Basic Design Consideration

Previous and Current lecture

- Previous
  - Introduction to clinical trial (Ch 1)
  - Basic statistical methods (Ch 2)
- Current (Ch 3)
  - Basic design and analysis
  - How different aspects of the effects of a drug is studied in different phases of drug development
    - Phase I: Volunteer trials
    - Phase II: Explorative patient trials
    - Phase III: Confirmative patient trials

Planning and conduct of clinical trial

- Inferential statistics forms a basis for a conclusion regarding a prespecified objective addressed in the underlying population.

Confirmatory analysis:

Hypothesis → Results → Conclusion

Example:
Does our substance reduce risk of cardiac events compared to Standard of Care?

Example:
Run a clinical trial and collect information on cardiac events

Example:
By means of statistical inference conclusions can be drawn regarding the hypothesis

Planning and conduct of clinical trial

- A clinical study is conducted to adress a medical question regarding a drug substance in treatment of a specific patient population with a specific disease
- In the clinical study protocol these questions are formulated in the objectives
- To ensure credibility, ensure high scientific quality, trust the results of the clinical study and minimize risk of fraud,
  - Medical questions must be pre-specified in advance before the study is conducted
  - The statistical methods aimed to adress the hypotheses should be pre-specified
  - The study must have high scientific quality and should be optimized for answering the research questions

Planning and conduct of clinical trial

- Additional exploratory/hypothesis-generating/brain-storming analyses usually done after the study is finished
  - Credibility of these are lower. Future studies designed specifically to scientifically re-adress and confirm the findings
  - Example: Medication Loniten against high blood pressure were found to stimulare hair growth. Active substance minoxidil now used in Regaine as prevention of hair loss

Planning and conduct of clinical trial

- How to design and conduct a clinical trial with high credibility and scientific quality?
- Pre-specified clinical study protocol
  - Specifies the research plan for a clinical investigation
  - Regulatory document/ethics approval
  - The most important document to ensure quality control of a clinical trial

The Clinical Study Protocol

Important elements:

- Study objectives
- Study procedures
- Target patient population / Eligibility criteria
- Treatments / Blinding and randomisation
- Study design
- Data collection / Data management
- Statistical methods

Objectives

- Multiple objectives need to be prioritized
- Which objectives are confirmatory?
  - Confirmatory objectives are often the same as the primary objectives
  - The type I error rate needs to be controlled for the confirmatory objectives
    - Incorrect rejection of a true null hypothesis
- Secondary objectives often have an exploratory purpose
  - To gain more understanding of the substance
- Safety and tolerability almost always part of the objectives.

Objectives: Example 1

Primary objective:

- To evaluate the effect of gastrozole 20 mg versus placebo for the prevention of gastric ulcers

Secondary objective:

- To evaluate symptoms of heartburn with gastrozole 20 mg and with placebo

… adressed by variables, for example :

Primary: Time to occurrence of gastric ulcer (assessed by physical examination)

Secondary: Patient Reported Outcome by self-assessed questionnaires on symptoms

How choose secondary variable?

The objective

- To evaluate symptoms of heartburn with gastrozole 20 mg and with placebo

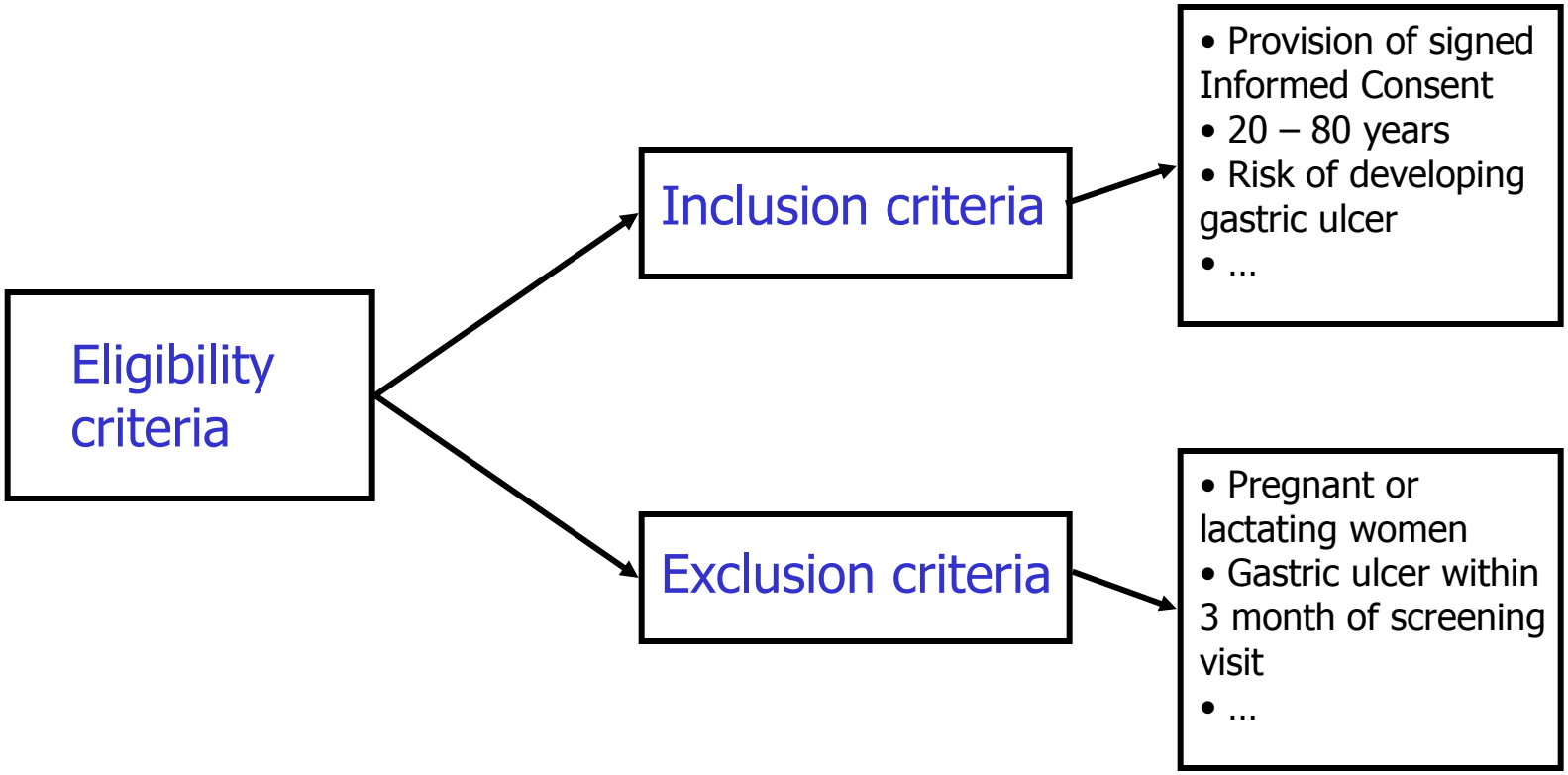
can be evaluated in several ways:

- time to sustained absence of heartburn, defined as the time to the first of 7 consecutive days free of that symptom
- maximal intensity of heartburn during the first and fourth week of treatment
- proportion of subjects with absence of heartburn the 7 days preceding 4 weeks of treatment
- **The way Patient Reported Outcome information is collected and summarized needs careful evaluation to prove valid and relevant!**

Target population

- Subjects included in a trial should be a representative sample of the target population
- The target population should have the specific medical need
- A homogeneous population reduce bias and minimize variability
- Important to be able to generalize the results
  - The later we are in the phase of drug development, the more able we are to make generalizations
- To be included in a trial a patient must be eligible

Target population



To be eligible a patient must meet *all* inclusion criteria

Patients meeting *any* of the exclusion criteria are excluded from the trial

Study design

Examples of common designs:

- Parallell group designs
- Crossover designs
- Group sequential designs
- Titration designs

Choice depends on:

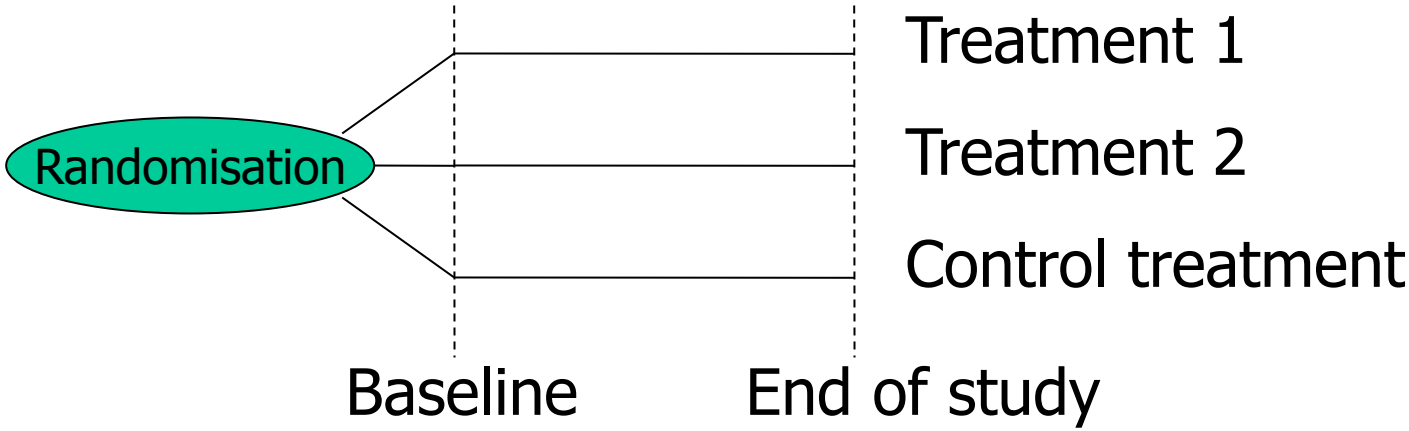
- Objective(s) of the study
- Theraputic area
- Time and cost
- Regulatory requirements
- Properties of the compund
- …

Study design

- Parallell group designs
  - Commonly used. Each patient randomized to 1 treatment and followed for a period. Common in late phase
- Crossover designs
  - Commonly used. Each patient randomized to 2 or more treatments in random order. Common in early phase
- Group sequential/Adaptive designs
  - Statistical testing of hypothesis at stages in study with possibility to stop or continue study to get more information as well as modify the design
- Titration designs
  - Same patient will be exposed to higher and higher doses (or placebo) based on safety and/or efficacy

Study design, Example 1

This study is a 26-week, multicenter, randomised, double blind, 2-arm, parallel group, placebo-controlled, efficacy and safety study, in patients with increased risk of developing gastric ulcers.



Statistical model, Example 1

Primary variable: Time to occurrence of gastric ulcer

To assess the difference between one of the active treatment groups (T) and the placebo group (P) the null hypothesis will test if the two groups have the same survival function ($S(t) = P(T > t)$):

$$H_0: S_T(t) = S_P(t)$$

Survival function is the probability that the time of ulcer (T) is later than some specified time t
The log rank test will be used

Statistical model, Example 1

Testing for difference in time to gastric ulcer

•Logrank test is a hypothesis test to compare the survival distributions of two samples.

• Nonparametric test

• Under H_0: $S_T(t) = S_P(t)$ (equal survival) the number of events for one of the treatments does at each time point has a hypergeometric distribution *.

• Summarizing over all time points with events, hypothesis testing can be done using the normal distribution.

** describes the probability of **k** successes in **n** draws without replacement from a finite population of size **N** containing exactly **K** successes.*

Example 2

Testing a drug that lowers the blood pressure on patients with hypertension

– This study is a 8-week, multicenter, randomised, double blind, 3-arm, parallel group, efficacy and safety study, in patients with moderate to severe hypertension.

Primary objective:

- To compare sitting diastolic blood pressure (DBP) lowering effect of hypersartan 16 mg with that of Placebo

Secondary objectives:

- To compare sitting diastolic blood pressure (DBP) lowering effect of hypersartan 8 mg with that of Placebo and 16 mg vs 8 mg

Primary variable:

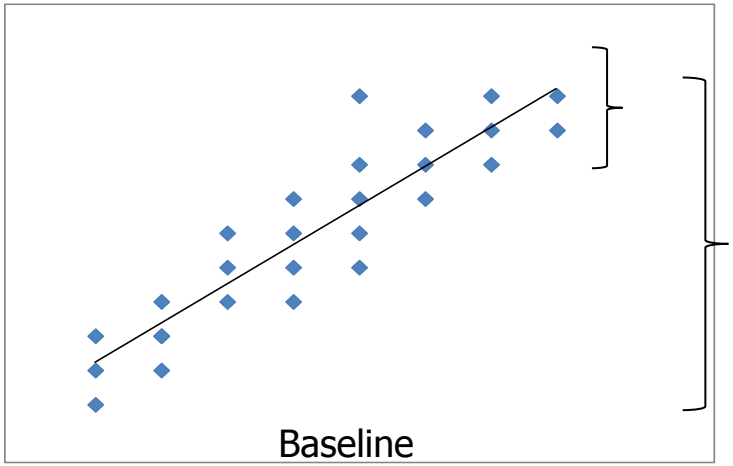
- Change in sitting DBP from baseline to the end of study

Statistical model, Example 2

If there were only 2 treatments and no baseline information available, a simple t-test would be sufficient. Here we have 3 treatments (ANOVA).

By adjusting for each individual´s level at baseline we can explain some of the variability and thereby increase precision in estimates

- We are conditioning on the baseline by having it as a covariate in the model (ANCOVA)

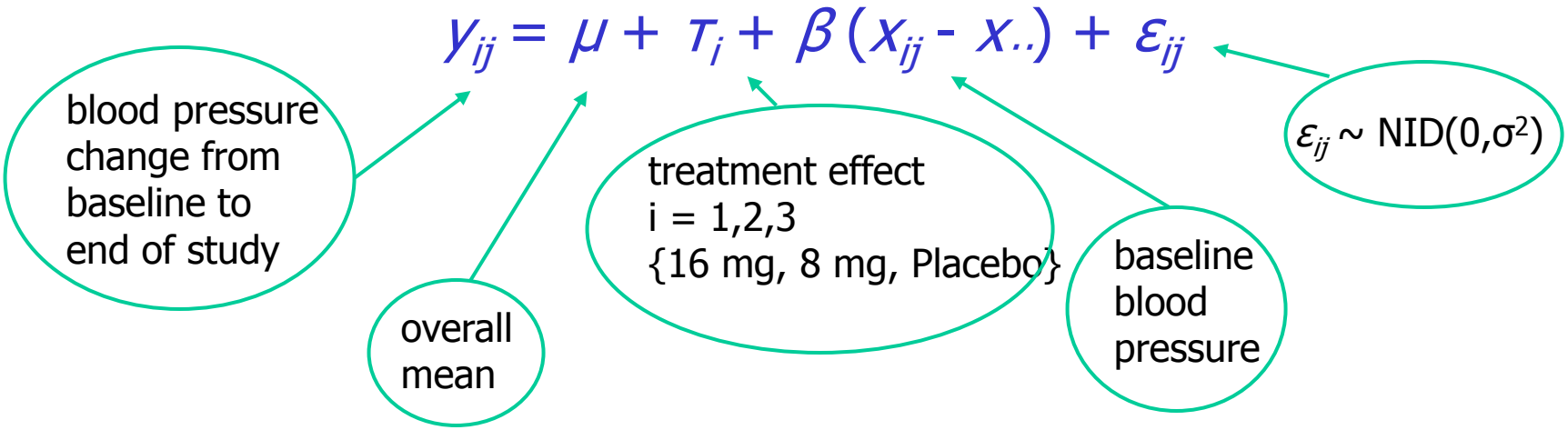


Small variation when conditioning (regression line)

Large variation without conditioning (no regression line)

Statistical model, Example 2

The change from baseline to end of study in sitting DBP will be described with an ANCOVA model, with treatment as a factor and baseline blood pressure as a covariate:



Differences between two treatments will be tested using the residual variance from the ANCOVA table, p-values and confidence intervals will be calculated from Student's t-distribution.

Statistical model, Example 2

The family-wise type I error* for the 3 primary objectives will be controlled at the 5% level using a step-wise testing procedure.

All 3 comparisons will be conducted at a significance level of 5%, but a comparison will only be confirmed as statistically significant if it is significant at a 5% level and all preceding comparisons were statistically significant at a 5% level.

H_{01}: $\tau_1 = \tau_3$ (16 mg vs Placebo)
H_{02}: $\tau_2 = \tau_3$ (8 mg vs Placebo)
H_{03}: $\tau_1 = \tau_2$ (16 mg vs 8 mg)

** The risk of incorrectly rejecting at least one true null hypothesis*

Results, Example 2

Objective	Treatment difference	Variable	LS Mean	Confidence interval (95%)	p-value	Statistically significant
Primary objective 1	**Hyp. 16 mg – Placebo**	**Sitting DBP**	**-7.6 mmHg**	**[-9.2, -6.1]**	**<0.001**	**Yes**
Primary objective 2	**Hyp. 8 mg – Placebo**	**Sitting DBP**	**-3.7 mmHg**	**[-4.6, 0.5]**	**0.07**	**No**
Primary objective 3	**Hyp. 16 mg – Hyp. 8 mg**	**Sitting DBP**	**-3.9 mmHg**	**[-1.8, -0.01]**	**0.04**	**No**

Not statistically significant due to stepwise testing

Are the results statistically significant?

Are the results clinically relevant?

Chapter 3 Reading instructions

- 3.1 Introduction: Read
- 3.2 Goals of clinical trials: Read
- 3.3 Target Population and Patient Selection: Read through
- 3.4 Selection of controls: Read through
- 3.5 Statistical considerations: Read
- 3.6 Other issues: Read through
- 3.7 Discussion: Read through