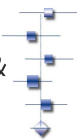


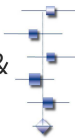
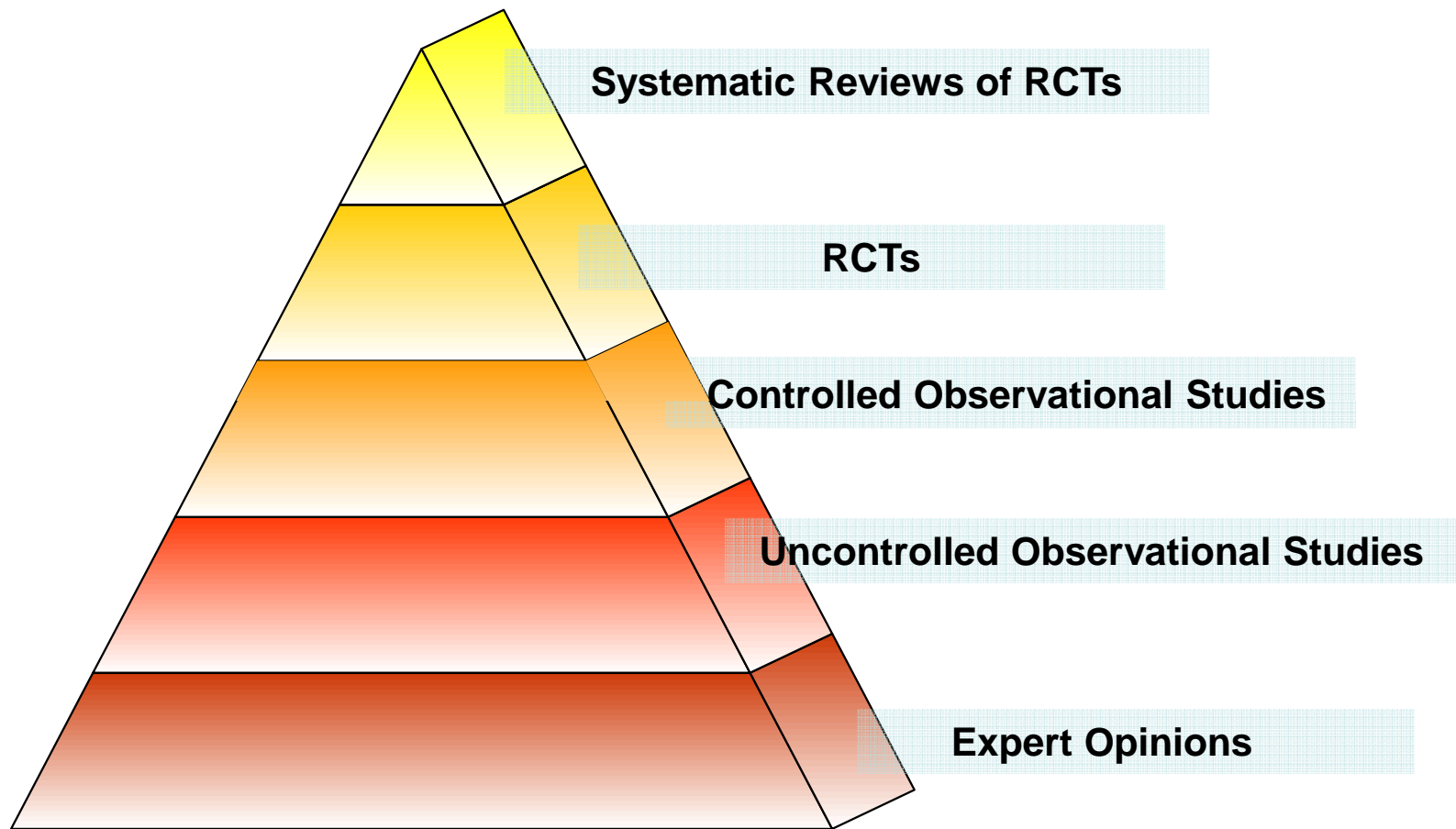
Randomized Controlled Trials

Gerald Gartlehner

DEPARTMENT FOR
EVIDENCE-BASED MEDICINE &
CLINICAL EPIDEMIOLOGY



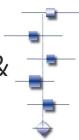
Hierarchy of the Evidence



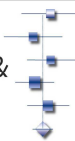
- Why do we need good studies ?
- What are the advantages of RCTs?
- How can we critically appraise RCTs?



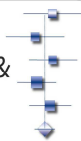
Why do we need good studies?

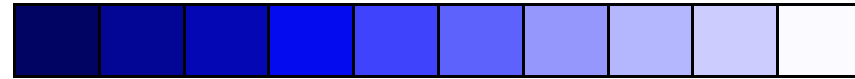


„...the last 5 cases that I have seen.....“



We need good studies when treatment effects are small but clinically important.

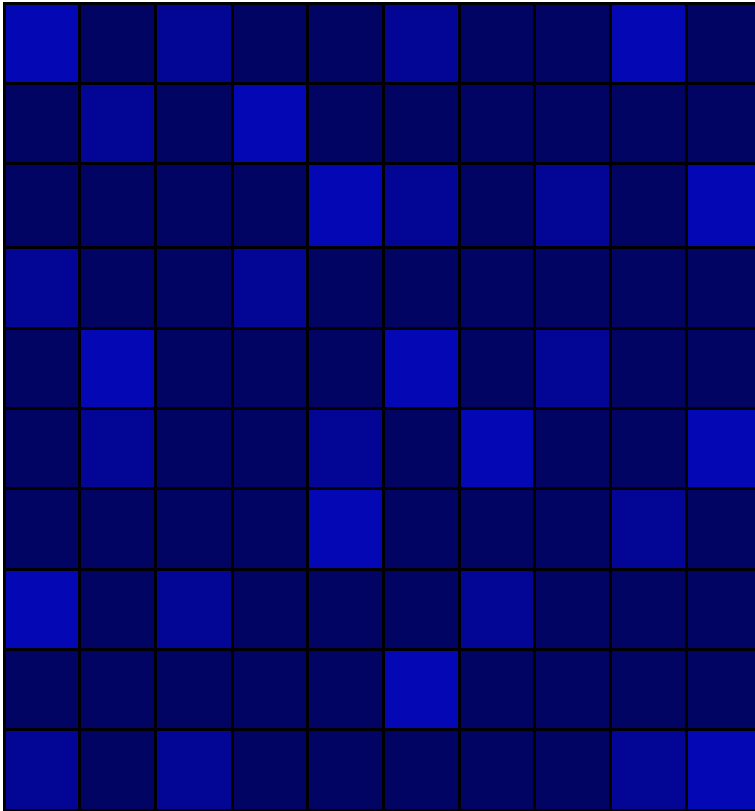




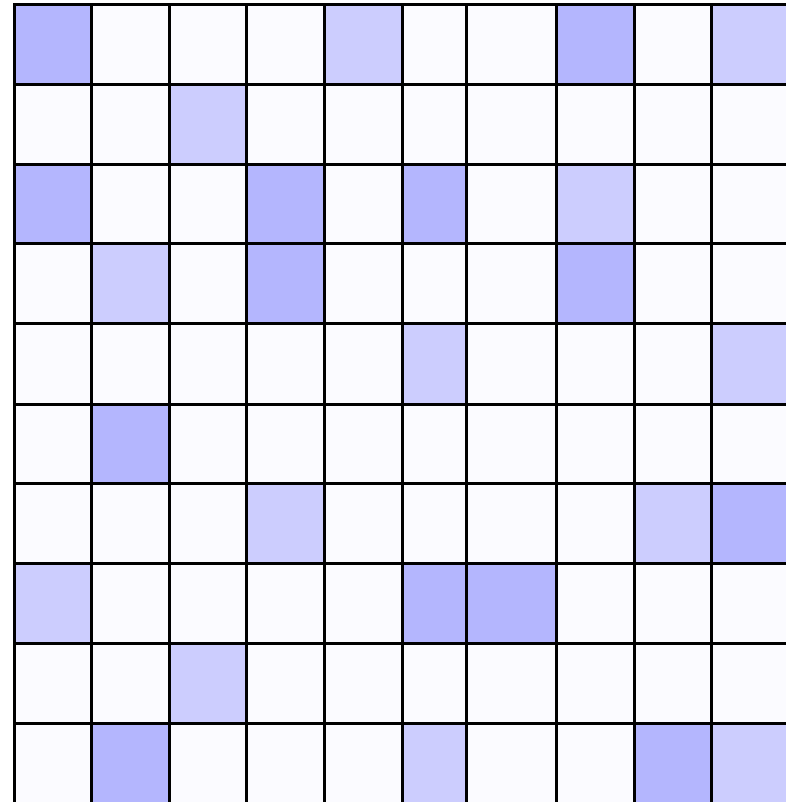
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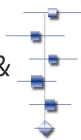
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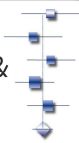
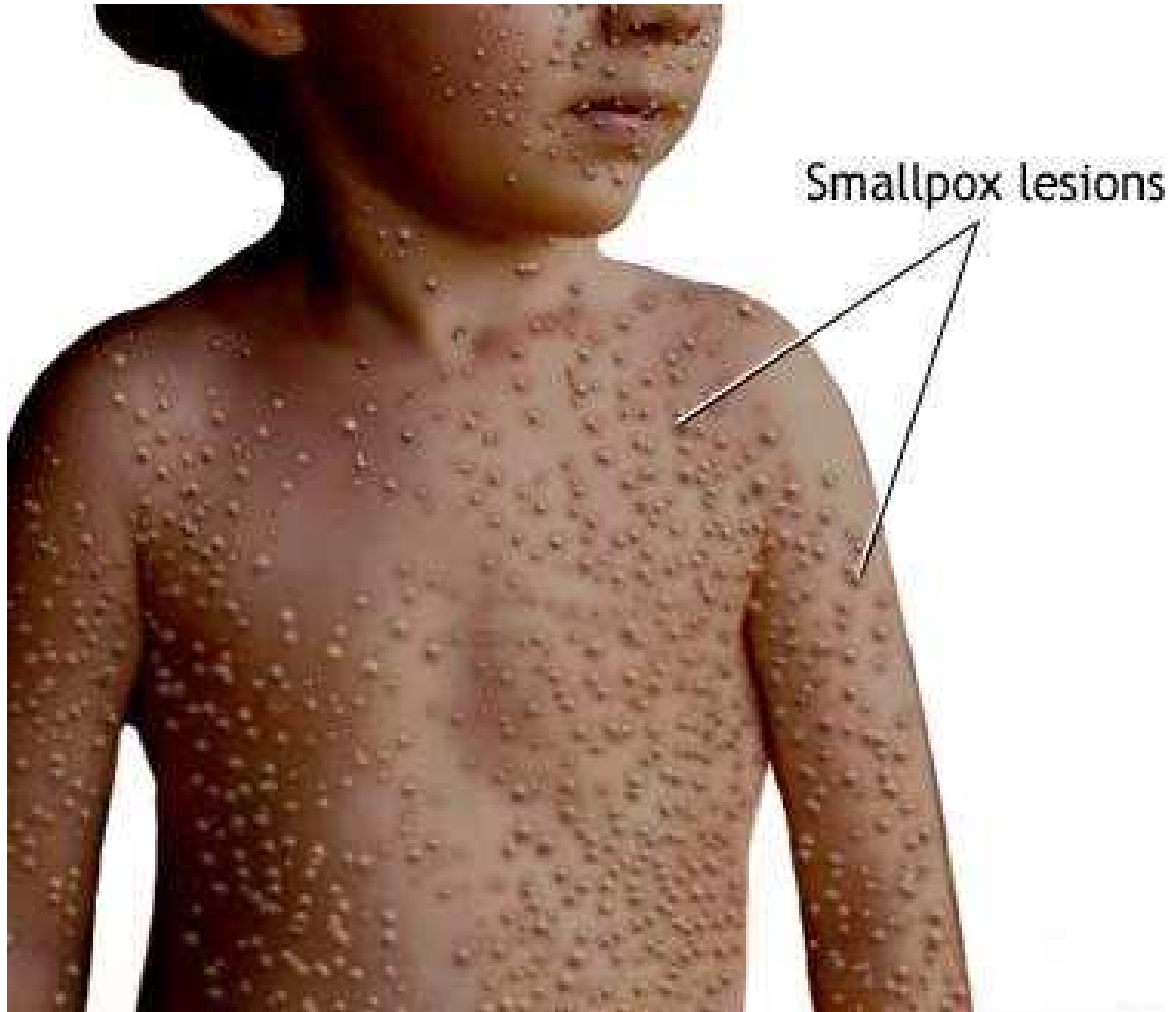


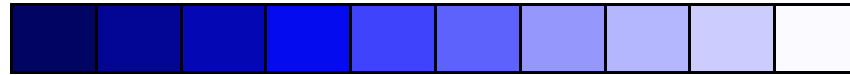
Group 1: average = 1,4



Group 2: average = 9,2



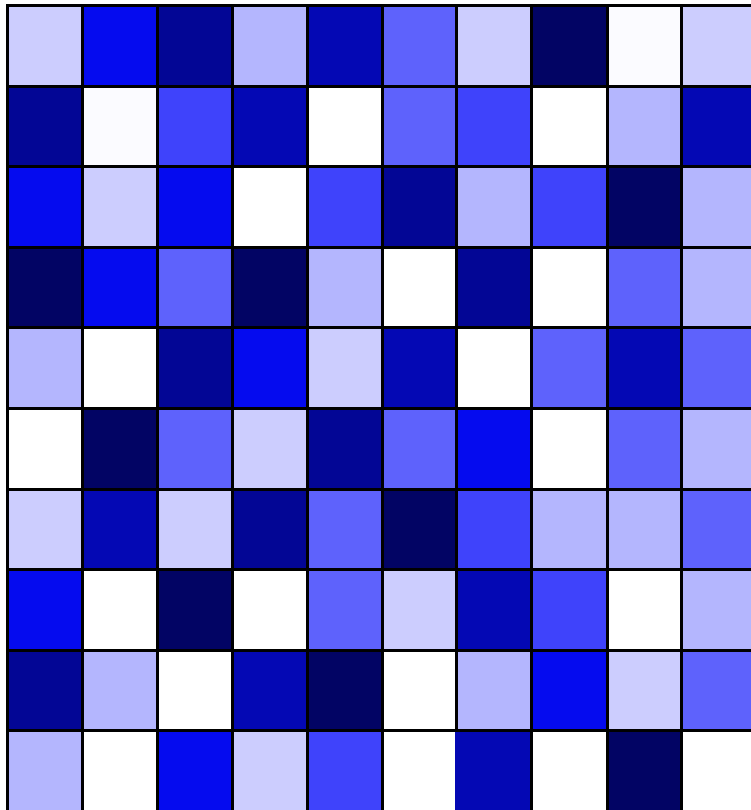




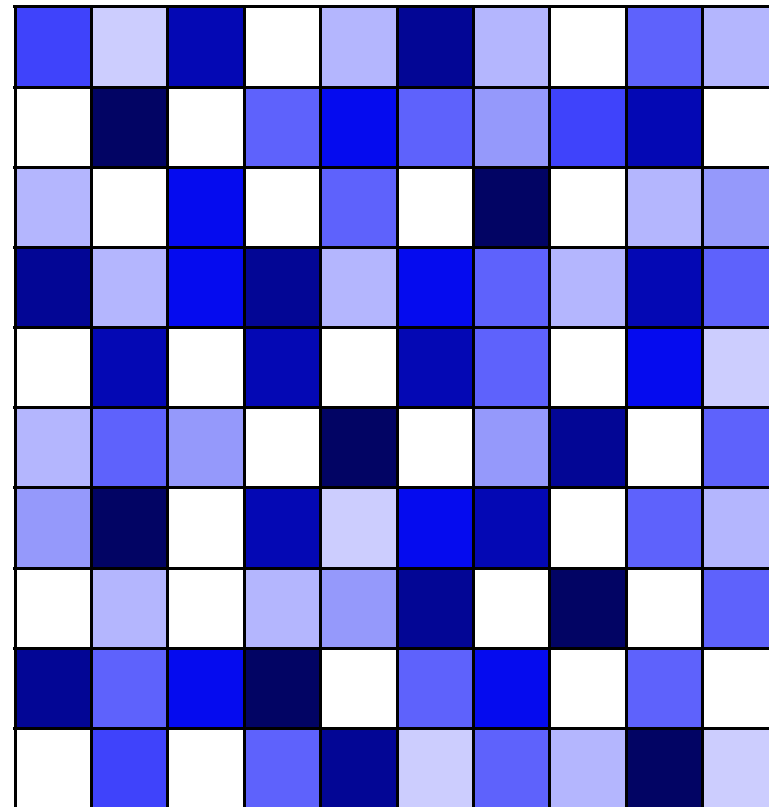
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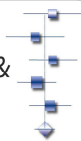
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Group 1: average = 5,4



Group 2: average = 5,9

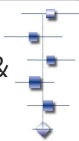
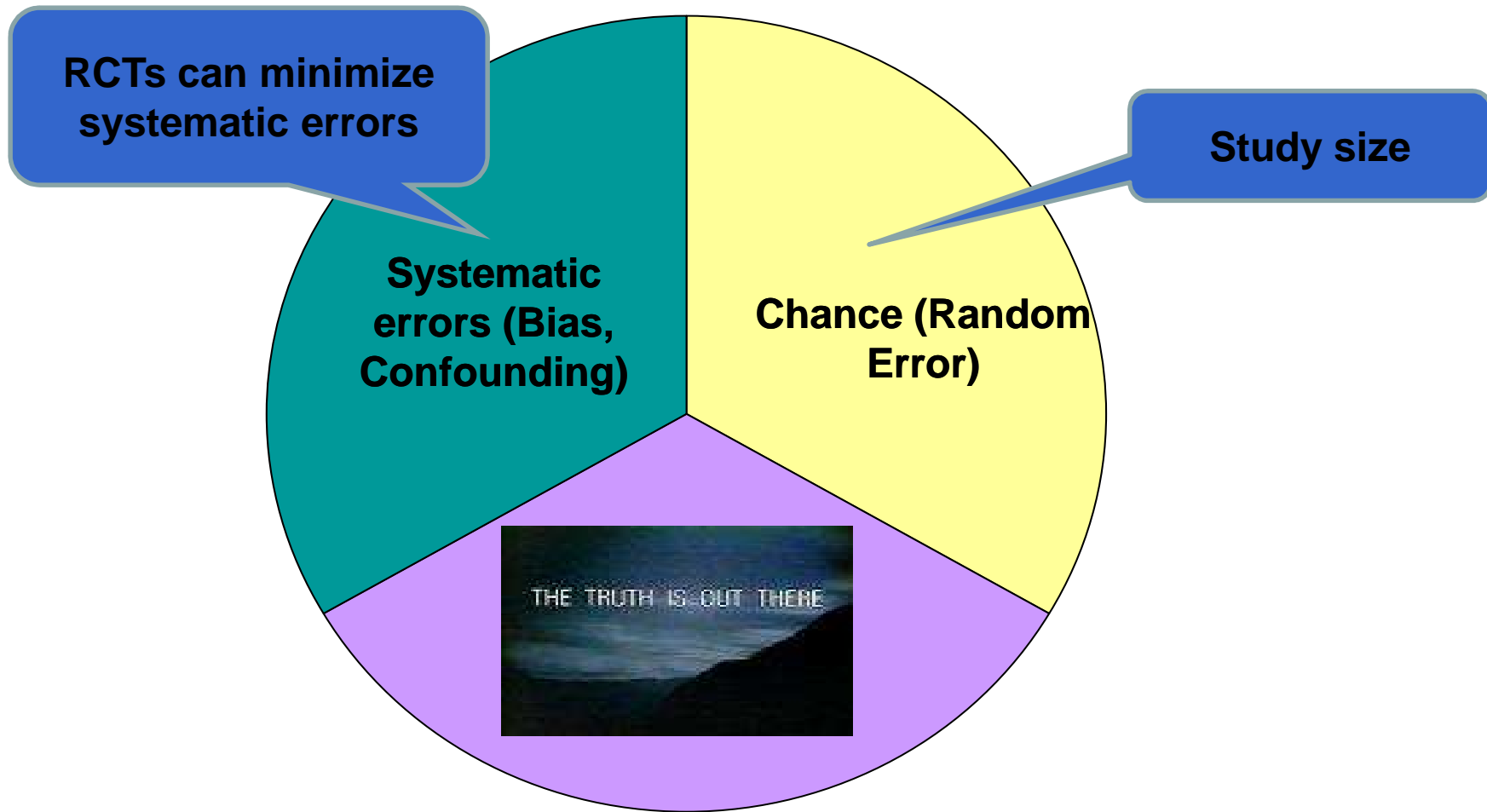


3 reasons why study results can be wrong

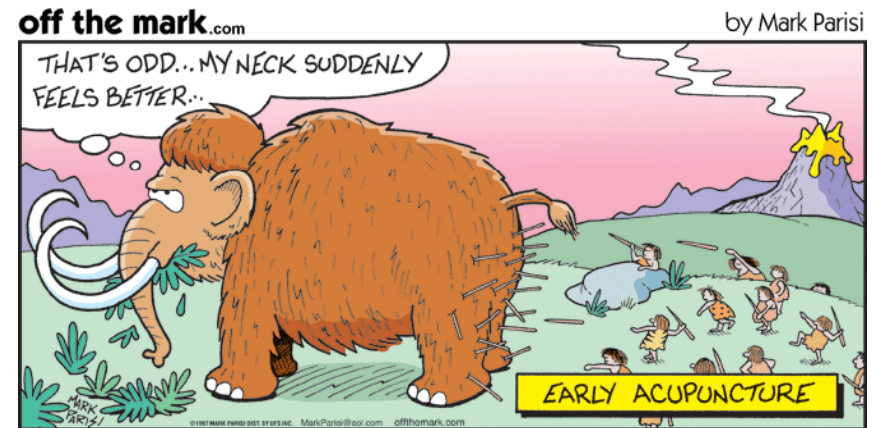
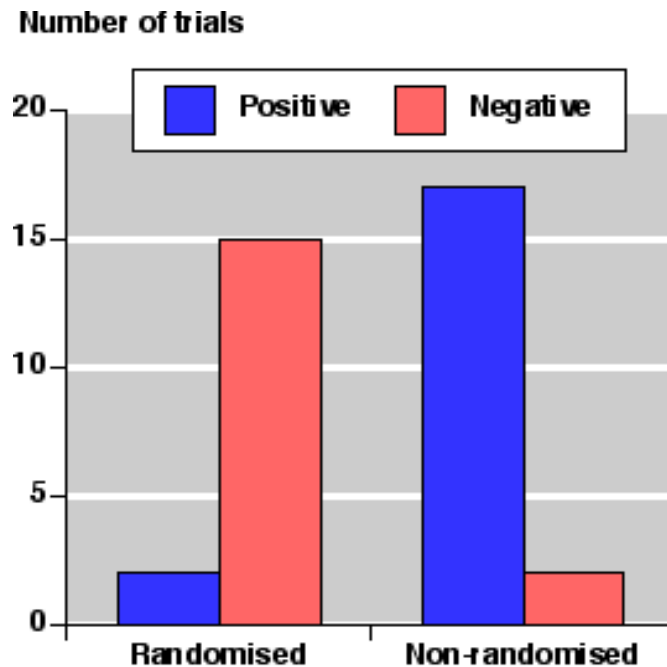
- Chance (Random Error)
- Confounding
- Bias



Components of any study result



The influence of bias and confounding



J Reeve, D Menon, P Corabian.

Transcutaneous electrical nerve stimulation (TENS):

a technology assessment. International Journal of Technology Assessment 1996 12:2: 299-324



RCTs are the best study design to
examine small but clinically important
treatment effects

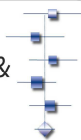
The guiding principle:

UNPREDICTABILITY



Key components of quality assessment for RCTs

- Adequate method of randomization?
- Adequate allocation concealment?
- Adequate blinding?
- High attrition?
- Adequate statistical analysis?



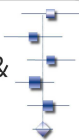
Why is randomization important?

Confounding:

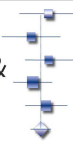
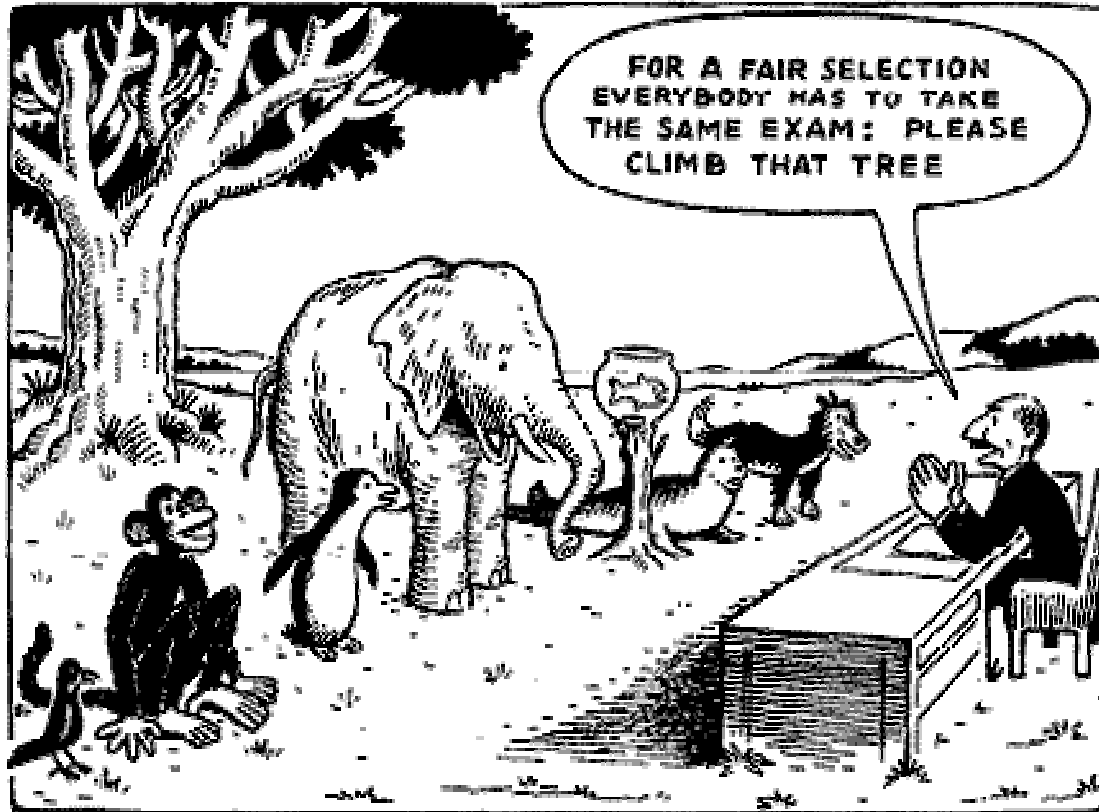
Prognostic factors are distributed unequally across groups.



Randomization distributes known and unknown confounders equally

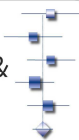


Selection Bias



What is adequate randomization?

- According to the play of chance (e.g. computer generated sequence)
- Inadequate randomization: pre-set plan, e.g. alternation, time of admission...

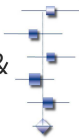


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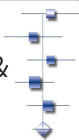


- Do group sizes have to be equal after randomization?
- Do baseline characteristics of treatment groups have to be similar after randomization?



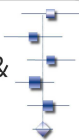
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- Adequate blinding?
- High attrition?
- Adequate statistical analysis?



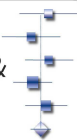
Randomization

- 2 interrelated aspects
 - generation of allocation sequence
 - concealment of sequence (allocation sequence must be unpredictable)



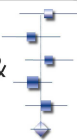
Allocation Concealment

- Allocation concealment keeps investigators unaware of upcoming assignments
- Inadequate allocation concealment leads to exaggerated estimates of the treatment effects



Allocation Concealment

- Sequentially numbered, opaque, sealed envelopes
- Numbered or coded containers
- Central randomization



Non-random allocation

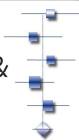
- Alternation
- Hospital numbers
- Date of birth
- Social security numbers

Non-random allocation makes allocation concealment impossible



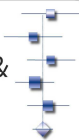
“According to the study protocol, patients fulfilling the inclusion criteria were alternately allocated to 1 of 2 therapeutic arms: citalopram 20mg/day or sertraline 50 mg/day, configuring a quasi-randomized trial.”

(Rocca et al., J. Clin. Psychiatry 2005)



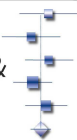
“All patients in China were randomized by telephone to Beijing. In India, patients were initially randomized using sealed opaque envelopes, but this procedure was changed to telephone randomization for subsequent patients.”

(The CREATE Trial Group. JAMA 2005)



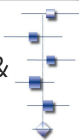
“...we tried to exclude possible selection bias by a type of randomization. On even days, we included all women in gestation week 38 who intended to deliver vaginally. On odd days, we included only intended elective cesareans in the study.”

(Schindl et al. Acta Obstet. Gynecol Scand 2003)



“..the randomization procedure was developed at the Clinical Coordinating Center...using a permuted block algorithm stratified by clinical center site and age group”

(WHI. JAMA 2002)



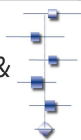
“Recruitment continued until 62 patients had entered the study; 31 patients were allocated to each of the two treatments on an alternating basis.”

(Thiels et al. Am J Psychiatry 1998)



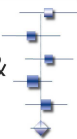
“Fifty-six women with anorexia nervosa diagnosed by using strict and lenient weight criteria were randomly assigned to three treatments.”

(McIntosh et al. Am J Psychiatry 2005)



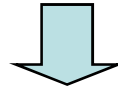
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- **Adequate blinding?**
- High attrition?
- Adequate statistical analysis?

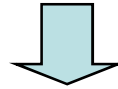




Generation of allocation sequence



ABAABBA...



Intervention



Outcomes Assessment



ALLOCATION CONCEALMENT

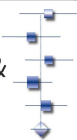


BLINDING



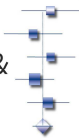
What is adequate blinding?

- Important when outcome measures involve subjectivity (e.g. pain, cause-specific mortality)
- Blinding is not always possible/necessary (e.g. surgical interventions, all-cause mortality)



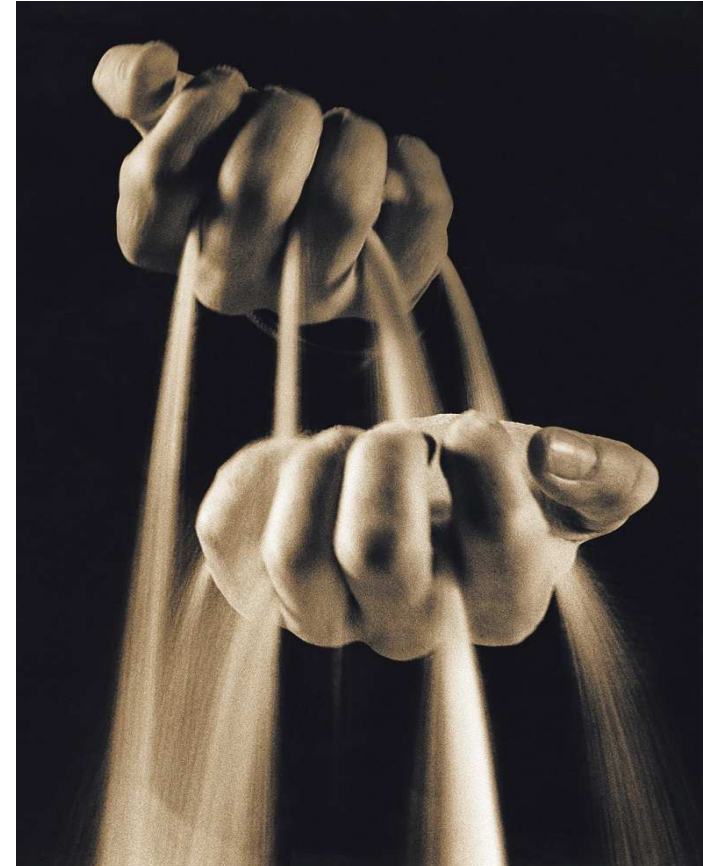
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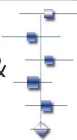
Attrition

Everyone who was randomized but did not reach the study endpoint, regardless of the reason (e.g. protocol violation, death, lack of efficacy, side effects, moved out of town....)



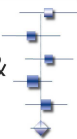
Attrition

- Characteristics of patients who drop out are unlikely to be the same as of those who remain in the trial
- Overall attrition not more than 20%
- Differential attrition not more than 15%

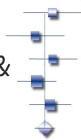
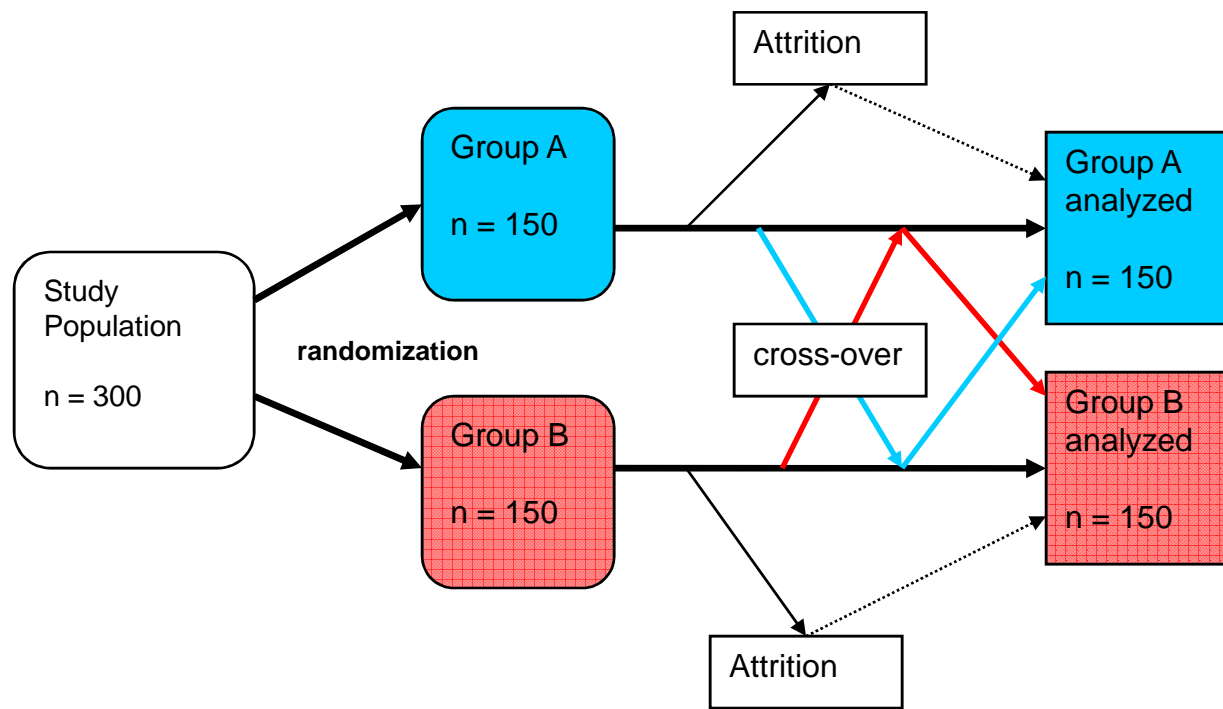


Key components of quality assessment for RCTs

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Intention-to-Treat Analysis (as randomized analysis)



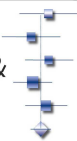
ITT - Advantages

- Retains balance in prognostic factors from randomization
- Admits non-compliance and protocol deviations, reflecting a real clinical situation
- Is the most cautious approach and limits type I error

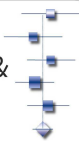


“A total of 21 patients were excluded from the ITT population: those for whom treatment was unblinded, those who never received treatment, those treated before randomization, and those enrolled at a center where blinding of the efficacy assessor was potentially compromised“

(Keystone et al., Arthritis & Rheumatism 2008)



DO NOT USE A POINT SYSTEM TO RATE INTERNAL VALIDITY



QUESTIONS??

