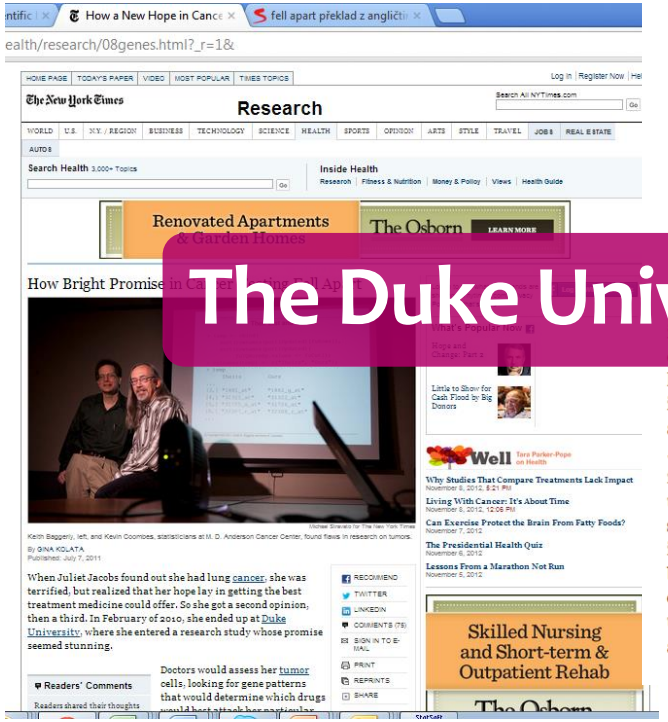
STATISTICS IN CLINICAL TRIALS FOR NON-STATISTICIANS

Adam Svobodník

AGENDA

1. Why shall I learn statistics if I am not a statistician?
2. Role of statistician in clinical trials
3. Phases of clinical trials
4. Basic terminology
5. P-value concept
6. Sample size calculation

Why shall I learn statistics if I am not a statistician?



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DERIVING CHEMOSENSITIVITY FROM CELL LINES: FORENSIC BIOINFORMATICS AND REPRODUCIBLE RESEARCH IN HIGH-THROUGHPUT BIOLOGY

BY KEITH A. BAGGERLY[1] AND KEVIN R. COOMBES[2]
University of Texas

7. Discussion.

The Duke University scandal

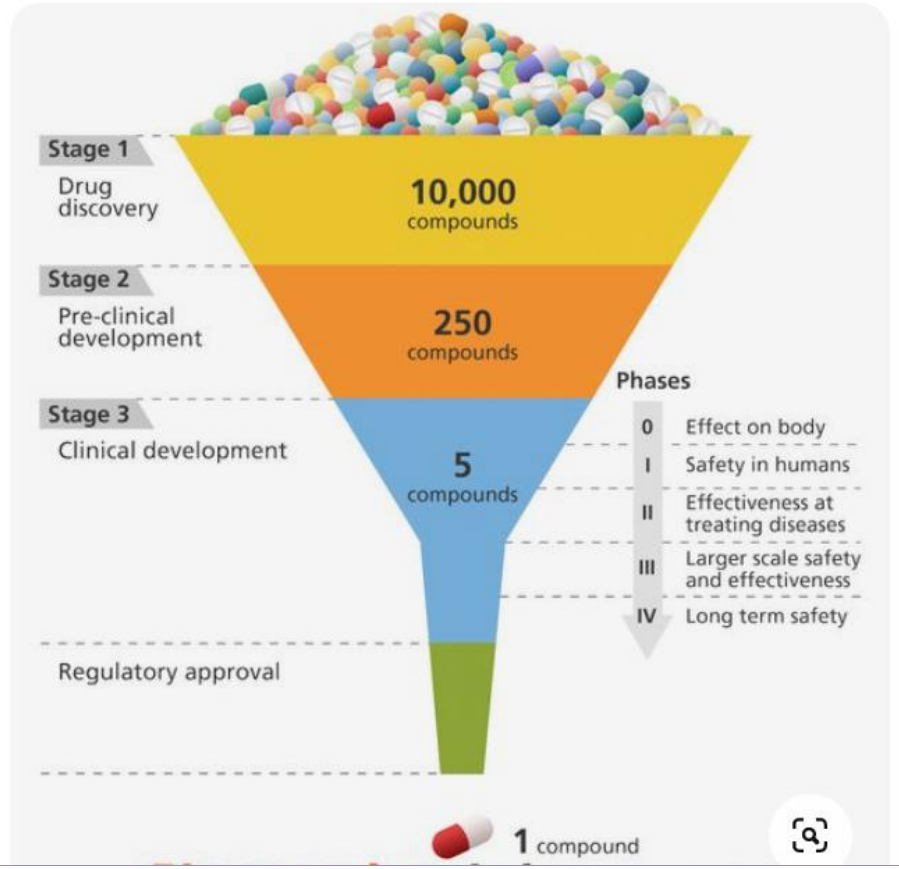
case studies examined above, forensic reconstruction identifies errors that are hidden by poor documentation. Unfortunately, these case studies are illustrative, not exhaustive; further problems similar to the ones detailed above are described in the supplementary reports. The case studies also share other commonalities. In particular, they illustrate that *the most common problems are simple*: for example, confounding in the experimental design (all TET before all FEC), mixing up the gene labels (off-by-one errors), and mixing up the group labels (sensitive/resistant); most of these mixups involve simple switches or offsets. These mistakes are easy to make, particularly if working with Excel or if working with 0/1 labels instead of names (as with `binreg`). We have encountered these and like problems before. As part of the 2002 Competitive Analysis of Microarray Data (CAMDA) competition, Stivers et al. (2003) identified and corrected a mixup in annotation affecting roughly a third of the data which was driven by a simple one-cell

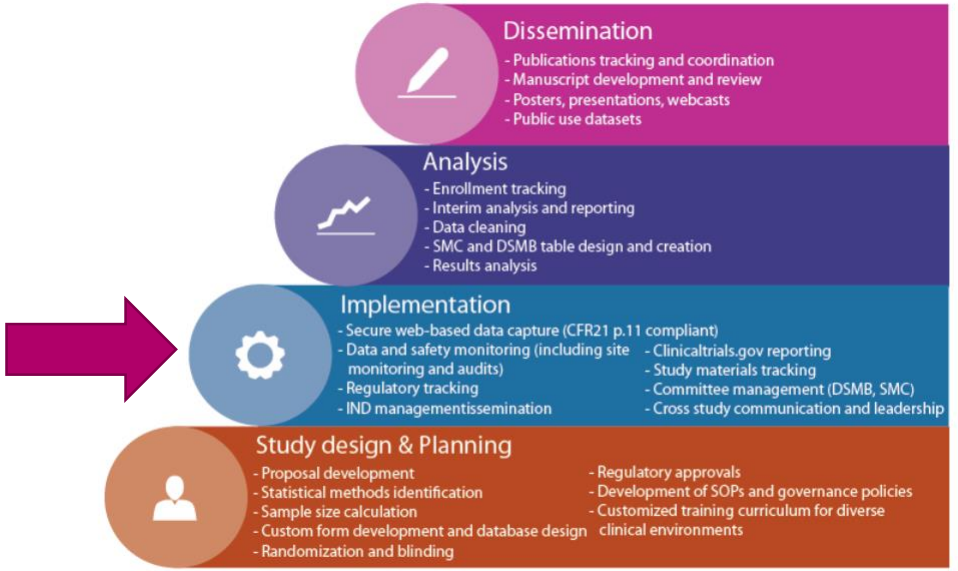
It is important to know basics of statistics in order to:

- Be able to plan clinical trials and communicate with statistician *(e.g. design, randomization, sample size)*
- Understand study protocol
- Understand all activities during trial *(e.g. Interim analysis)*
- Be able to understand study results and manuscripts

Role of statistician in clinical trials

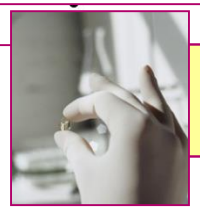
Role of statistician in Clinical trials





Phases of clinical trials

PROCESS OF NEW DRUG DEVELOPMENT



Laboratory experiments

Preclinical testing

Clinical trials: Phase I
Phase II
Phase III

Registration and approval from regulatory authorities

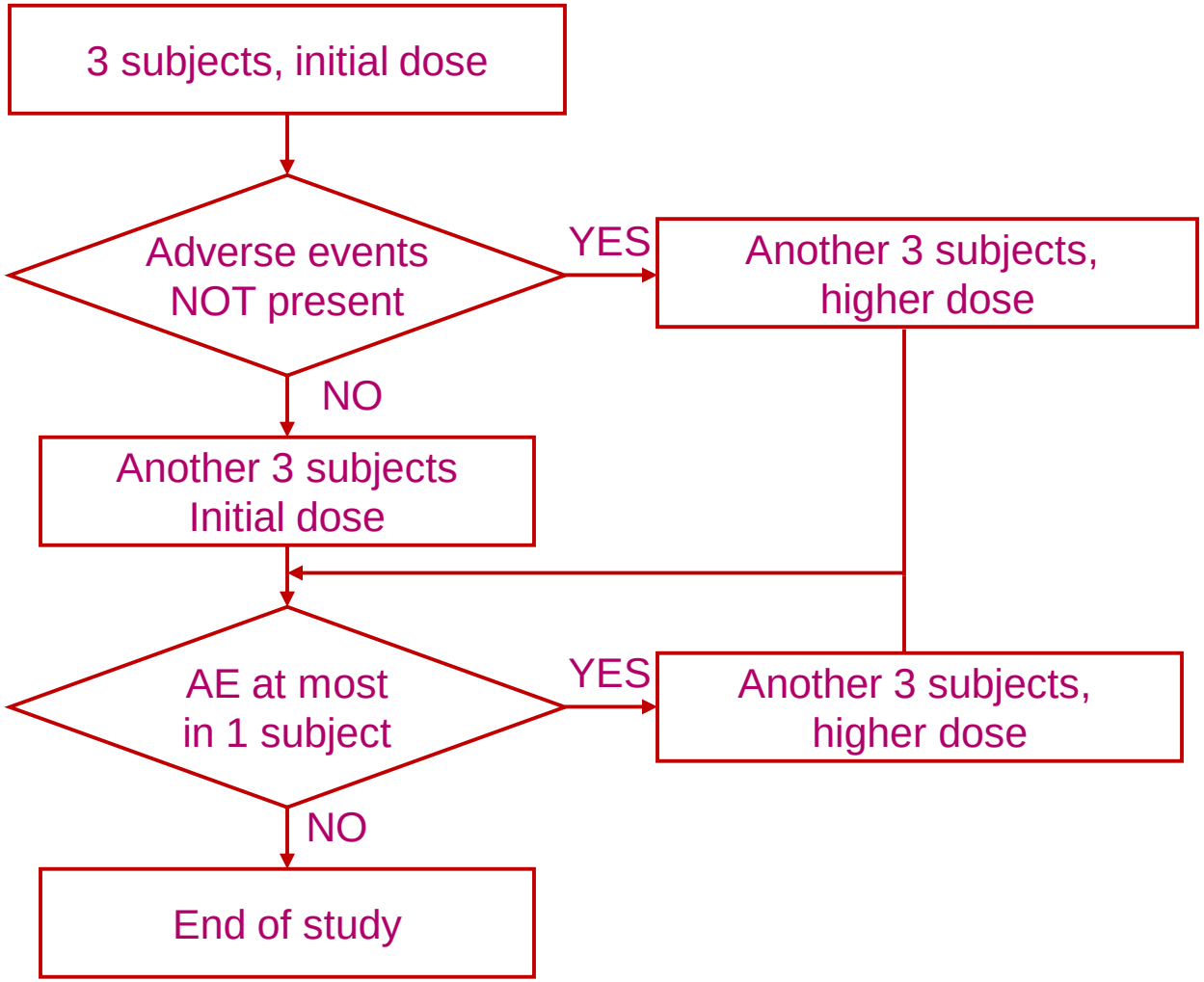
Clinical trials: Phase IV

10-15 YEARS

PHASE 1 clinical trials

- **Objectives:**
  - Assessment of basic product pharmacokinetic parameters in humans
  - Estimation of the maximal tolerated dose MTD (cytostatics etc.)
  - Evaluation of Adverse Events (AE)
  - Dose finding study
- **Study subjects:**
  - 12-20
  - Mostly healthy volunteers
  - Not vulnerable subjects
- **Design:**
  - Ideal design enable exact evaluation of the "dose – response" curve
  - Because of ethical reasons, adaptive designs are used: dosage for subsequent subject is based on the response of previous subject
  - The first dose used is based on results of preclinical testing (animal testing)

PHASE 1 – example of subjects' enrollment 1



PHASE 2 clinical trials

- **Objectives:**
  - Verification of the treatment effectiveness
  - Evaluation of tolerance and safety
  - Decision whether Phase III trials will be performed
- **Study subjects:**
  - 20 – 200
  - Number of study subjects
    - fixed
    - enrollment by groups
    - sequential (including evaluation of response of each subject continuously)
- **Design:**
  - Randomization is rare
  - Experiments with one arm
  - Treatment effectiveness and safety is compared to known products or placebo

PHASE 3 clinical trials

- **Objectives:**
  - Comparison of the effectiveness and safety of the test product with placebo or other type of control (active treatment control)
  - Getting data for regulatory authorities
  - “Cost – effectiveness” analyses
- **Study subjects:**
  - 100 – 1 000
  - number of subjects
    - fixed
    - enrollment by groups
    - sequential (including evaluation of response of each subject continuously)
- **Design:**
  - Parallel
  - „Cross – over“
  - Factorial
  - Randomization

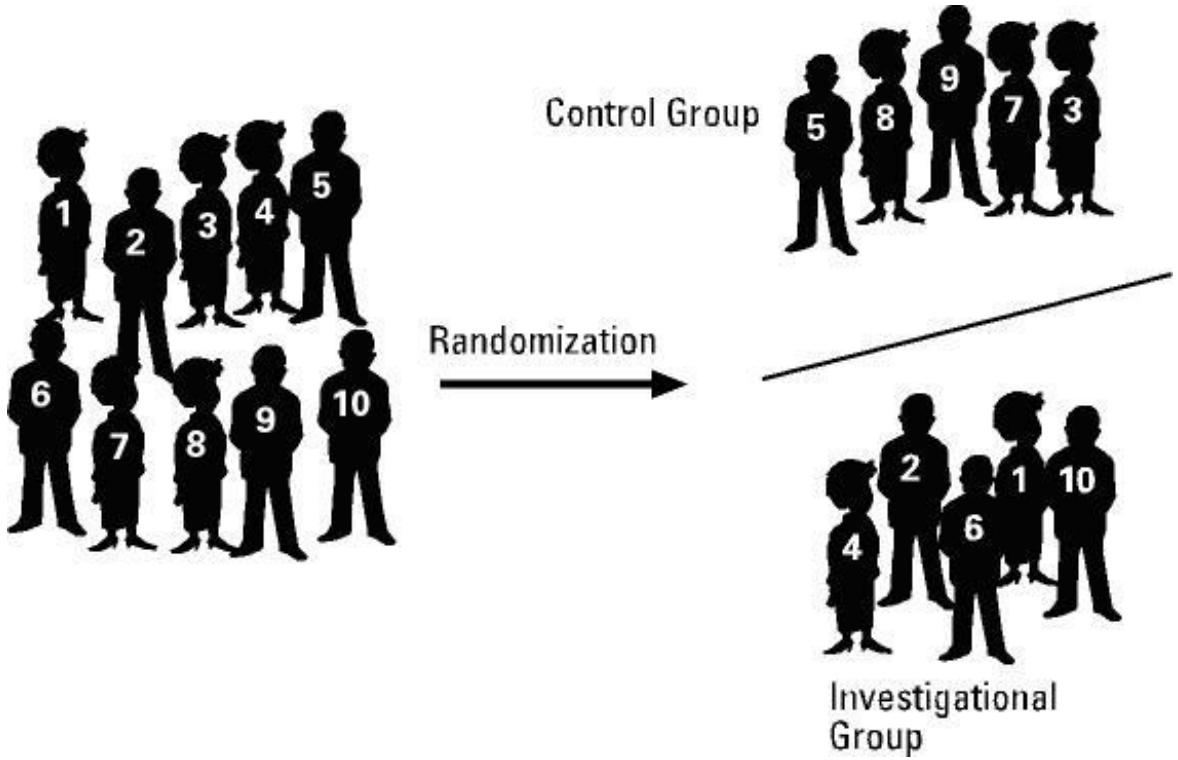
PHASE 4 clinical trials

- **Objectives:**
  - Verification of product characteristics in „real settings“
  - Detailed analyses of adverse events
  - Evaluation of QoL
  - Changes in dosage
  - „Cost-effectiveness“ studies
- **Design**
  - **Descriptive studies** (analysis of existing databases)
  - **„Cross - sectional“** studies (analysis of structured sample of patients)
  - **„Case - control“** studies (retrospective studies with selected paired control groups)
  - **Cohort studies** (retrospective or prospective comparison of selected cohort with control group)

Basic terminology

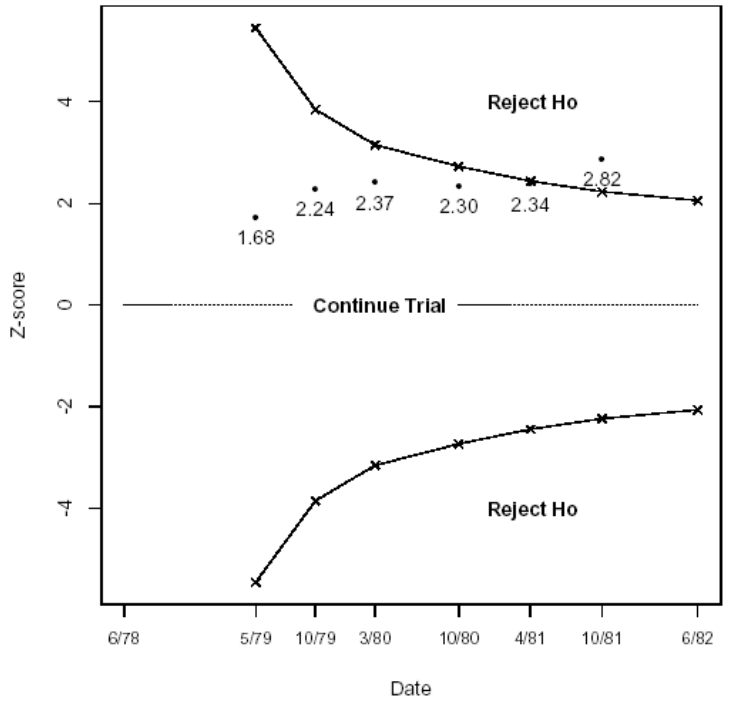
Randomization

Methodology and process of random (or pseudorandom) assignment of subjects to two or more treatment arms.



Interim analysis

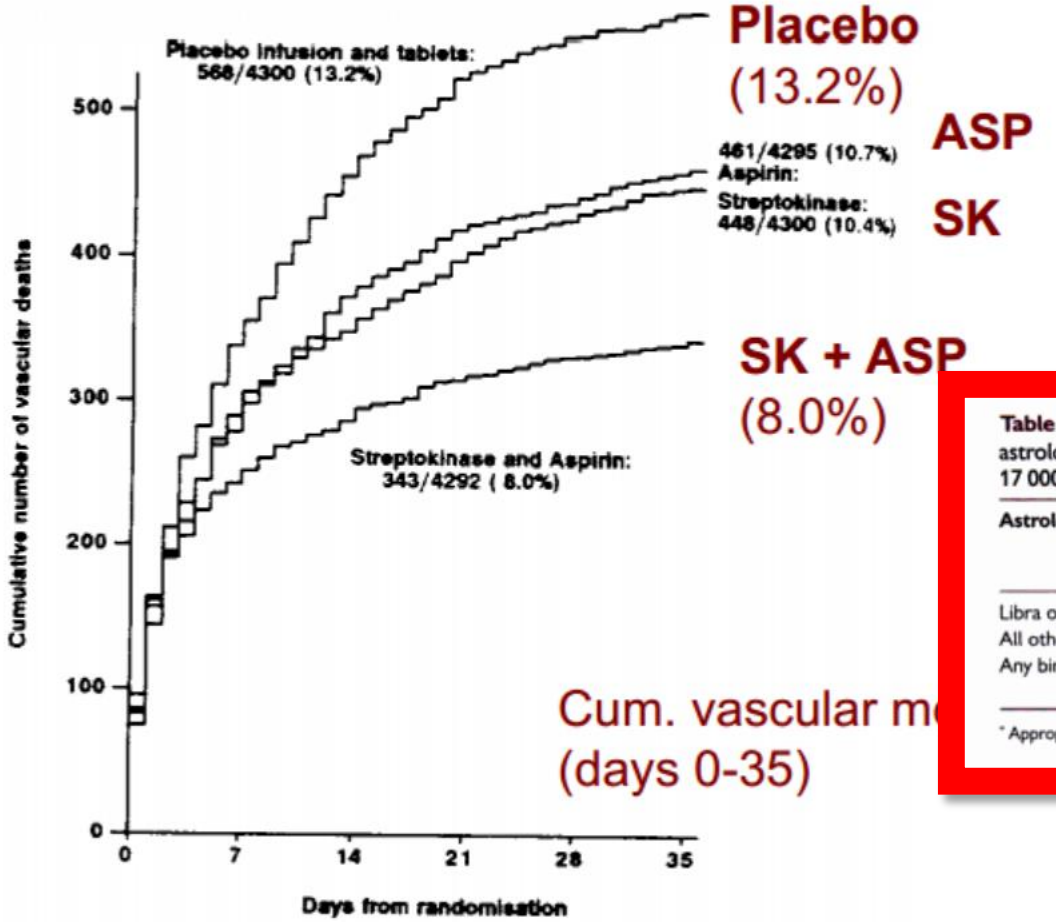
Interim analysis is analysis of the data at one or more time points prior to the official close of the study with the intention of possibly terminating the study early.



O'Brien-Flemming interim monitoring boundaries for the primary endpoint are based on predetermined number of planned interim analysis with overall type error of α=0.05.

Example of subgroup analyses: Clinical trial ISIS-2

- 17 187 patients
- Effect of aspirin (ASP) and streptokinasis (SK) on long-term survival of patients with suspected MI
- Study proved (in all patients) mortality reduction for ASP, SK and its combination



Subgroup analysis proved no effect for the astrological sign of Libra and Gemini

Table 2 False-negative mortality effect in a subgroup defined only by the astrological birth sign: the ISIS-2 (1988) trial of aspirin among over 17 000 patients with acute myocardial infarction

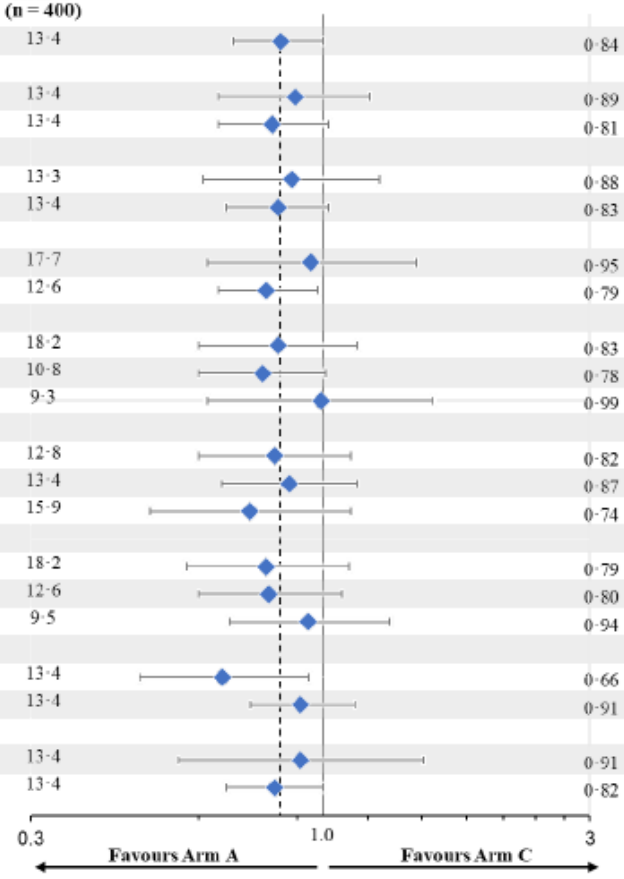
Astrological birth sign	No. of 1-month deaths (aspirin versus placebo)	Statistical significance
Libra or Gemini	150 vs. 147	NS
All other signs	654 vs. 869	$2p < 0.000001$
Any birth sign*	804 vs. 1016 (9.4%) (11.8%)	$2p < 0.000001$

* Appropriate overall analysis for assessing the true effect in all subgroups.

Example of subgroup analyses

Figure S3. Forest-Plot Analyses for OS in Key Subgroups (ITT Arm A vs. Arm C)

Subgroup	No. of Patients	Median Overall Survival, mo		Hazard Ratio for Death (95% CI)
		Arm A (n = 451)	Arm C (n = 400)	
All patients	851	16·0	13·4	0·84 (0·69-1·00)
Age				
< 65 yr	306	15·8	13·4	0·89 (0·65-1·21)
≥ 65 yr	545	16·6	13·4	0·81 (0·65-1·02)
Sex				
Female	215	14·7	13·3	0·88 (0·61-1·26)
Male	636	16·6	13·4	0·83 (0·67-1·02)
Race				
Asian	175	22·1	17·7	0·95 (0·62-1·47)
White	650	15·8	12·6	0·79 (0·65-0·98)
ECOG performance-status score				
0	355	22·0	18·2	0·83 (0·60-1·15)
1	396	14·2	10·8	0·78 (0·60-1·01)
2	100	7·4	9·3	0·99 (0·62-1·57)
PD-L1 status				
0	278	14·2	12·8	0·82 (0·60-1·12)
1	374	14·9	13·4	0·87 (0·66-1·15)
2/3	199	23·6	15·9	0·74 (0·49-1·12)
Bajorin risk factor score				
0	338	24·5	18·2	0·79 (0·57-1·11)
1	318	15·8	12·6	0·80 (0·60-1·08)
2	195	9·5	9·5	0·94 (0·68-1·31)
Investigator choice of chemotherapy				
Cisplatin	273	21·7	13·4	0·66 (0·47-0·94)
Carboplatin	578	14·2	13·4	0·91 (0·74-1·14)
Prior adjuvant or neoadjuvant regimen				
Yes	118	13·4	13·4	0·91 (0·55-1·51)
No	733	16·0	13·4	0·82 (0·67-1·00)



Examples of false outcomes of subgroup analyses

Observation	Refutation
Aspirin is ineffective in secondary prevention of stroke in women[29,30]	31
Antihypertensive treatment for primary prevention is ineffective in women[32,33]	34
Antihypertensive treatment is ineffective or harmful in elderly people[35]	36
Angiotensin-converting enzyme inhibitors do not reduce mortality and hospital admission in patients with heart failure who are also taking aspirin[37]	38
β blockers are ineffective after acute myocardial infarction in elderly people,[39] and in patients with inferior myocardial infarction[41]	40
Thrombolysis is ineffective >6 hours after acute myocardial infarction[42]	43
Thrombolysis for acute myocardial infarction is ineffective or harmful in patients with a previous myocardial infarction[42]	44
Tamoxifen citrate is ineffective in women with breast cancer aged <50 years[45]	46
Benefit from carotid endarterectomy for symptomatic stenosis is reduced in patients taking only low-dose aspirin due to an increased operative risk[47]	48
Amlodipine reduces mortality in patients with chronic heart failure due to non-ischaemic cardiomyopathy but not in patients with ischaemic cardiomyopathy[49]	50

Table 1: **Examples of subgroup analyses that have shown apparently clinically important heterogeneity of treatment effect which has subsequently been shown to be false**

ITT and PP analysis

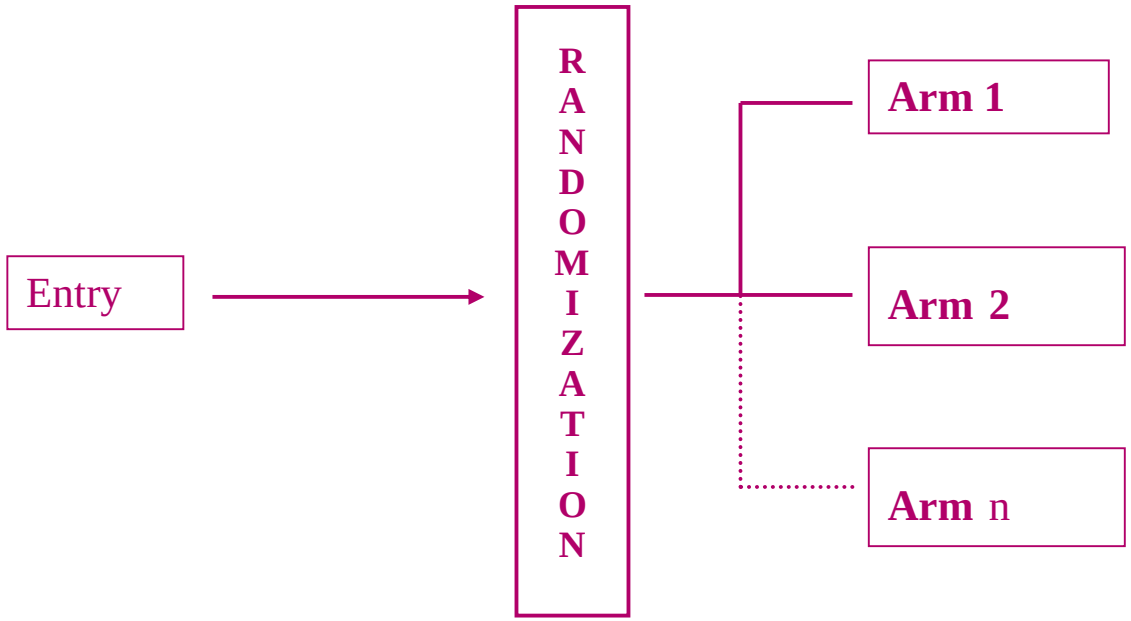
Intention-to-treat (ITT) analysis is based on data of all randomized subjects regardless of:

- **fulfilling of inclusion criteria**
- **taking medicine in accordance to randomization code**
- **compliance with study protocol**
- **premature withdrawal from study**

Per-protocol (PP) analysis is based only on data of subjects compliant to study protocol.

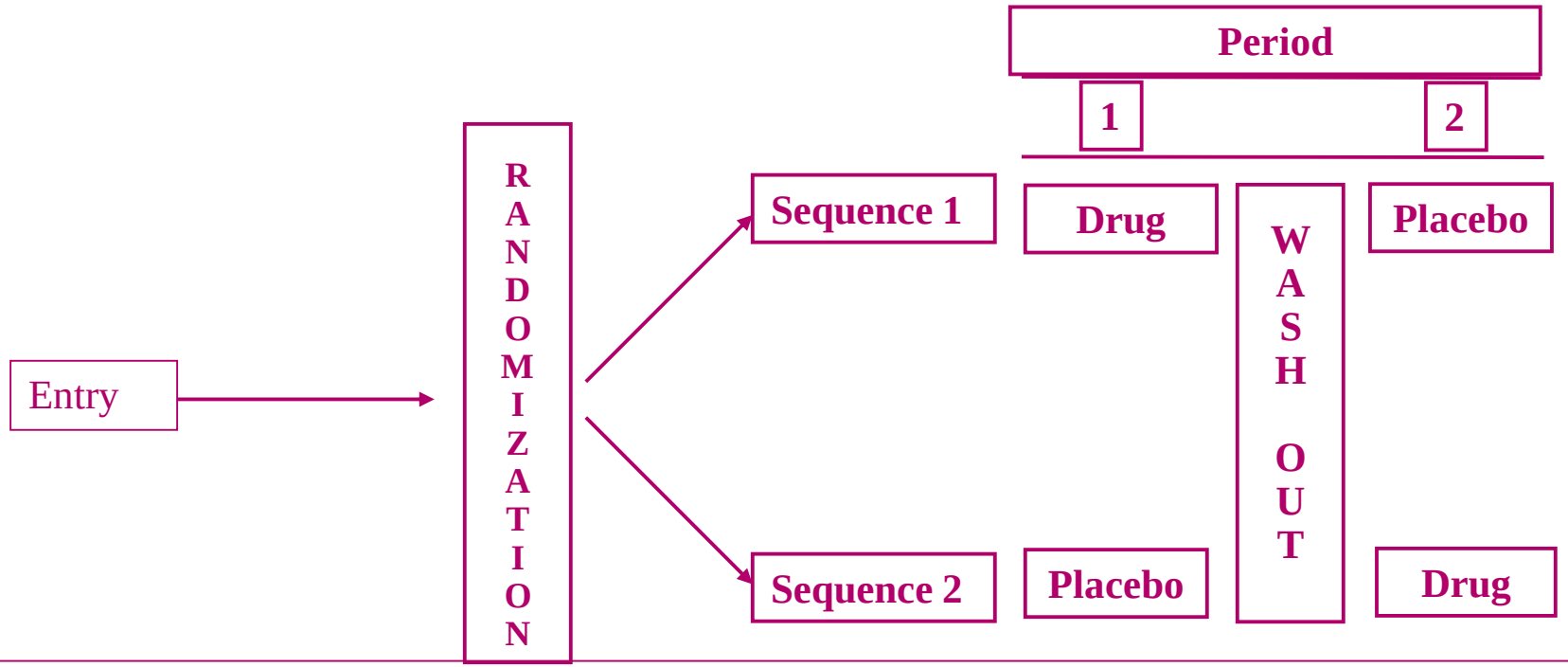
Parallel design

Subjects are randomized to receive one of the tested treatments and use only this treatment during the whole experiment.

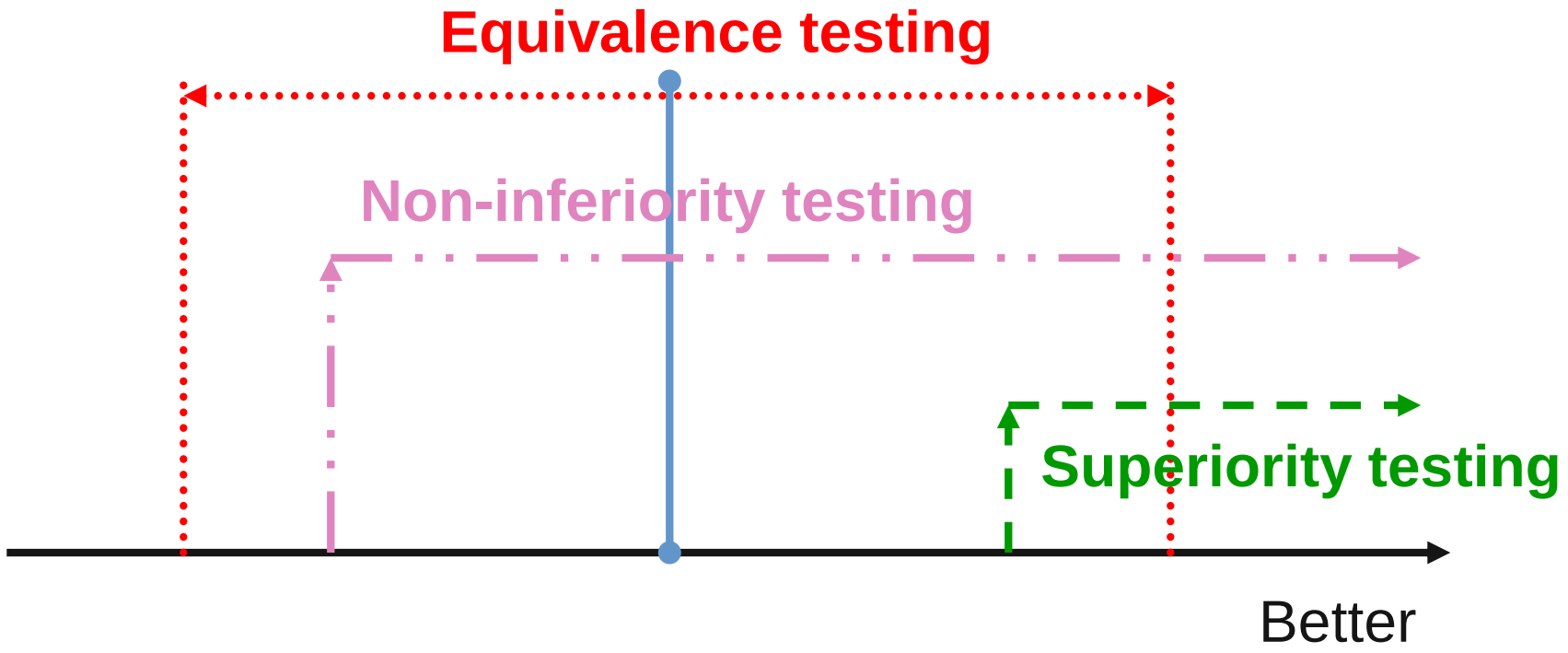


Cross-over design

All subjects are exposed to all treatments tested in experiment. Randomization is performed only to assign different sequences of treatments applied.



Hypotheses in clinical trials

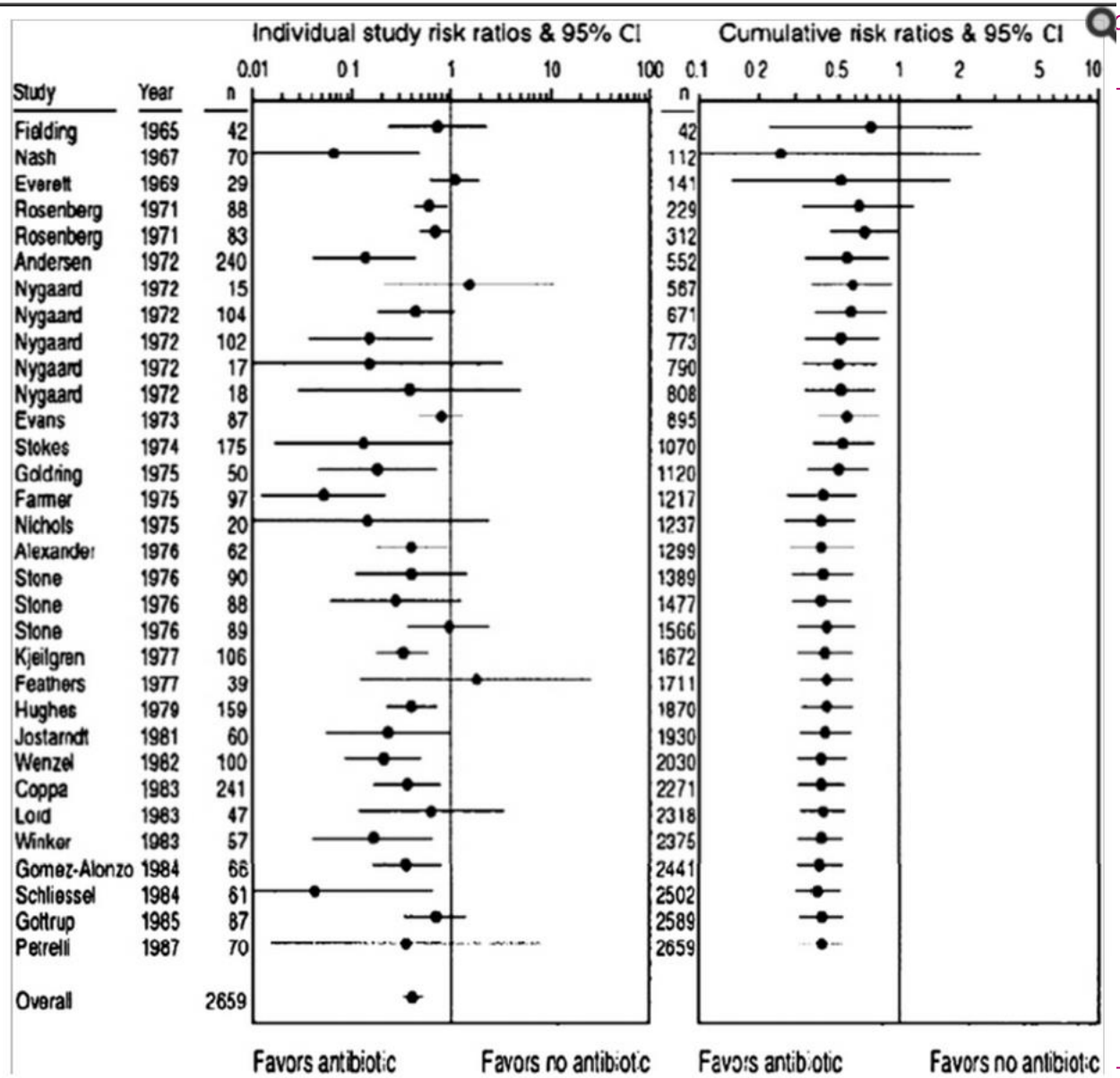


Meta-analysis

Meta-analysis refers to the analysis of analyses… the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings. (Glass, 1976, p3)
Meta-analysis techniques are needed because only summary statistics are typically available in the literature.

Problems with meta-analysis:
- **„publication bias“ („funnel shape“)**
- **multiple results from one population**
- **heterogeneous assessment of efficiency and safety in different studies**

Meta-analysis

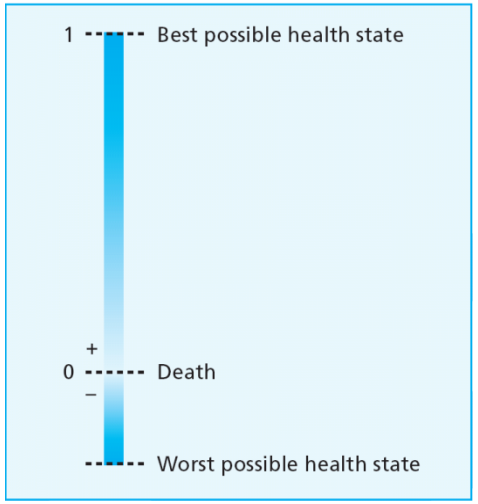


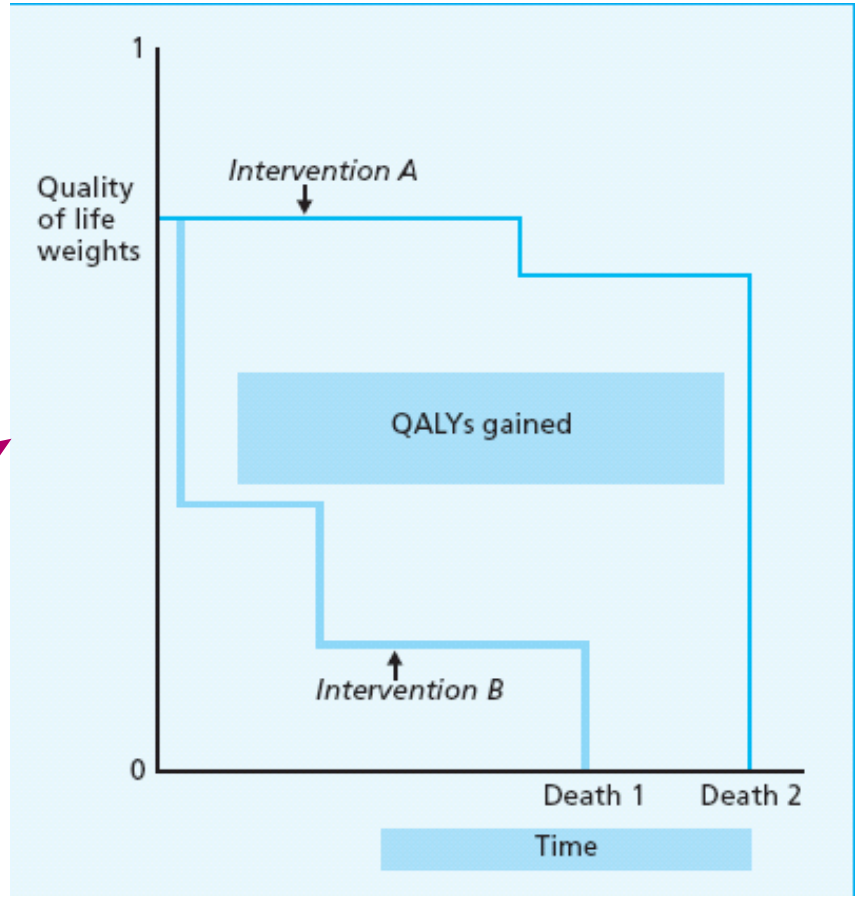
Economical analysis in clinical trials

Basic classification of economical analysis:
„Cost-minimization“ analyses (CMA)
„Cost-effectiveness“ analyses (CEA)
„Cost-utility“ analyses (CUA)
„Cost-benefit“ analyses (CBA)

The main objective of pharmacoeconomical analyses in clinical trials is to compare two or more treatments from the view of costs and benefits.

QALY





Calculating QALYs: an example

Intervention A: Four years in health state 0.75	3 QALYs
Intervention B: Four years in health state 0.5	2 QALYs
Additional number of QALYs generated by A	1 QALY

QALY

Intervention	£/QALY at 1990 prices
Cholesterol testing and diet therapy (all adults aged 40–69)	220
Neurosurgical intervention for head injury	240
GP advice to stop smoking	270
Neurosurgical intervention for subarachnoid haemorrhage	490
Antihypertensive treatment to prevent stroke (ages 45–64)	940
Pacemaker implantation	1,100
Hip replacement	1,180
Valve replacement for aortic stenosis	1,410
Cholesterol testing and treatment (all adults aged 40–69)	1,480
Docetaxel (as opposed to paclitaxel) in treatment of recurrent metastatic breast cancer	1,890*
CABG (left main-vessel disease, severe angina)	2,090
Kidney transplantation	4,710
Breast cancer screening	5,780
Heart transplantation	7,840
Cholesterol testing and treatment incrementally (all adults aged 25–39)	14,150
Home haemodialysis	17,260
CABG (one-vessel disease, moderate angina)	18,830
Hospital haemodialysis	21,970
Erythropoietin treatment for anaemia in dialysis patients (assuming 10% reduction in mortality)	54,380
Addition of interferon-α2b to conventional treatment in newly diagnosed multiple myeloma	55,060§
Neurosurgical intervention for malignant intracranial tumours	107,780
Erythropoietin treatment for anaemia in dialysis patients (assuming no increase in survival)	126,290

* Adjusted to 1990 prices using *Hospital and Community Health Service Pay and Prices Index, Unit Costs of Health and Social Care*. PPSSRU, 1996. (2,431 ÷200.7 x 155.6 = 1,890. § Translated into 1990 prices, as above

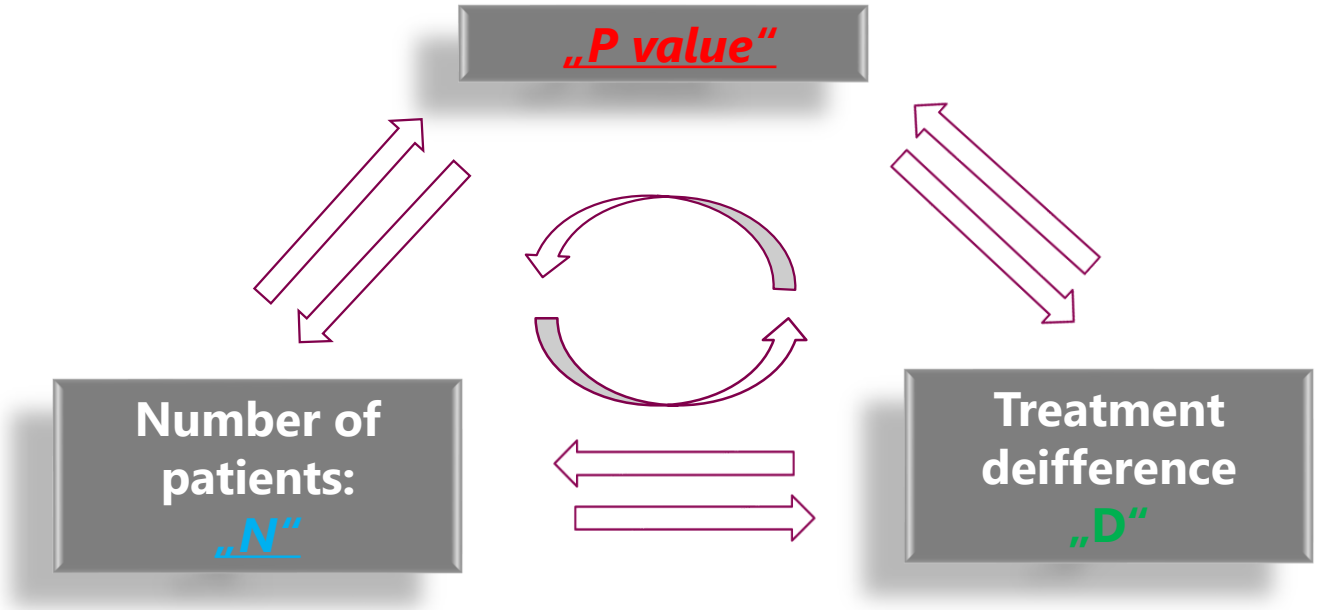
P-value concept

Clinical vs. statistical significance

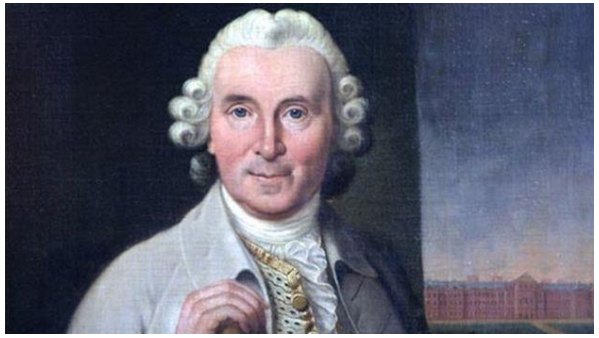
Situation A:
N=20
$P_{(A)}$ = 80%
$P_{(B)}$ = 50%
P= 0,160

X

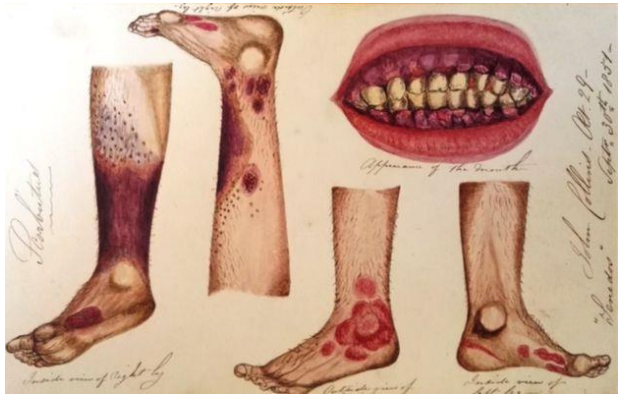
Situation B:
N=20 000
$P_{(A)}$ = 80%
$P_{(B)}$ = 81%
P<0,05



James Lind, 1747,……



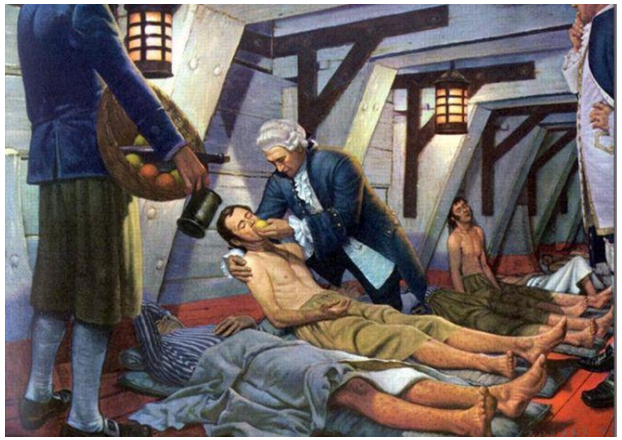
…finding of treatment for scurvy

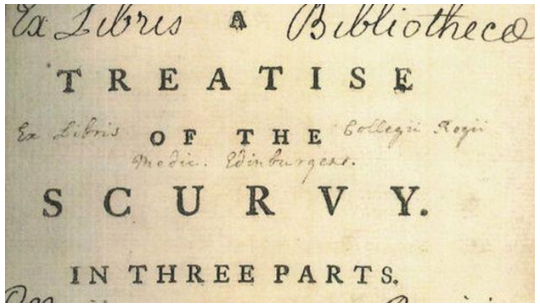


How many patients do I need for a study?

Clinical trial with 12 patients, treatment arms:

- cider
- vitriol
- seawater
- herbal mixture from Peru
- vinegar
- oranges and lemon

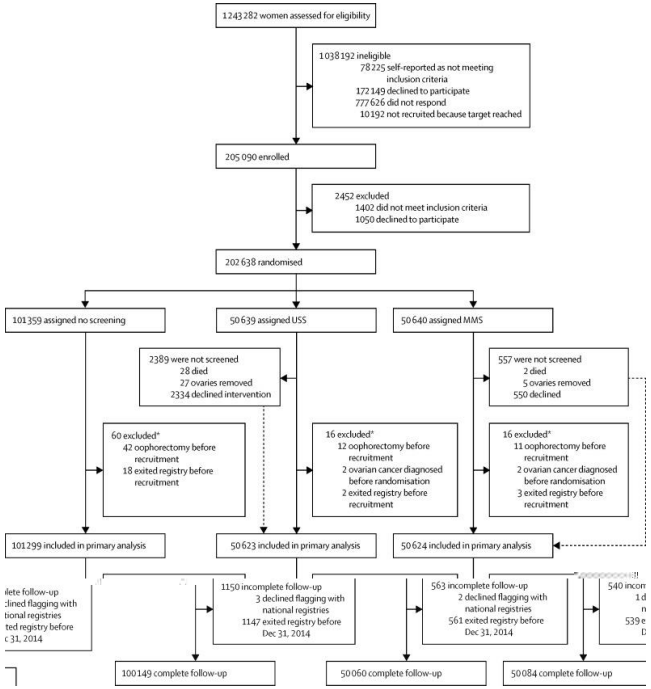




How many patients do I need for a study?

Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomized controlled trial

Clinical trial:
1 243 282 patients,
202 638 randomised



Classification of experiments