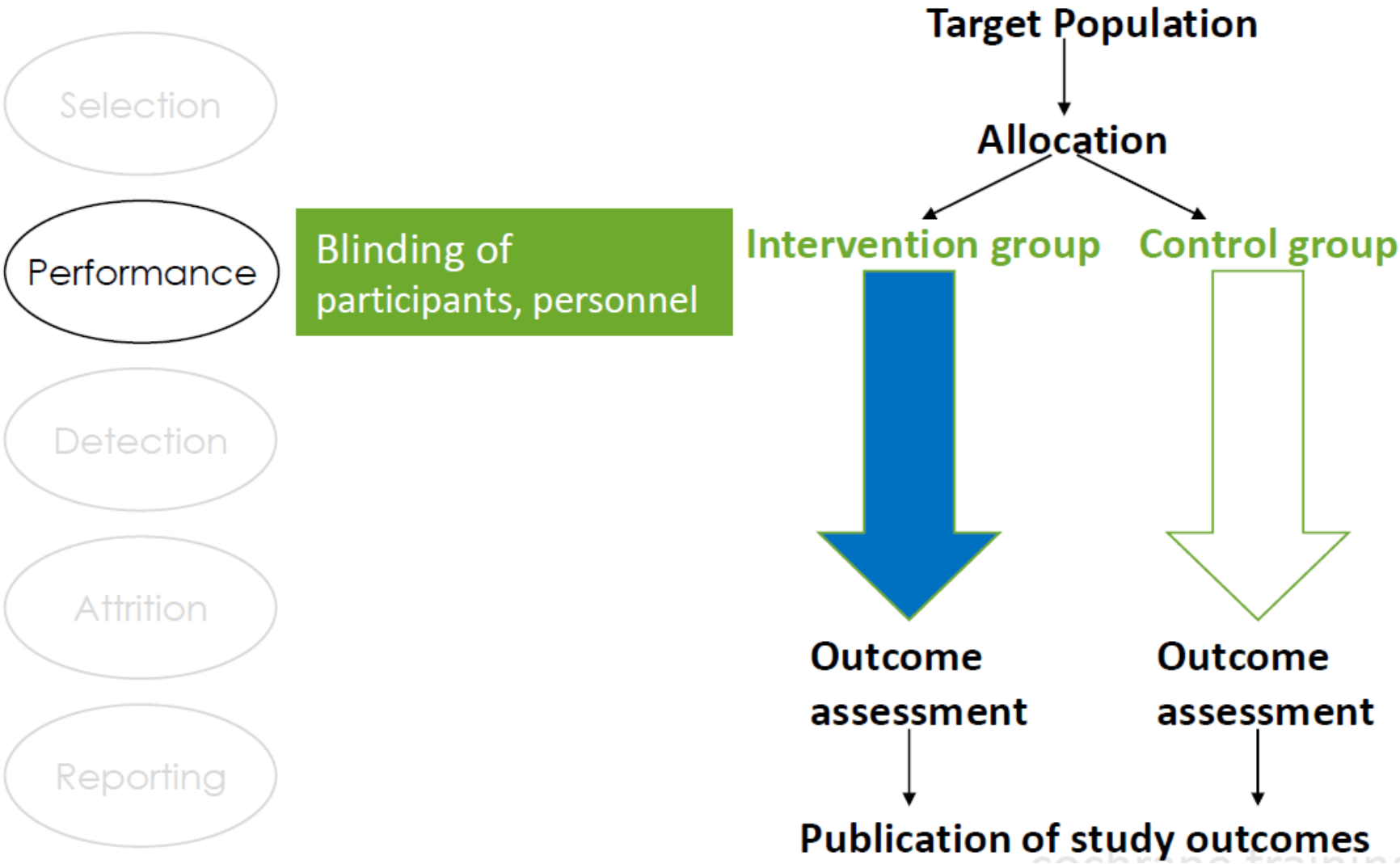
Blinding

- It prevents **selection bias** in intervention assignment by protecting the allocation sequence **before and until** assignment
- It can always be successfully implemented regardless of the study topic

- It seeks to prevent **performance and detection bias** by protecting the sequence **after** assignment
- Not always feasible – for example, in trials comparing surgical with medical interventions

CECITA’

Sources of bias



Sources of bias

Selection

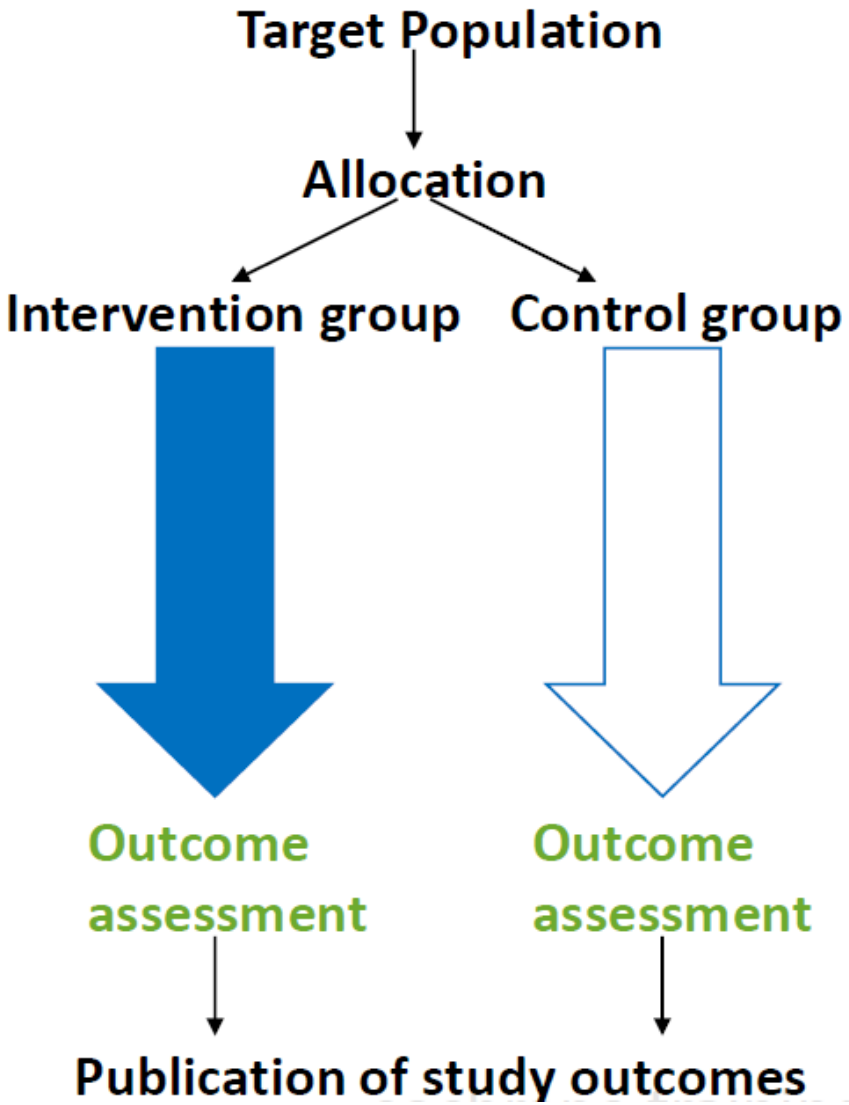
Performance

Detection

Blinding of outcome assessment

Attrition

Reporting



6 ragioni per introdurre la cecità

- Se dite al paziente che è stato randomizzato al placebo, non è contento
- Se dite alle persone che l'efficacia del trattamento è dovuto all'effetto placebo, si arrabbiano
- Se dite al clinico che il paziente prende il trattamento, il clinico vedrà un miglioramento (anche in assenza di cambiamento)
- Se dite al paziente che non si dovrebbe grattare, si gratta uguale, ma vi dice che si gratta di meno (Effetto Rosenthal)
- Illusione di specifici effetti come le tradizioni millenarie sono molto radicate (agopuntura nei meridiani vs a caso)
- Avete inventato la panacea che, ogni volta che la somministrate, fallisce miseramente… cercate cercate fino a analizzare il beneficio su 100 variabili…(così funziona la statistica)

COSA POTREBBE FARE

- Usually reduces differential assessment
- May improve compliance and retention
- May reduce biased supplemental care or treatment (co-intervention) [and testing]

Blinding

Criteria for a judgment of 'YES' (low risk of bias)

Any one of the following:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding;
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias

Criteria for a judgment of 'NO' (high risk of bias)

Any one of the following:

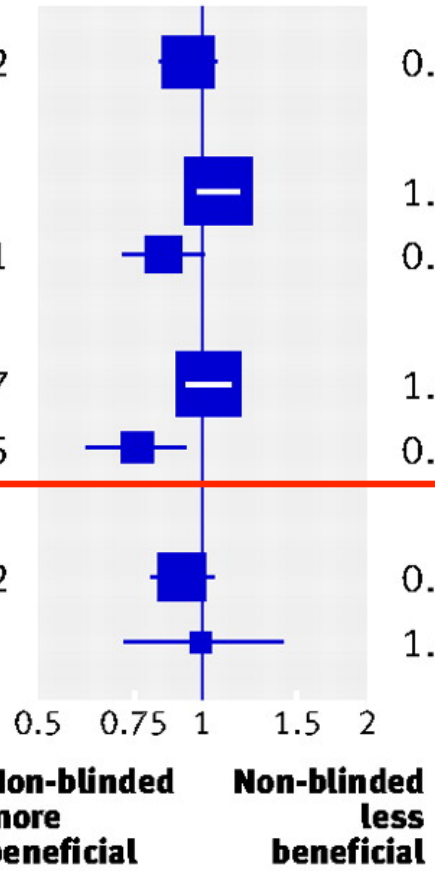
- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgment of 'UNCLEAR' (uncertain risk of bias)

Insufficient information to permit judgment of 'Yes' or 'No', or the study did not address this outcome.

Ratios of odds ratios comparing intervention effect estimates in 314 non-blinded trials versus 432 blinded trials.

Comparison (No of meta-analyses)	No of trials*	Ratio of odds ratios	Ratio of odds ratios (95% CI)	P value of test of interaction	Variability in bias† (P value)
Overall (76)	314 *v* 432		0.93 (0.83 to 1.04)	–	0.11 (<0.001)
All cause mortality (18)	79 *v* 121		1.04 (0.95 to 1.14)	0.011	0.01 (0.27)
Other outcomes (58)	235 *v* 311		0.83 (0.70 to 0.98)		0.18 (<0.001)
Objective outcomes (44)	210 *v* 227		1.01 (0.92 to 1.10)	0.01	0.08 (<0.001)
Subjective outcomes (32)	104 *v* 205		0.75 (0.61 to 0.82)		0.14 (0.001)
Drug intervention (57)	250 *v* 372		0.92 (0.81 to 1.05)	0.66	0.10 (<0.001)
Other intervention (19)	64 *v* 60		1.00 (0.71 to 1.39)		0.22 (0.003)



* Non-blinded *v* blinded

† Between-meta-analysis heterogeneity variance

Wood, L. et al. BMJ 2008;336:601-605

Blinding: take home messages

Detection bias –

- Blinding? Double blinding? Triple blinding?
- Who needs to be blinded?
- Is the outcome sensitive to blinding?
  - Blinding: clearly very difficult in many intervention trials (i.e. surgical)
  - Solution: Blinded assessors should be used routinely for measuring outcome

Sources of bias

Selection

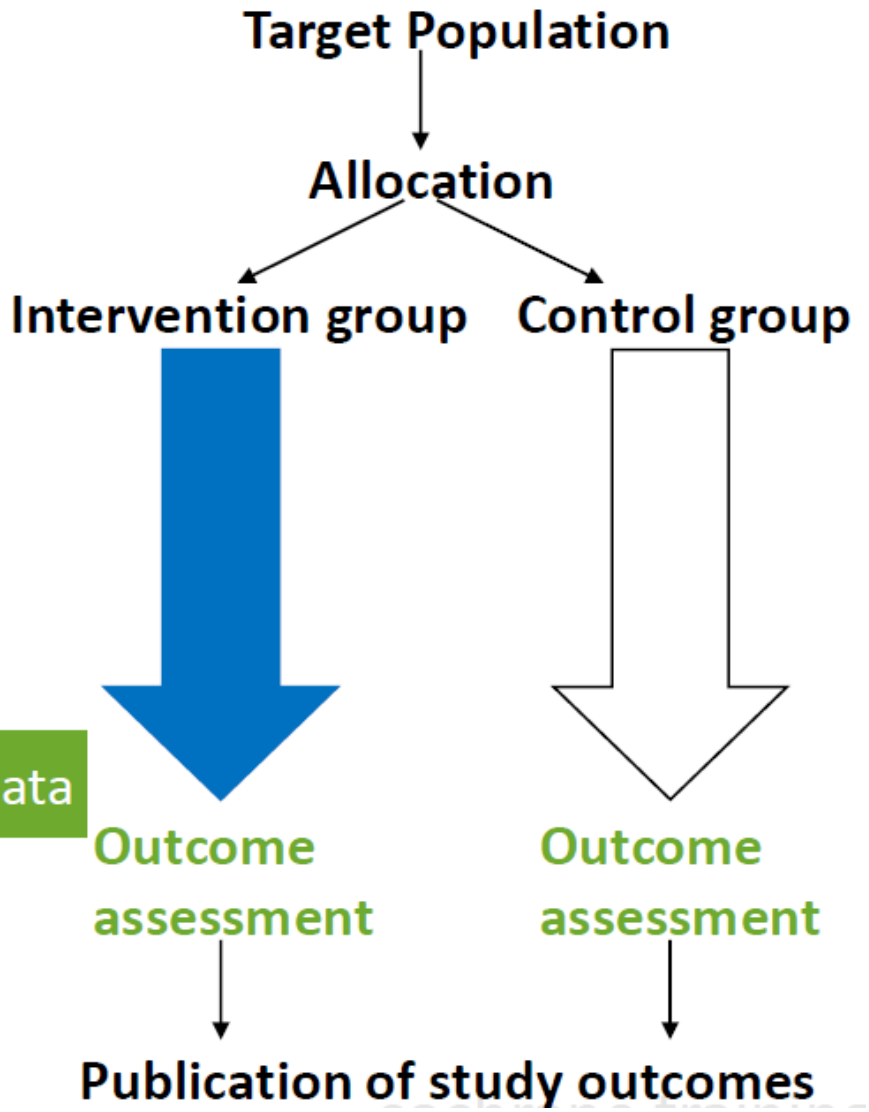
Performance

Detection

Attrition

Reporting

Incomplete outcome data



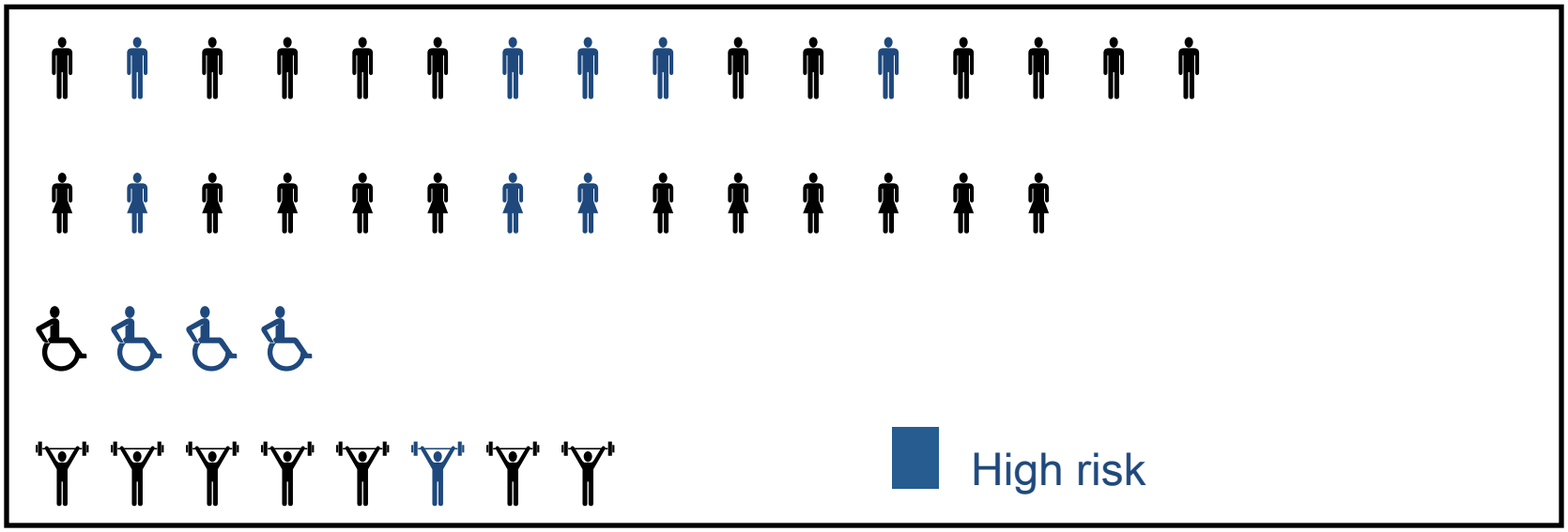
ATTRITION

Attrition bias -

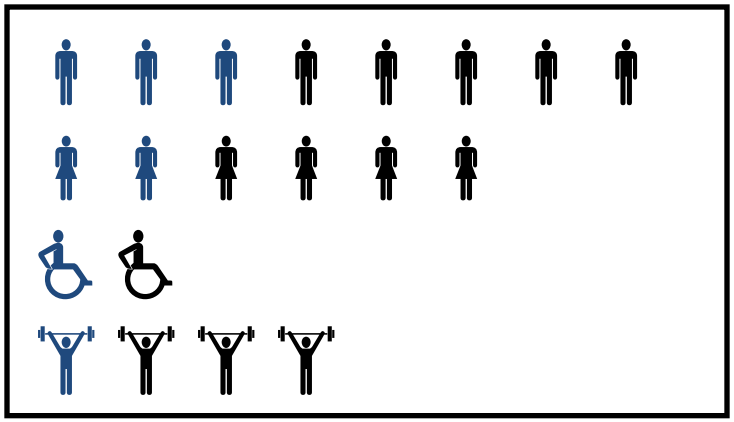
- Systematic differences between groups in losses of participants from the study

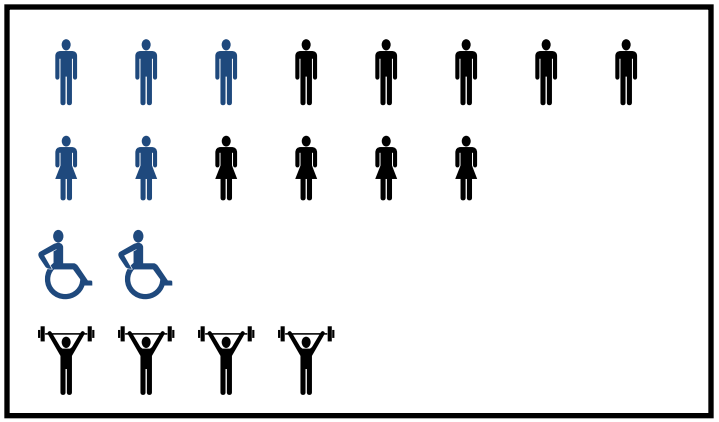
Systematic ≠ Random differences

Patients eligible for my trial

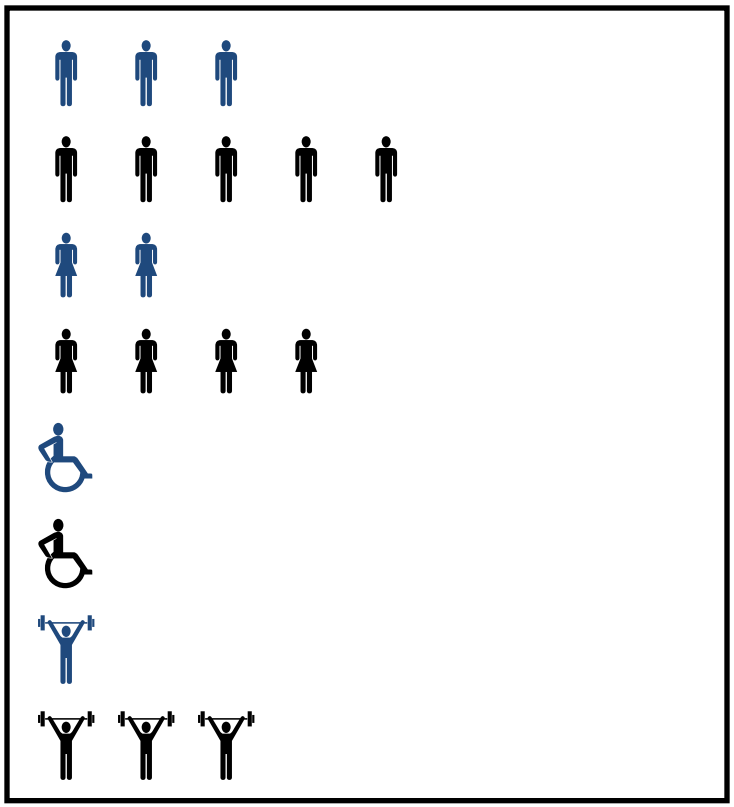


R

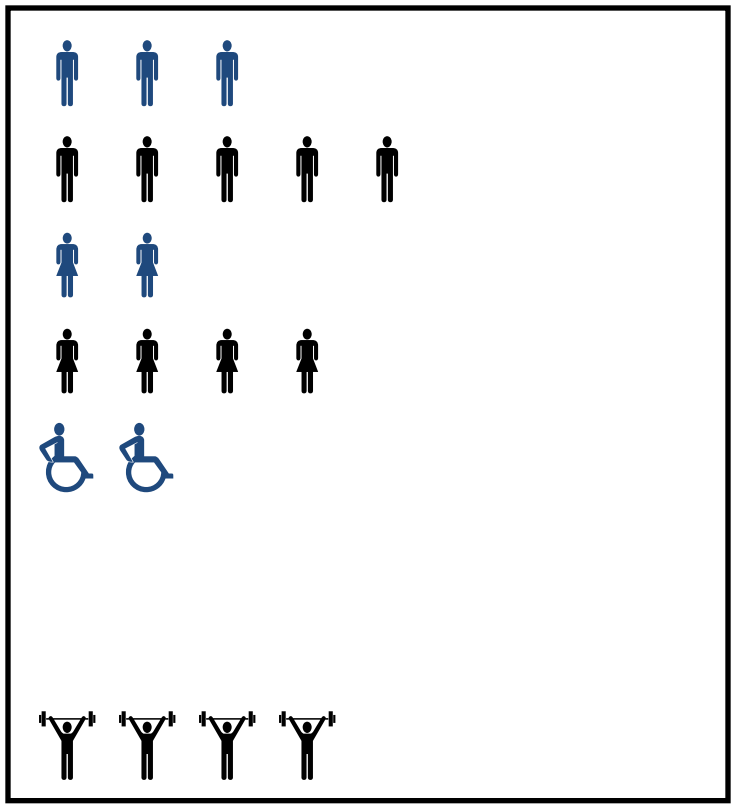




Perfect Randomisation = Perfect Balance



R

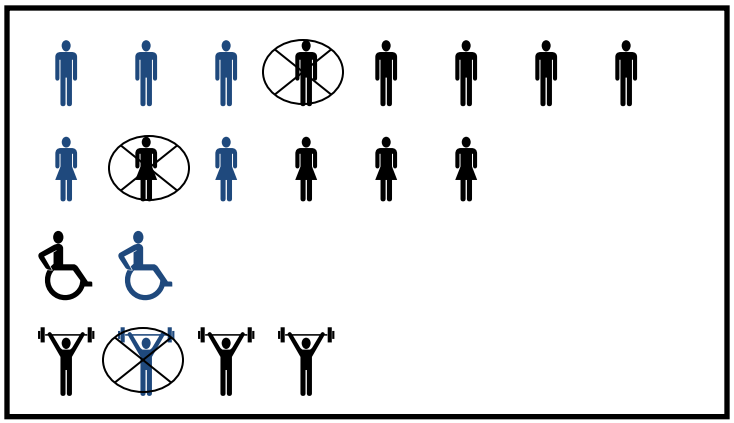


7/20

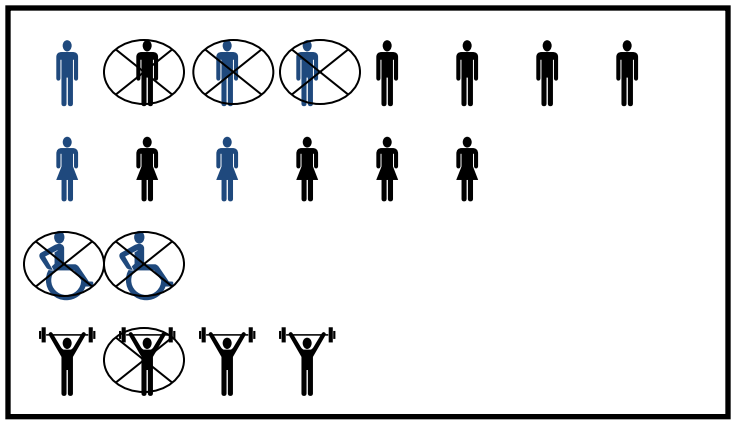
7/20

High risk

Attrition



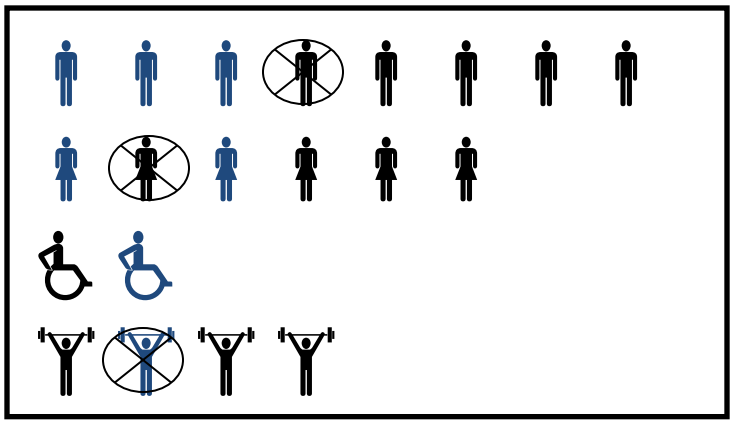
R



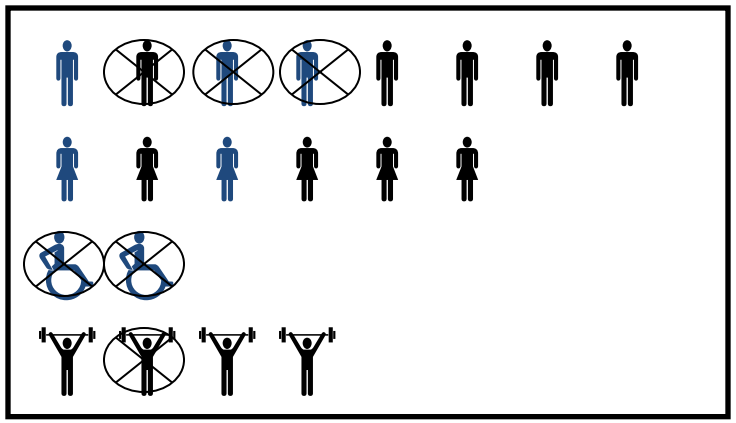
7/20	=	7/20
6/17	≠	3/14

⊗ Lost to FU

Losses



R



In totale:

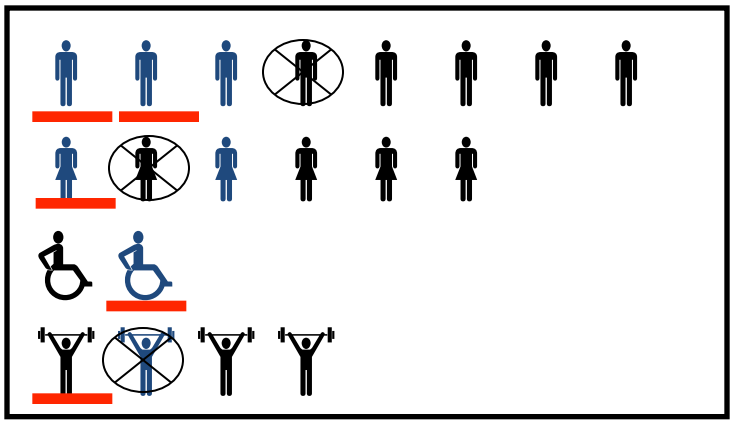
9 pazienti persi su 40 randomizzati = 23%

E’ tanto?

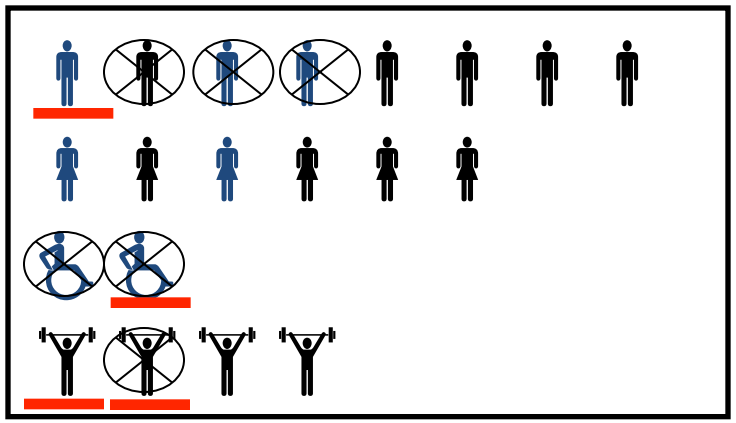
La perdita è sbilanciata tra i due gruppi?

Lost to FU

Event Rates



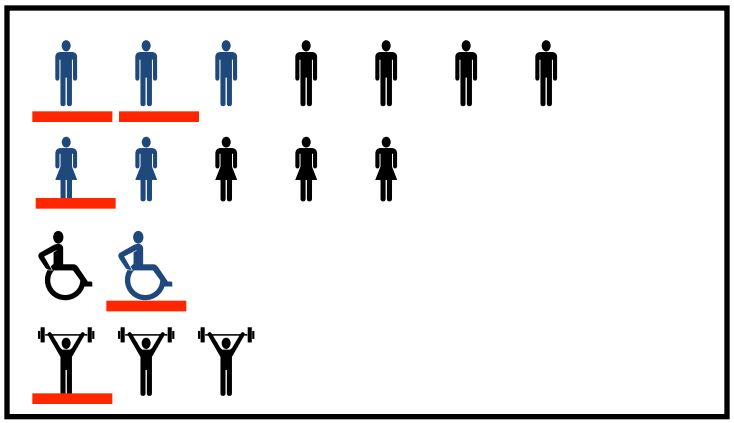
R



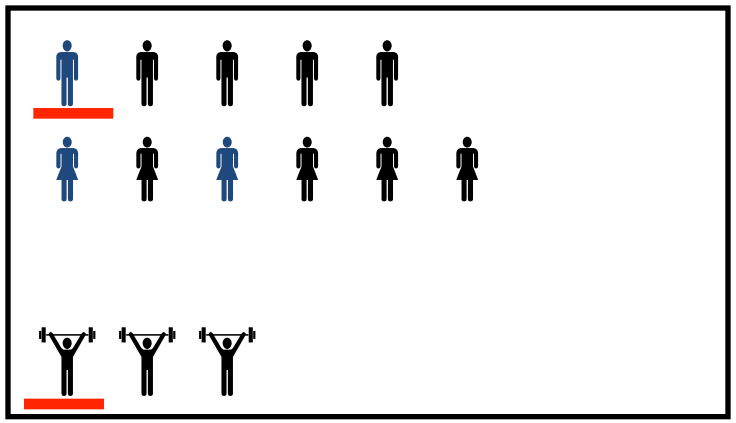
5/20 = 4/20

— **Event** ⊗ Lost to FU

Attrition impact on rates



R



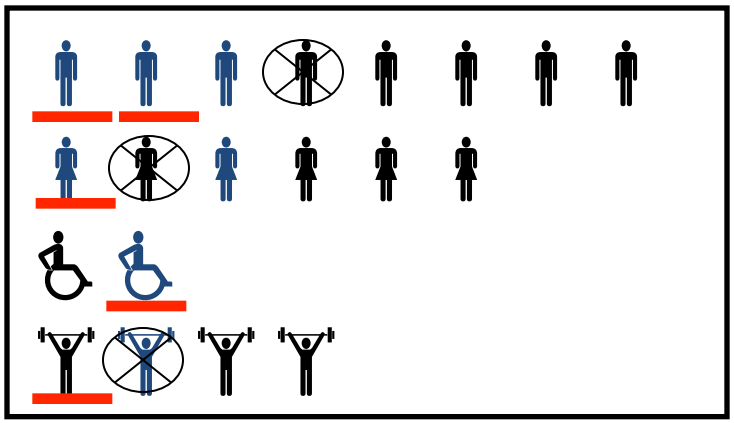
5/17 ≠ 2/14

6/17 ≠ 3/14

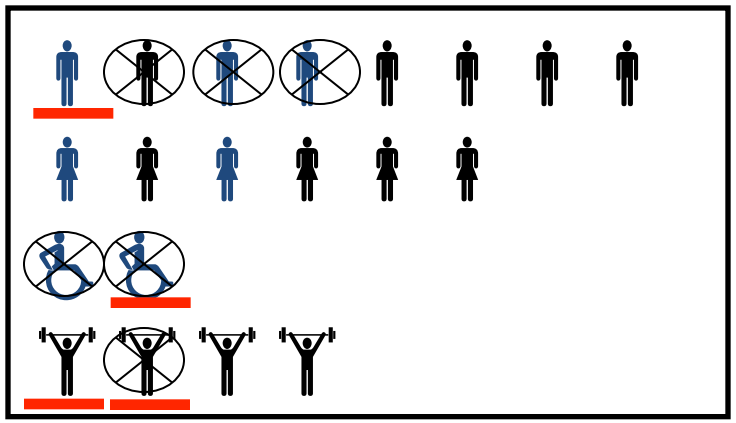
Per protocol

— **Event** ⊗ Lost to FU

Attrition impact on rates



R

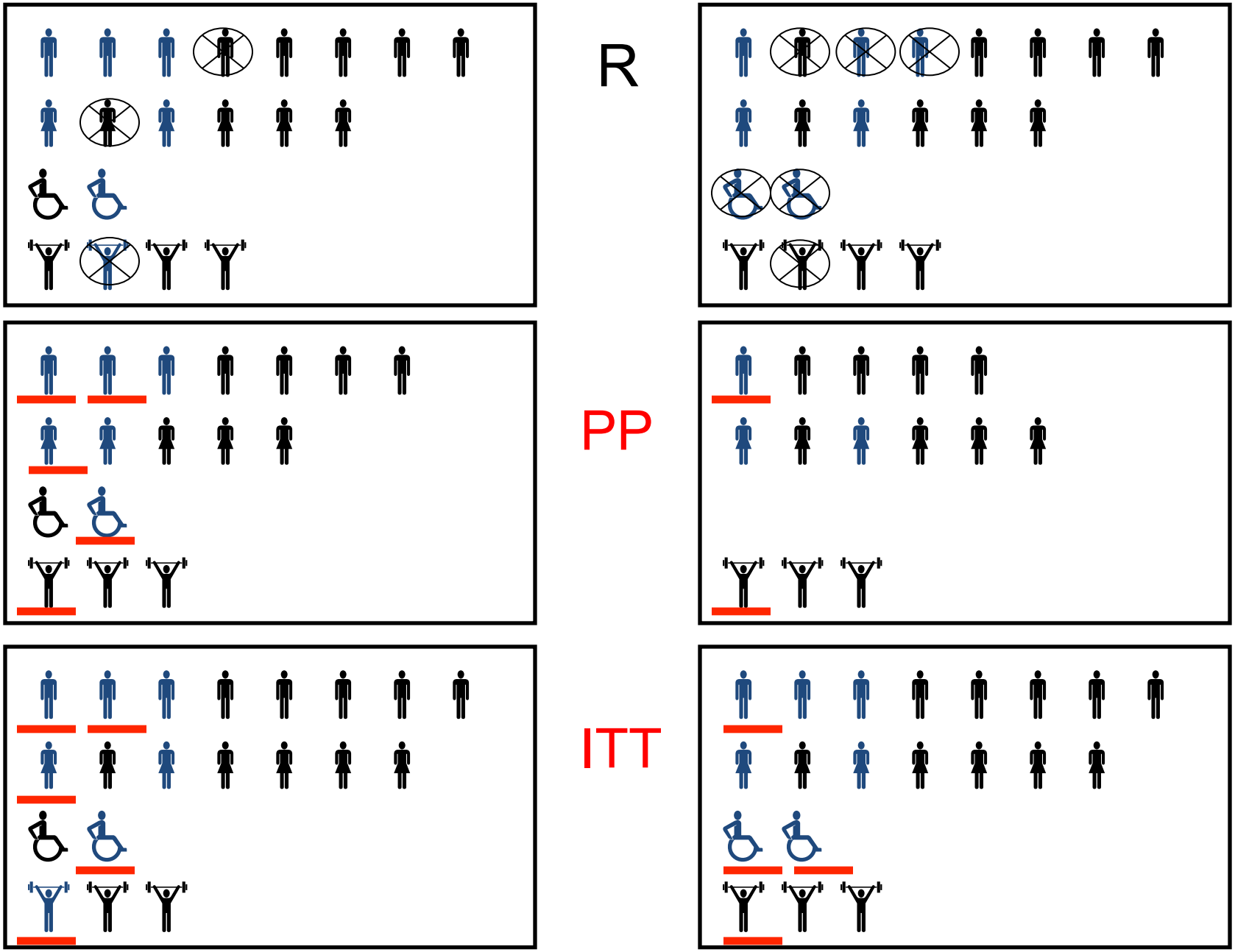


5/20 ≈ 4/20

Intention to Treat

— **Event** ⊗ Lost to FU

Summary



Tassonomia

Le esclusioni dopo la randomizzazione non sono tutte uguali

Attrition bias -

- Systematic differences between groups in losses of participants from the study

Look at withdrawals, cross-over, drop-outs and losses to follow up

Participant adherence to studies

- Exclusions people who are screened as potential participants for randomized trial but who do not meet all of the entry criteria and, therefore are not randomized [spesso il termine è utilizzato per esclusioni dopo la randomizzazione]
- Withdrawals are participants who have been randomized but are deliberately not included in the analysis [eg, ineligibility, no adherence, poor quality data, and occurrence of competing events]
- Lost to follow up investigator unable to assess the occurrence of the event in some participant

Participant adherence to studies

- *Cross over* participant although assigned to the control follows the intervention or assigned to the intervention follows the control
- *Drop in* particular case of cross over, unidirectional, assigned to the control, begins following the intervention
- *Drop out* assigned to an intervention fails to comply with the intervention (if the control is placebo or no intervention drop out equivalent to a cross over)
- *Drop out* sometimes referred to participants who are unwilling or unable to return for follow-up visits

Participant adherence to studies

- Lost to follow up ≠ withdrawal
- Drop out = lost to follow up (latter more appropriate)

Friedman LM, Furberg CD, DeMets DL. Fundamentals of clinical trials. Third Ed Springer. New York 1998

Cochrane – Incomplete data outcome

Per protocol analysis

Analysis of the results of only those participant who completed the trial and who complied with their allocated intervention (overestimate effects)

Available case analysis

Data are analysed for every participants for whom the outcome was obtained

Intention to treat analysis

- Keep participants in the intervention groups o which they were randomised, regardless of the intervention they actually received CONSENSUS
- measure outcome data on all participants IMPOSSIBLE
- include all randomised participants in the analysis CONTENTIOUS (can inflate precision [if events are many] or involves imputing of data)

Criteria for a judgment of 'YES' (low risk of bias)

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to impact to any clinically relevant extent on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to impact to any clinically relevant extent on observed effect size

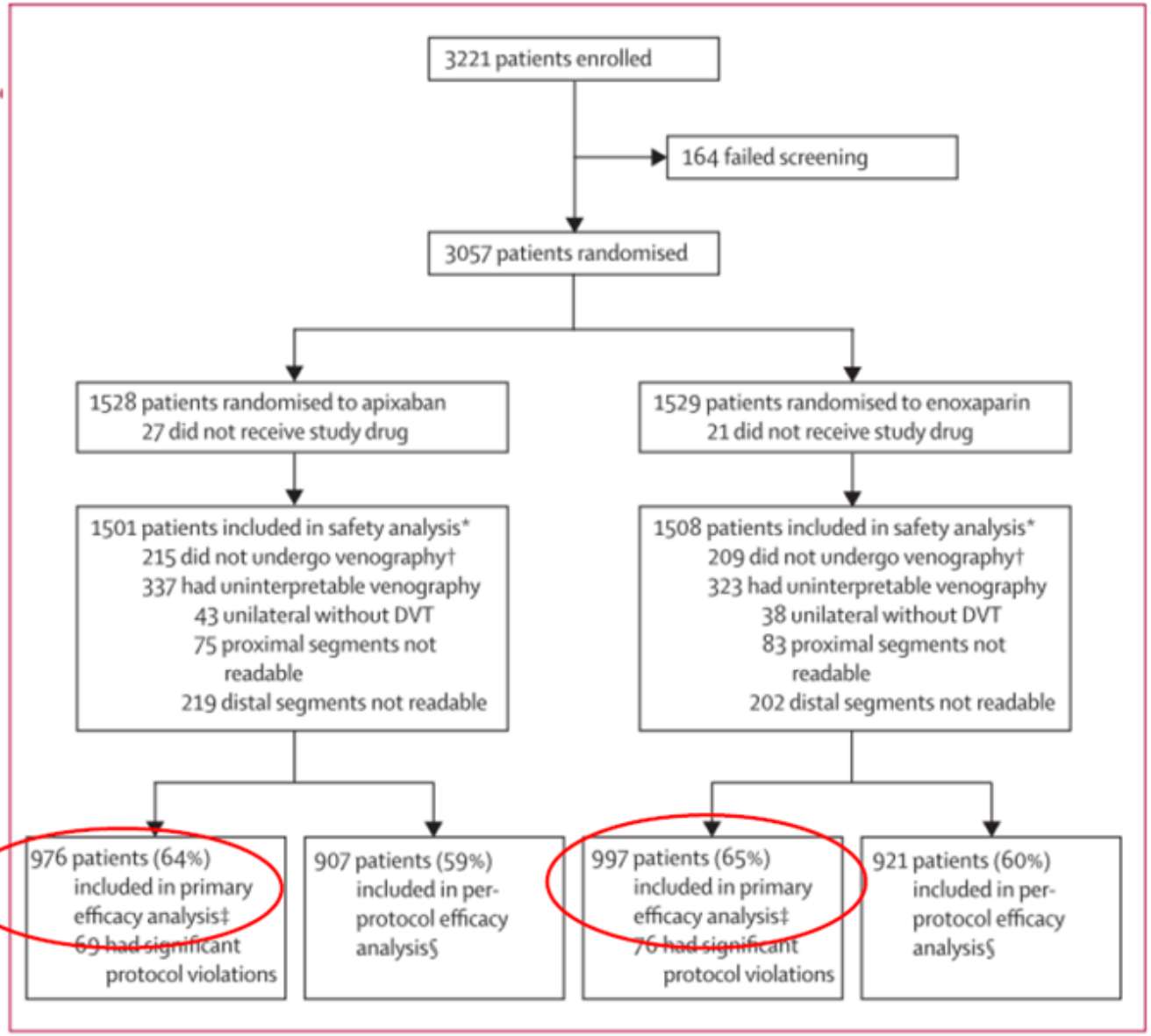
Criteria for a judgment of 'NO' (high risk of bias)

Any one of the following:

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'As-treated' analysis with substantial departure of the intervention received from that assigned at randomization;
- Potentially inappropriate application of simple imputation

Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial

Michael Rud Lassen, Gary E Raskob, Alexander Gallus,



Sources of bias

Selection

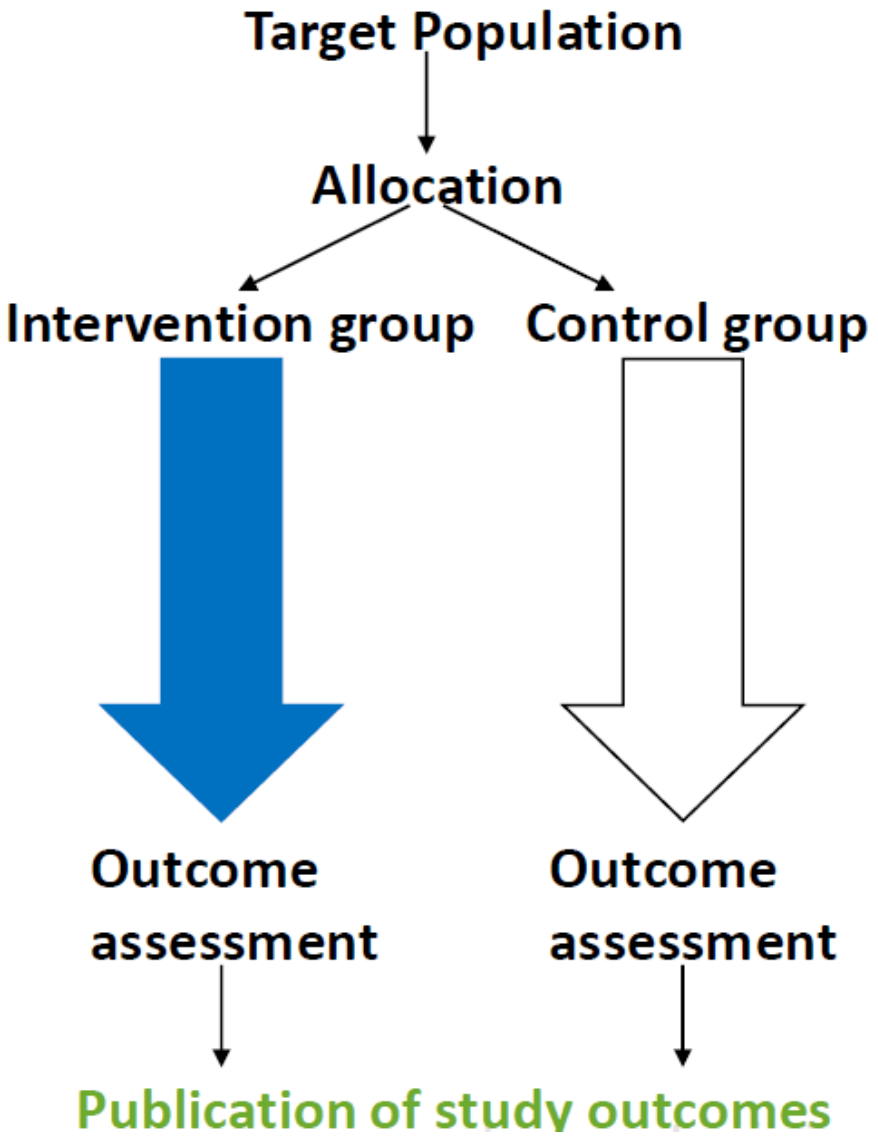
Performance

Detection

Attrition

Reporting

Selective reporting



What is publication bias (1)?

- Definition

"Publication bias refers to the greater likelihood that studies with positive results will be published"

JAMA 2002;287:2825-2828

What is publication bias (2)?

- An alternative definition:

Publication bias is the selective or *multiple* publication *or suppression* of trial results so that the scientific record is distorted

Extension: applied to trial parts - outcomes, subgroups, adverse events REPORTING BIAS

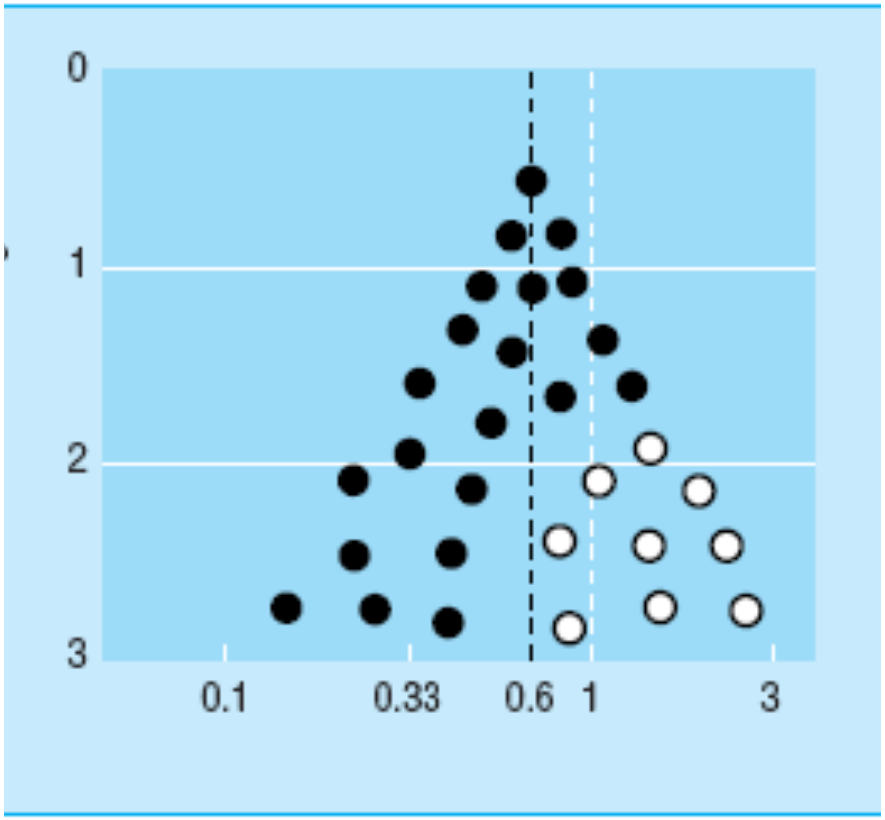
The likelihood of finding studies is related to the results of those studies (positive vs negative/ detrimental)

Why does it matter?

- Distorts the scientific record
- Hides the “truth”
- Influences doctors’ decision making
- Misleads policy makers
- Causes harm to patients
- Costly for the health service
- A form of scientific and research misconduct

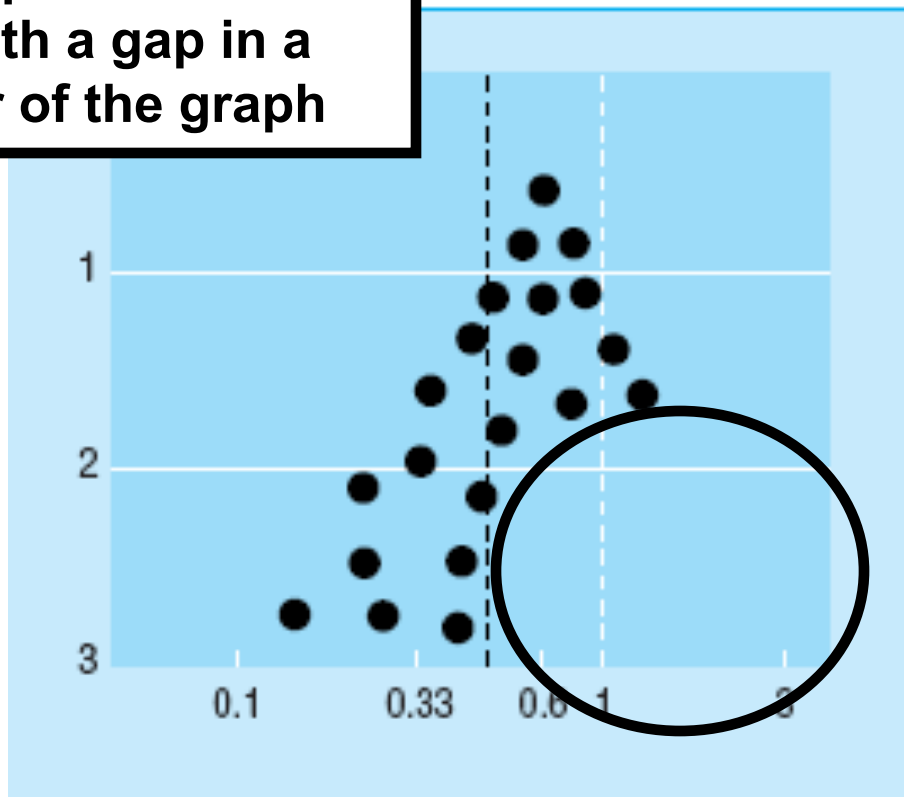
- TO U: It will matter if the studies you don’t find differ systematically from the ones you have found
- You might arrive at different answers, or even THE WRONG ANSWER

Publication of All Trials



Publication Bias

Asymmetrical appearance of the funnel plot with a gap in a bottom corner of the graph



Funnel plots

- A funnel plot is a scatter plot of treatment effect against a measure of study size / precision.

- Precision in the estimation of the true treatment effect increases as the sample size increases.
- Small studies scatter more widely at the bottom of the graph
- In the absence of bias the plot should resemble a symmetrical inverted funnel

Publication Bias

- **In this situation the effect calculated in a meta-analysis will overestimate the treatment effect**

- **The more pronounced the asymmetry, the more likely it is that the amount of bias will be substantial.**

Outcome reporting bias

Reporting bias is selection bias

- Reporting bias is perhaps the greatest source of selection bias
- Originally defined as the publication or non-publication of studies depending on the direction and statistical significance of the results
- Is a complex phenomenon

Full	n and effect size, plus precision / *p*-value for continuous data	
Partial	Effect size or precision (± n or *p*-value)	**Incompletely reported outcomes**
Qualitative	*p*-value	
Unreported		

(Chan, 2004)