Schweizerischer Verein der Amts- und Spitalapotheker
Association suisse des pharmaciens de l'administration et des hôpitaux
Associazione svizzera dei farmacisti dell'amministrazione e degli ospedali
Swiss Association of Public Health Administration and Hospital Pharmacists

GSASA

Workshop

Hospital Pharmacy Practice Research
Ausgewählte Slides

Fribourg, 14.11.2018

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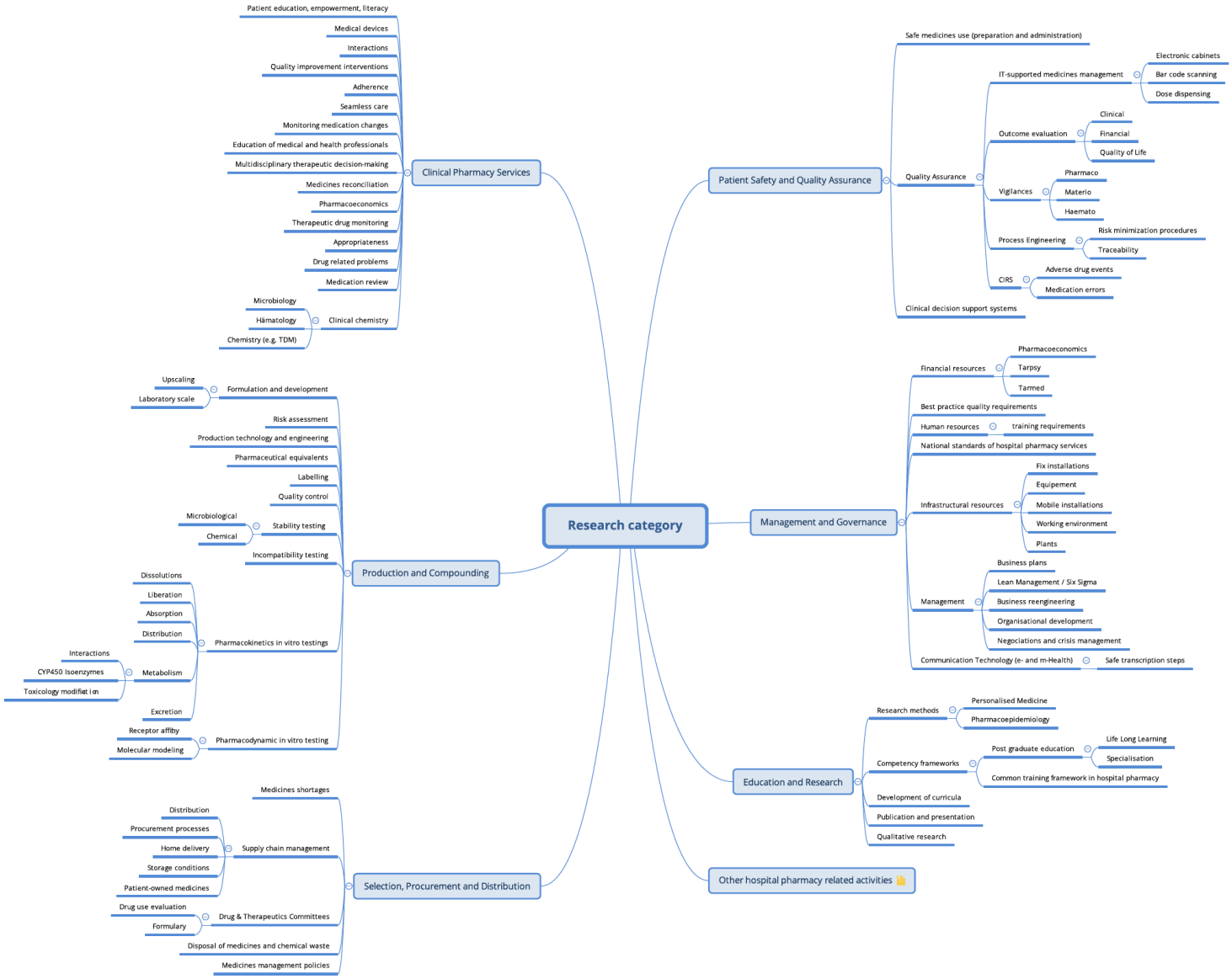
Find research question according to the **44 European Hospital Pharmacy Statements**



Qualitative or quantitative research?

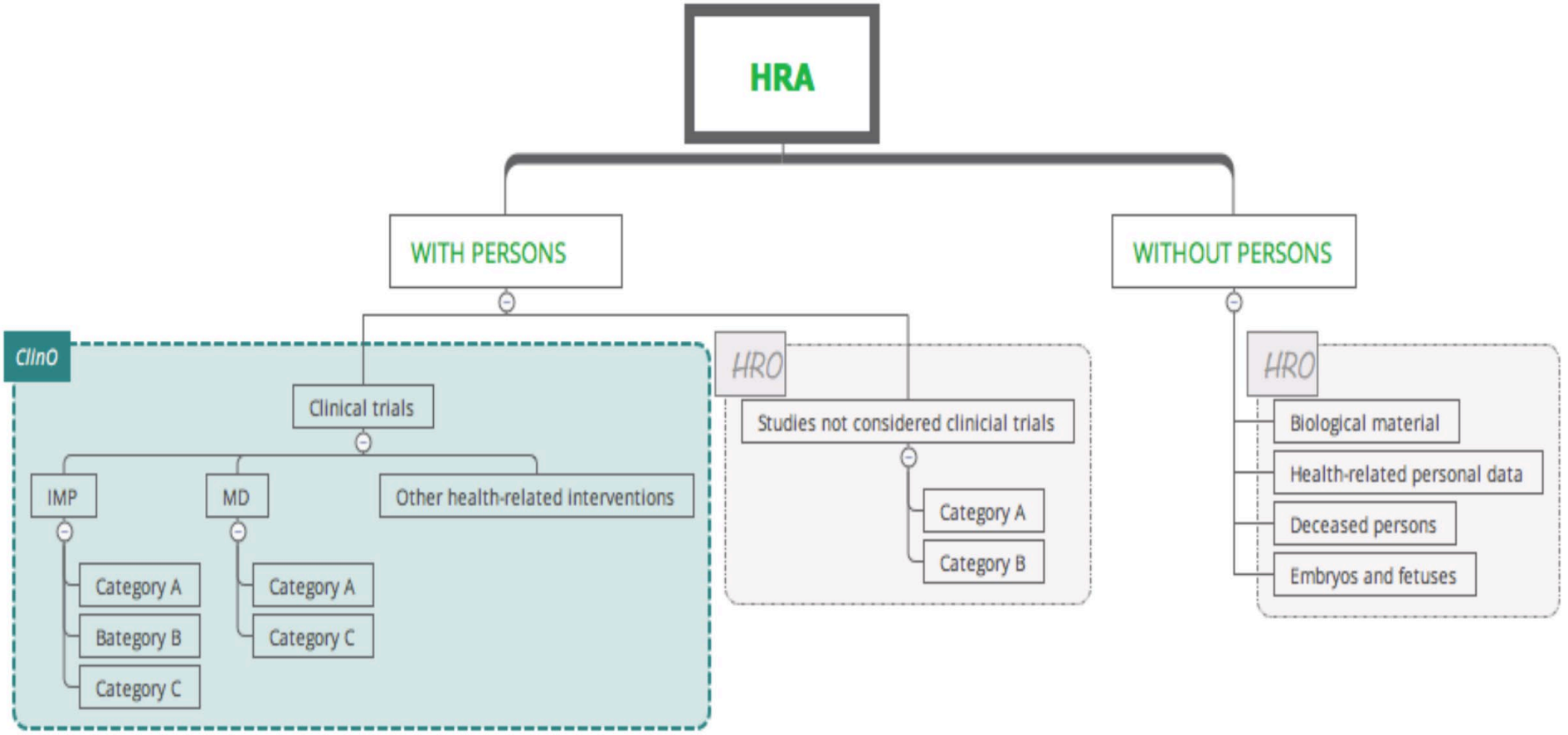
Qualitative

- Hypothesis generating
- Close relationship between researcher and subject
- Flexible research strategy
- In depth data
- Usually: small samples
- To understand events, actions, values and meanings from the respondent's perspective and
- To understand why people do what they do

Quantitave

- Hypothesis testing
- Distant relationship between researcher and subject
- Fixed research strategy
- Prevalence data
- Uually: big sample size

HRA (Swiss Human Research Act – Overview)



Clinical trials with medicinal products (ClinO Art 19, for IMP)

- Category A if MP is authorised in CH and use is
  - in accordance with prescribing information
  - indication or dosage different from specification in prescribing information
    - but within the same ICD group
    - but dosage is lower than specified
  - in accordance with internationally accepted quality criteria
- Category B if MP is authorised in CH and use is different from Category A
- Category C if MP is not authorised in CH

Clinical trials with medical devices (ClinO Art 20, for MD)

- Category A if MD
  - bears conformity marking and
  - is used in accordance with instructions
- Category C if MD
  - does not bear conformity marking
  - is not used in accordance with the intended purposes or
  - is prohibited in CH

Clinical trial - definition

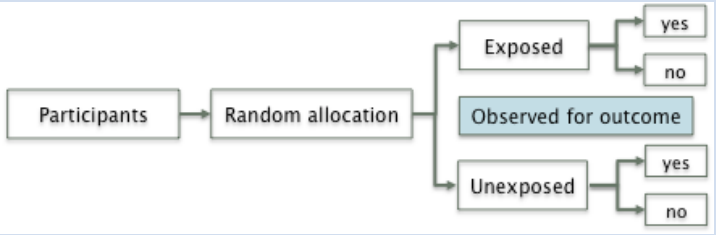
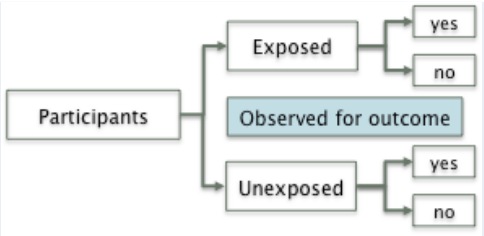
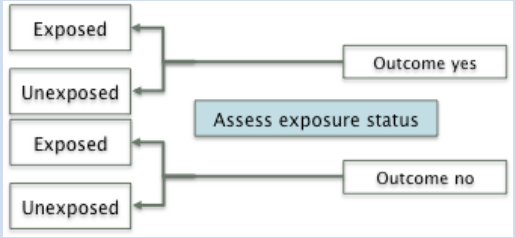
- *"Any research project that prospectively assigns human subjects to a health related intervention to determine its effects on health, structure or function of the human body"*
  (Federal Act on Research involving Human Beings, [Human Research Act HRA], CH, SR 810.30], of 30 September 2011, in force 1 January 2014)
- applies to research concerning
  - human diseases
  - structure and function of the human body
- and carried out
  - on persons (and deceased persons)
  - on embryos and fetuses
  - using biological material
  - using health-related personal data
- does not apply to
  - IVF embryos (in accordance with the stem cell research act)
  - anonymised biological material
  - anonymously collected or anonymised health-related data
- principles
  - informed consent
  - risk-benefit ratio must not be to the disadvantage of the person
  - mentally disabled persons might be included if results cannot be obtained with healthy persons
  - individual protection must be warranted

Surrogate versus clinical endpoints (often in Phase II and Phase III trials)

Research area	Surrogate endpoint	Clinical outcome
Cardiology	Cholesterol level Blood pressure	CV-related mortality
Oncology	Tumor response	Cancer-related mortality
Infectiology	CD4 cell count	Development of AIDS HIV-associated mortality
Rheumatology	Bone mineral density	Osteoporosis-induced fractures

- Can be measured earlier in the course of a disease than clinical outcome
- Less influence by competing risks
- Reduction of sample size and of costs

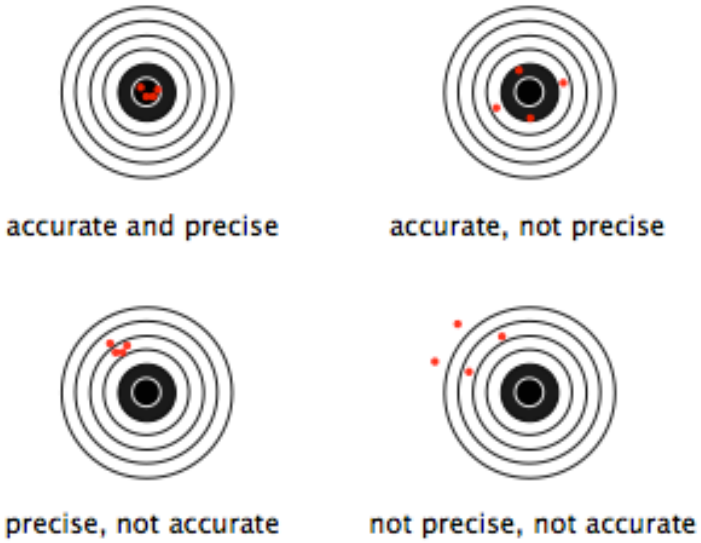
First things first - Exploring exposure and outcome

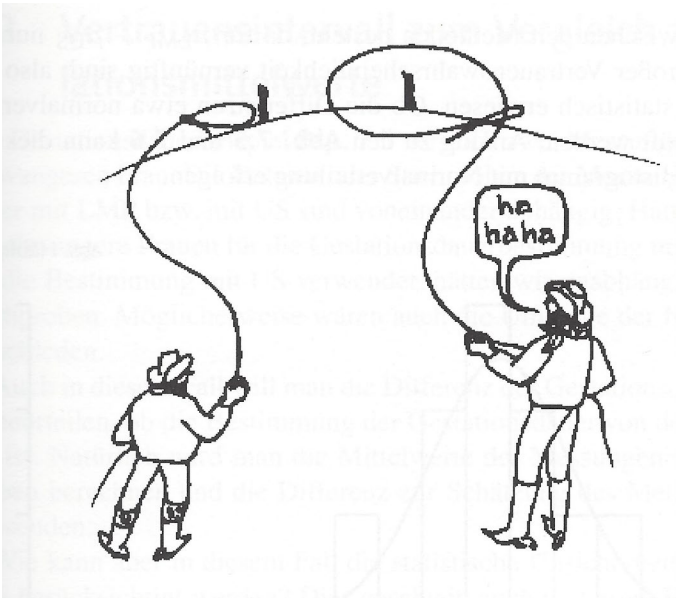
Study type	Visualisation
Randomised Clinical Trial RCT Lowest risk of bias Randomised allocation to intervention Intervention occurs before the outcome Not always possible, e.g. smoking as intervention	
Cohort studies Observational (observed over time for the outcome) Low risk of bias Not always possible Not randomised to exposure	
Case-control studies Individuals with the (rare) outcome are identified and their exposure status is determined (OR as effect measure, best friend / seibling controlled) Risk of confounding: Is another cause possible? E.g. smoking and lung cancer Incidence itself cannot be measured	
Cross-sectional studies Exposure and outcome assessed at the same time Prevalence is measured, not incidence Recall errors (informations bias) Temporal relationship between exposure and outcome often not clear	

Research closely related and derived from RCT (might be difficult to delimit)

- Compassionate use
- Parallel Trial / Early Access Program
- Experimental Therapy ("Heilversuche", off-label uses)
- No ethical approval needed if indicated for a single person or a defined group of special patients
- Ethical obligations (to fulfill also in non-clinical trials)
  - systematic use of prior evidence
  - adequate design and sample size
  - feasibility
  - complete, non-selective publication
  - timely reporting of serious adverse events to approval bodies ad review boards
- Example:
  Treatment of 10 autistic children with Calcium Levofolinate (mechanism: improve cerebral folate deficiency; effect on autism as a calcium channelopathy)

Clinical trials and analysis – accuracy and precision (ICH Guideline Q2 Analytical Validation)





- Analysis (Quality Control)
  - Accuracy
  - Precision (repeatability, intermediate precision)
  - Specificity, Sensitivity
  - Detection / Quantitation Limit, Linearity Range
- Exposure and Outcome
- Bias and Confounding
  - Bias = systematic deviation form target (no accuracy, by erroneous selection or information et cetera)
  - Confounding = alternative explanation for an association (e.g. genotype, further exposition(s), metastases / primary tumor, smoking and lung cancer)
- Statistical analysis aimed to produce an estimate of a treatment effect, thus
  - needs suitable Confidence Interval
  - is expected to provide evidence

Evidence Levels - No evidence or evidence of no effect?

Recommendation Grade	Evidence Level	Criteria
A	1a	systematic Review of **RCT**s
	1b	single **RCT** with small CI
	1c	**Survival** Improvements (all patients died before therapy was available, now some or all patients survive with this therapy)
B	2a	systematic Review of **Cohort Studies**
	2b	single **Cohort Study**
	2c	**Outcome** Research
C	3a	systematic Review of **Case Control Studies**
	3b	single **Case Control Study**
C	4	**Case Series**
D	5	**Expert Opinion** on “First Principles”

- Philips B et al. Levels of Evidence. 2009. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009.

Nutritonal Medicine‘s Problem:
A matter of confounding with baseline characteristics

The captain‘s body weight

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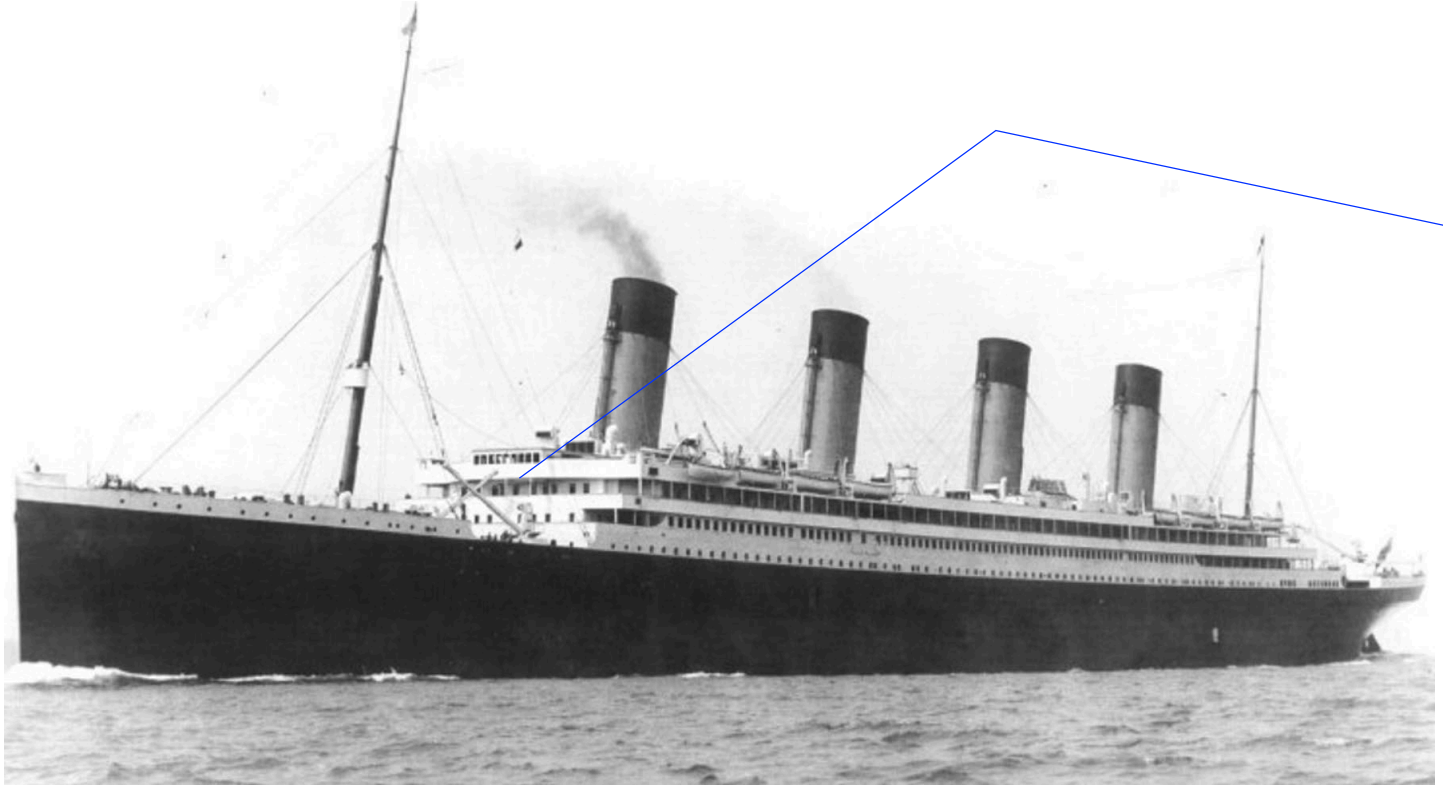
The ocean liner with the captain – The ocean liner alone



- Is the weight of the liner really constant? (no input/output allowed, e.g. blind passengers, whale hunting, seagulls, …)
- Compare: Are nutrition’s and wound healing’s blackboxes constant? Do not measing an artefact which has nothing to do with the object!

The importance of considering genetic heterogeneity and personalised requirements (many RCT are potentially wrong)

pale = normal metabolisers of new drug
dark = ultrafast metabolisers of new drug

randomisation

new active ingredient

existing reference

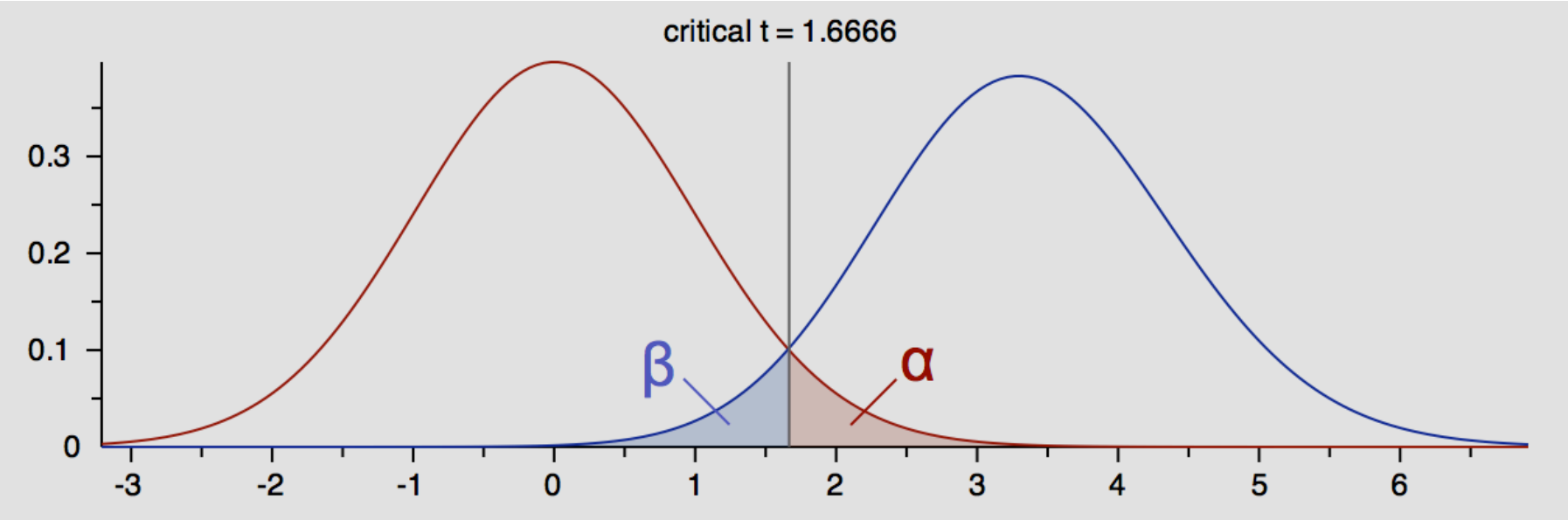
hypothesis: new drug is more effective

Treatment group

Ratio in treatment group: 3 normal, 7 fast
Better effect of new drug is not recognised
Hypothesis is rejected
Type II error

Reference group

Statistical Testing: Error probabilities α (error of the 1st kind) and β (error of the 2nd kind)?



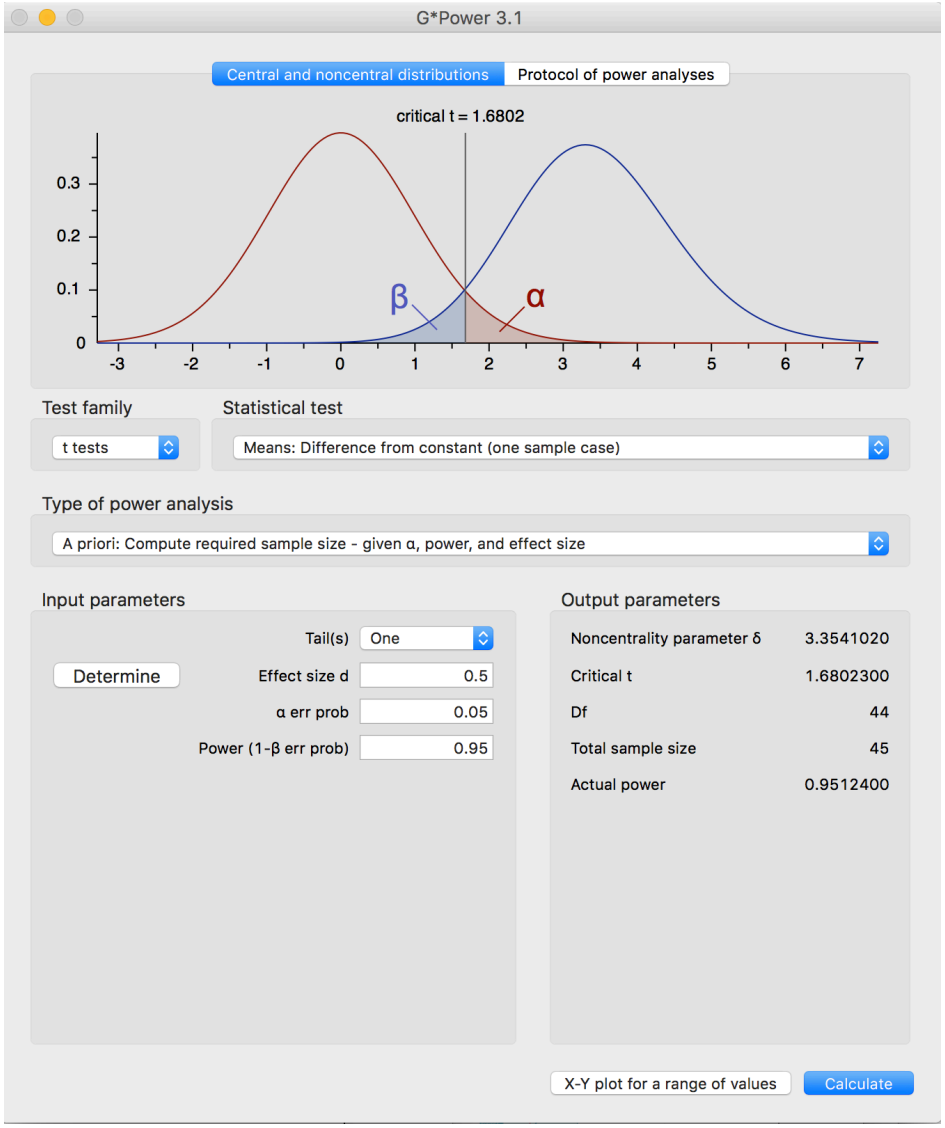
- Wrong attribution, if
  - a value of the red area is attributed to blue population
  - if a value of the blue area is attributed to red population
- d = power = 1-β = complement of the error probability of the 2nd kind

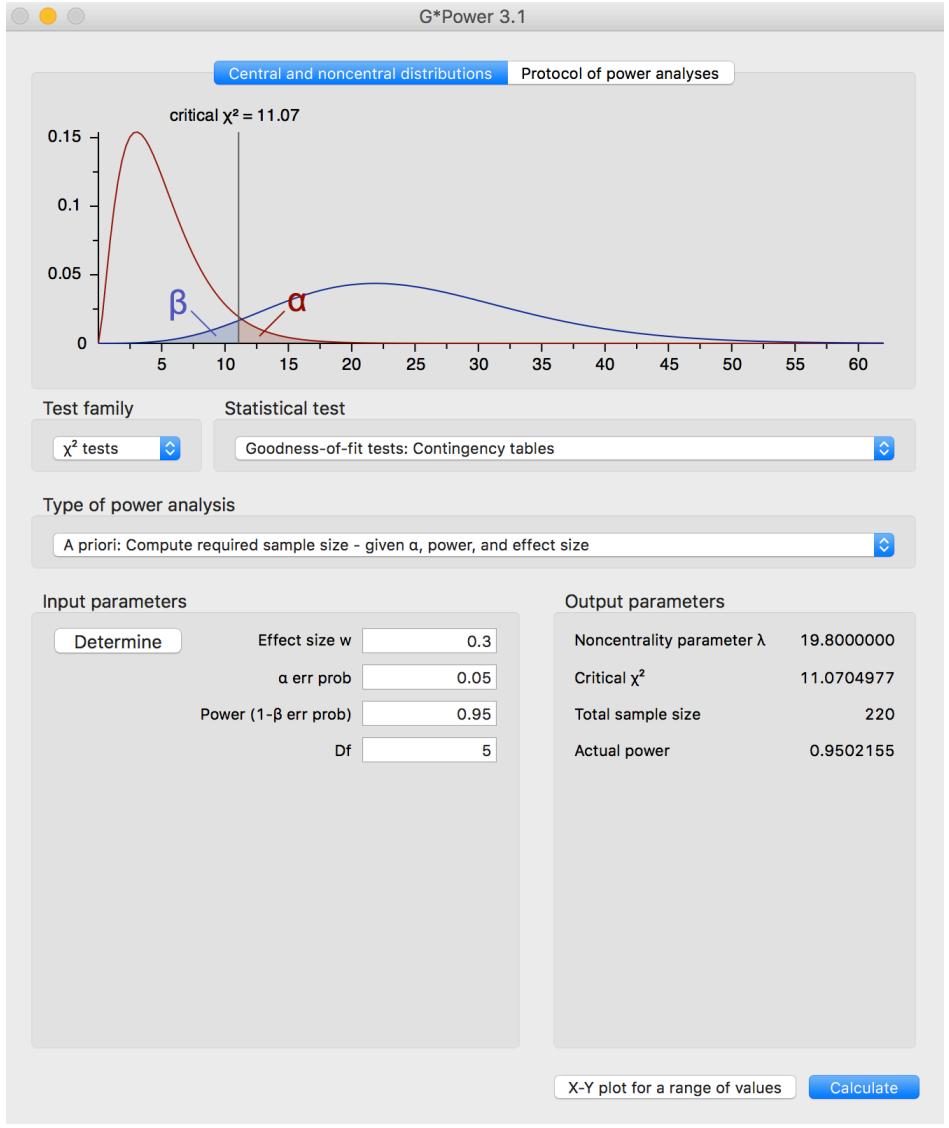
Power Analysis by aid of tables
(Power = d = complement of the error probability of a 2nd kind = 1 - β)

	α = 5%			α = 10%		
d	β = 5%	β = 7.5%	β = 10%	β = 5%	β = 7.5%	β = 10%
0.001 = 0.1%	47'409	41'675	37'516	37'516	32'436	28'779
0.002 = 0.2%	11'853	10'419	9'379	9'379	8'109	7'195
0.005 = 0.5%	1'897	1'667	1'501	1'501	1'298	1'152
0.01 = 1%)	475	417	376	376	325	288

- Example single random sample
  - Aim:
    - True H_0 rejected with α_{max} 5% and true H_1 rejected with β_{max} 5-10%
    - H_0: $\pi \leq x = \pi_0$, H_1: $\pi > x = \pi_0$ where x is a (literature) reference value, (e.g. a mortality rate)
- **In reality, N depends on practical issues: Cost? Time? Available patients?**

Power Analysis: Estimation of the required sample size (Power = complement of the 2nd kind error probability)



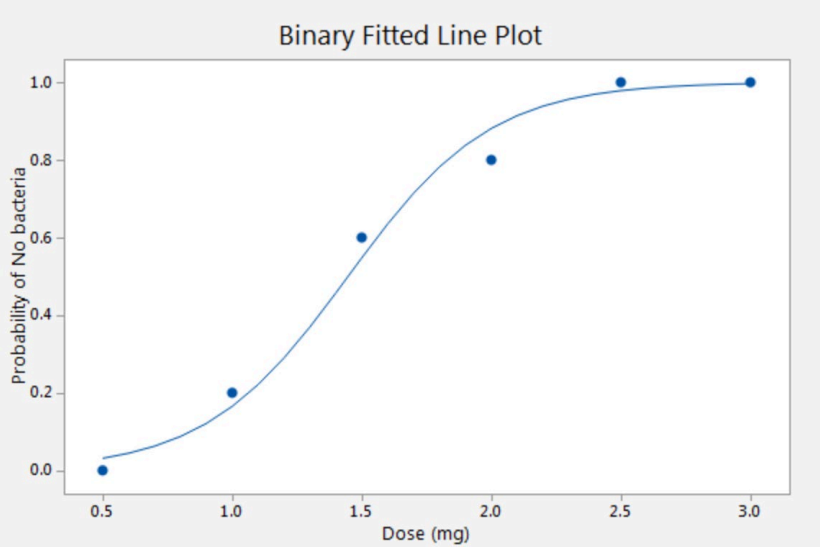


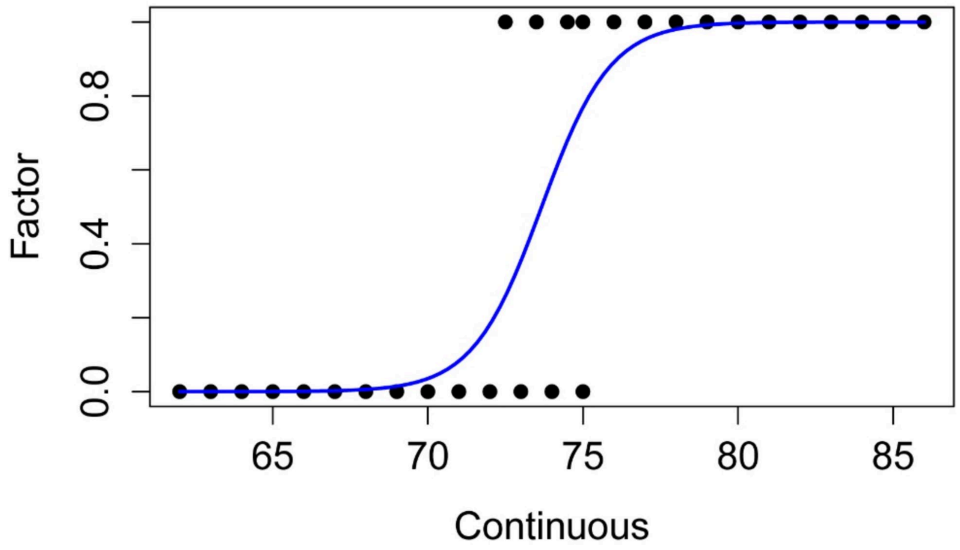
Binary Logistic Regression

- To analyse whether there is a dependency between multiple independent variables (x) and a binary dependent variable (y)
- Binary means y/n, male/female, taken/not taken...
- Logistic regression function

$$P(y=1) = 1 / (1 + e^{-(\beta 0 + \beta_1 * x_1 + \beta_2 * x_2 + \ldots \beta_k * x_k + \varepsilon)})$$

where β and ε are coefficients





Data Mining (needs big data)

- Relate databases (Grocery Store, Demographical, and lifestyle diseases DB
- Clean, preprocess, integrate, build demographical classes (age, races)
- Q&A: find relevant associations and rules between dietary patterns, demographics and lifestyle diseases