A statistician’s contribution to drug research and development

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My-Dagen: MATEMATIK I YRKESLIVET

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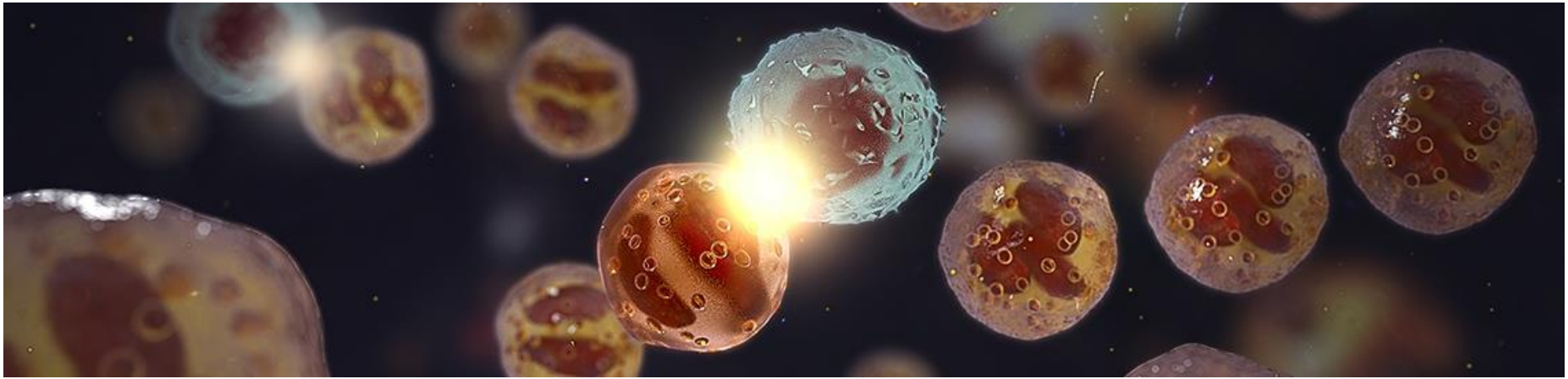
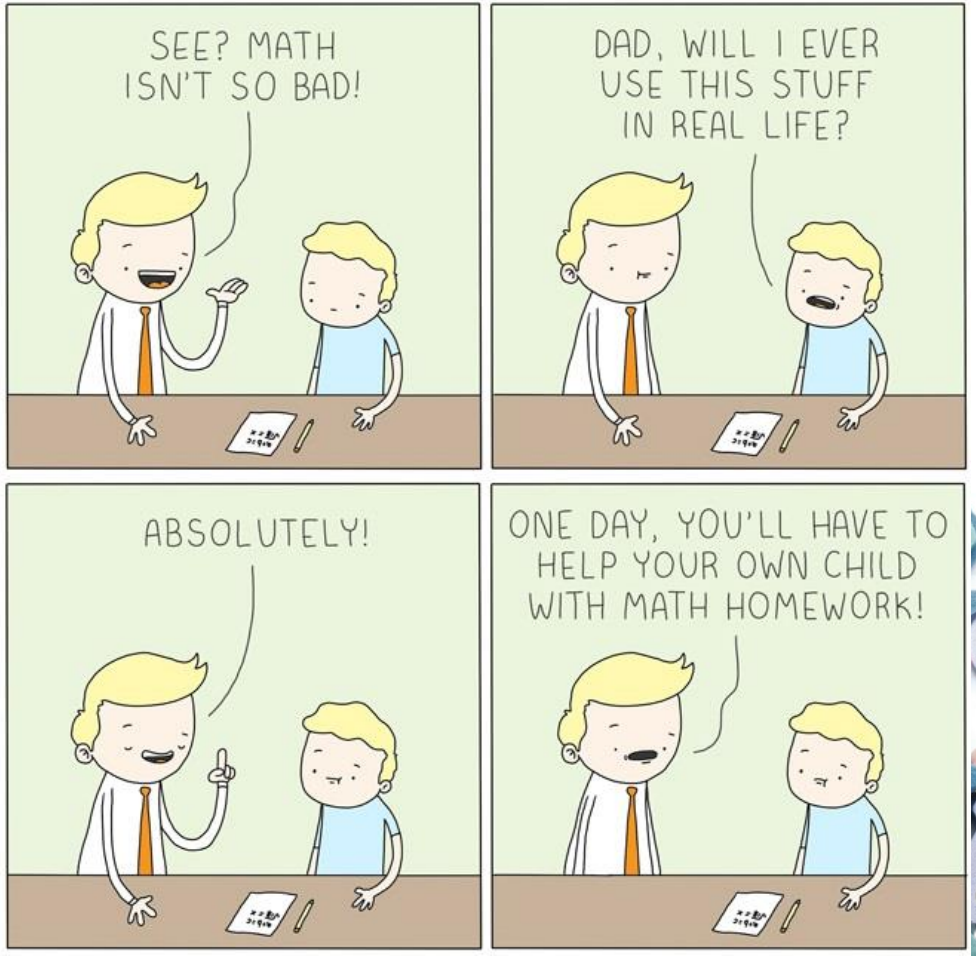


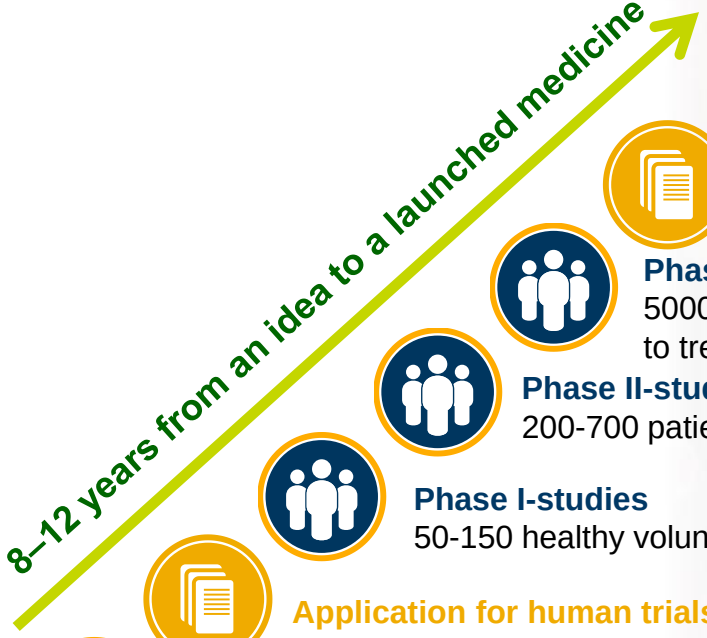
Wondering where math can take you?



We push the boundaries of science to deliver life-changing medicines.

“Together, we can be confident that, by leading in science, we will transform the lives of patients around the world.”
Pascal Soriot

Time and patience are behind every new medicine



Phase IV-studies and RWE register studies
Long-time effects and health economics are researched

Application for approval and launch

Phase III-studies
5000 patients (or more) in different ages, even those who take pharmaceutical to treat other conditions, could be included in the test group

Phase II-studies
200-700 patients with the condition to be treated are included in these studies

Phase I-studies
50-150 healthy volunteers are administered the pharmaceutical under strict control

Application for human trials

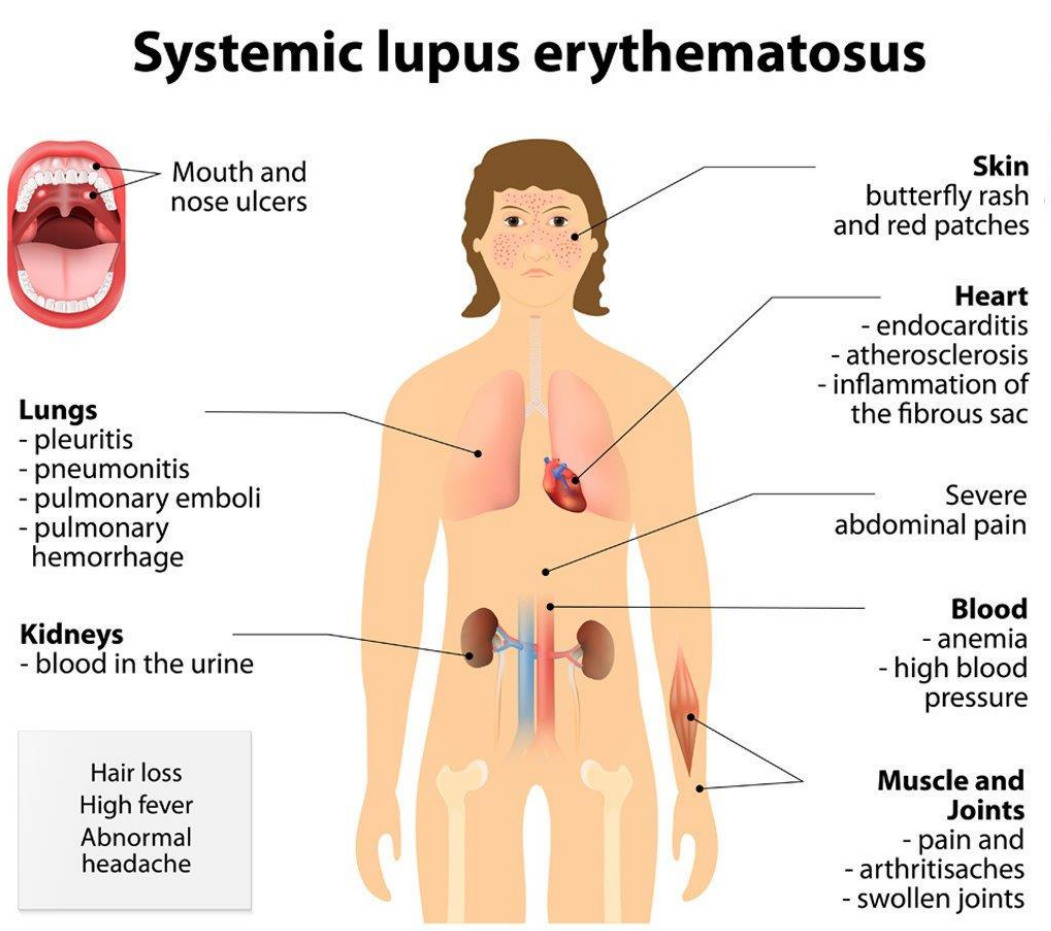
Find potential pharmaceutical candidate
Thousands of chemical substances are analysed and tested

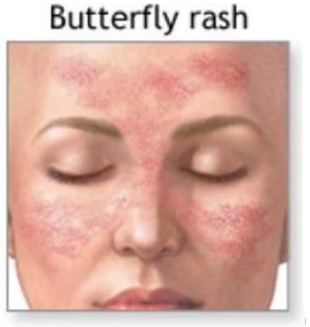
Each drug-project includes many studies such as

Statisticians are shy, but we learn to collaborate with others…

Intravenous infusion	Subcutaneous administration	Pediatric study	Another disease
• Physician	• Physician	• Physician	• Physician
• Clinical Operations manager	• Clinical Operations manager	• Clinical Operations manager	• Clinical Operations manager
• Safety experts	• Safety experts	• Safety experts	• Safety experts
• **Statistician**	• **Statistician**	• **Statistician**	• **Statistician**
• Programmer	• Programmer	• Programmer	• Programmer
• Data manager	• Data manager	• Data manager	• Data manager
• Supply chain expert	• Supply chain expert	• Supply chain expert	• Supply chain expert
• Regulatory affairs	• Regulatory affairs	• Regulatory affairs	• Regulatory affairs
• …	• …	• …	• …

I work on a lupus drug





Statistics

A branch of applied mathematics concerned with the collection and interpretation of quantitative data and the use of probability theory to estimate population parameters

Concerned with the treatment of quantitative information from group of individuals

Descriptive Statistics

In a clinical trial, a new drug resulted in pain relief an average of 25 minutes earlier than a known drug

Inferential Statistics

The new drug results in pain relief significantly faster than the known drug.

CI: (20min, 30min)

p-value = 0.003

Biostatistics

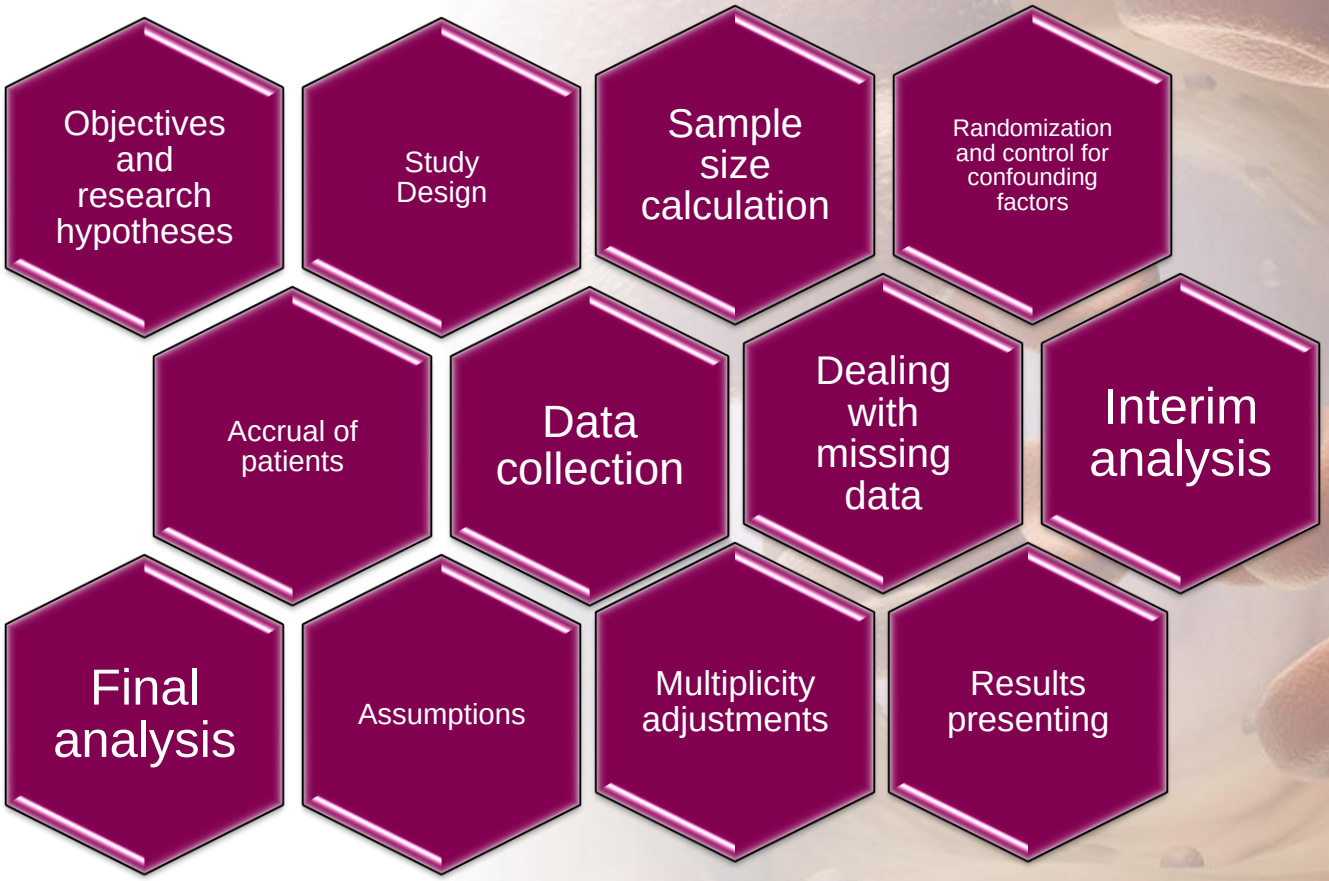
Statistics focused on the biological and health sciences

Concerned with all aspects of data:

- Planning the study
- Collecting and organizing the information
- Analyzing the data
- Interpreting the results

- Is a new pharmaceutical for autoimmune disease effective in decreasing organ damage? Is the new drug more effective than placebo or *standard of care*?
- Is the use of a drug associated with adverse events?
- Is there heterogeneity in treatment effects in subgroup of patients?
- How do clinical measures correlate with each other?

Statistical Analysis Plan



Hypothesis testing

Null Hypothesis (H_0) — No effect, no difference

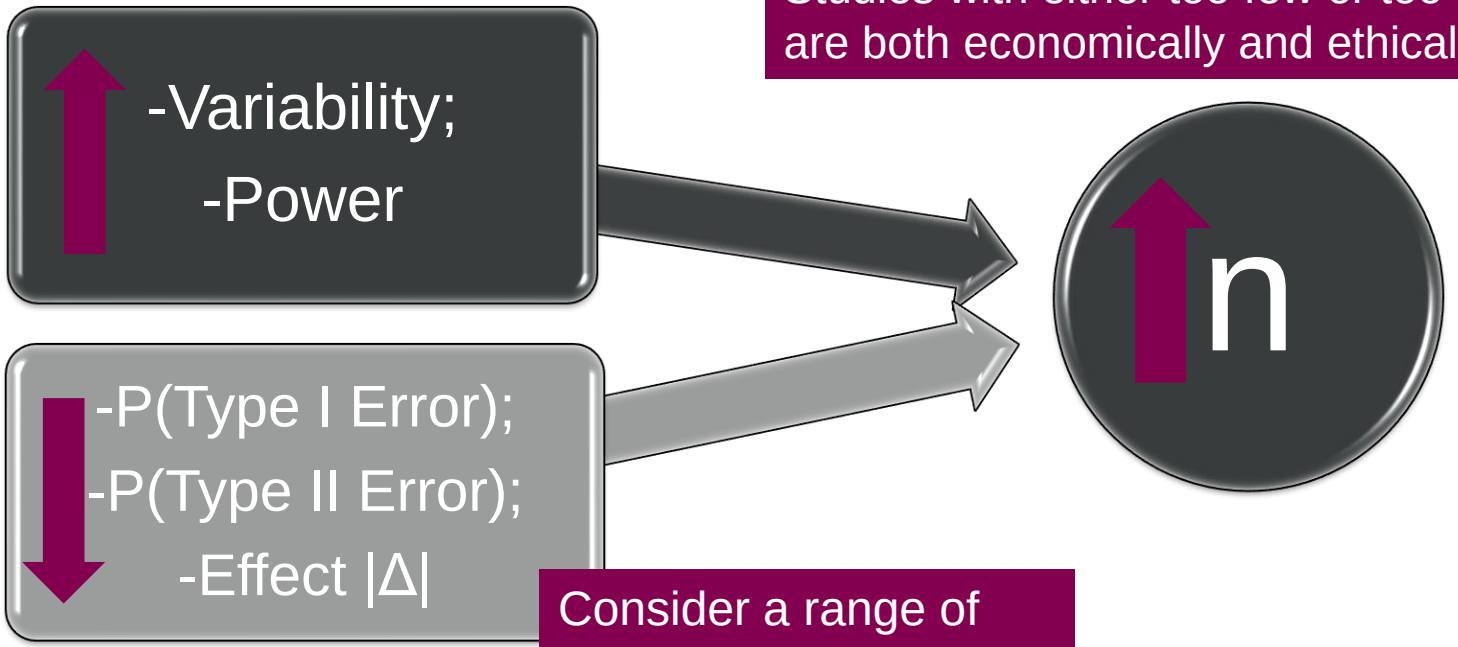
- After one year of treatment there is **no difference** in the mean change from *baseline* of number of swollen joints between patients on active treatment and placebo.
- There is *no difference* in the percentage of patients with no organ damage in the placebo group and active treatment group of patients

Alternative Hypothesis (H_1) — Effect, difference

- There is a difference between active treatment and placebo in the mean change of swollen joints
- There is a difference between the two groups in the percentage of patients with no organ damage.

Sample Size calculation

Studies with either too few or too many patients are both economically and ethically unjustified

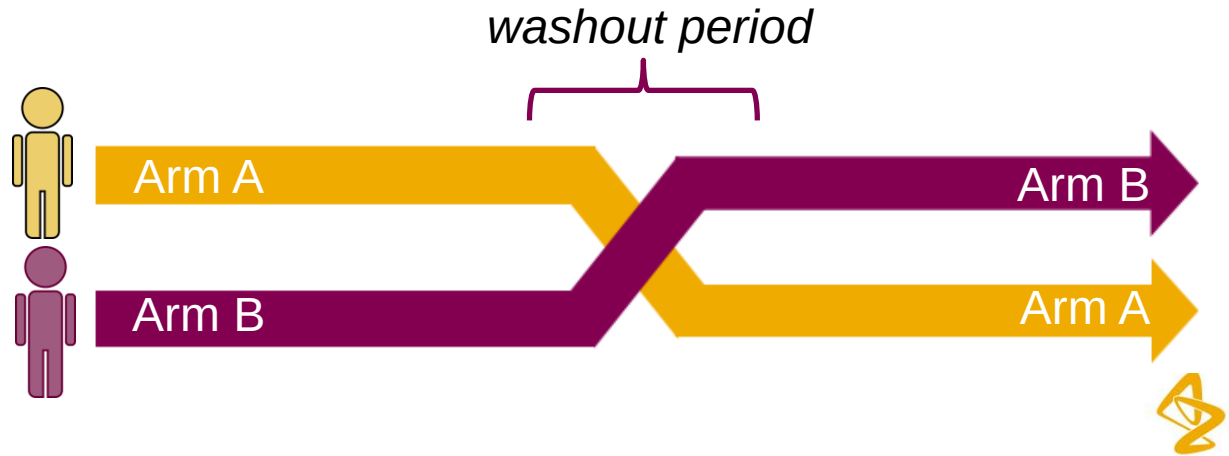


Consider a range of sample size values linked to assumptions.

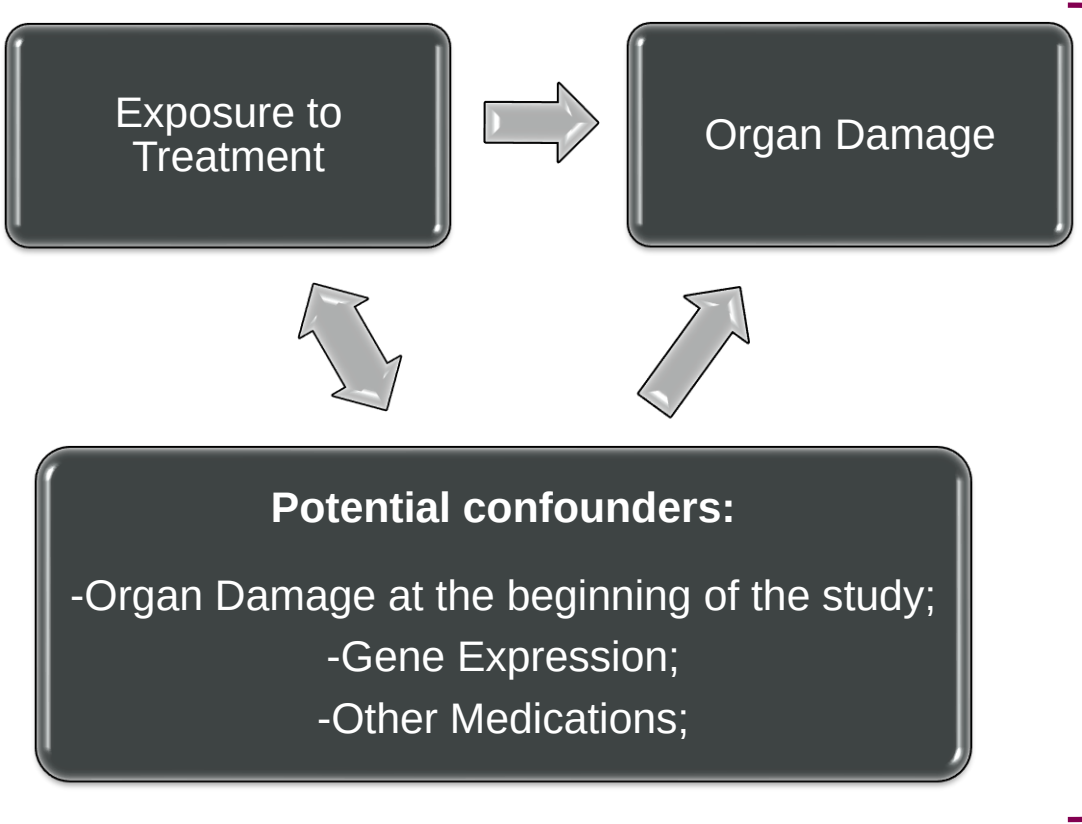
Study Design

Parallel study

Crossover study



Controlling for confounding factors



-Randomization;

-Control in statistical models;

-Matching.

Missing Data

Missing Completely at Random (MCAR)

- The probability of missing is independent of any characteristic of the subjects;
- The chance of missing data is the same for individuals in different treatment groups.

Missing at Random (MAR)

- The probability a variable is missing depends only on obsereved variables.

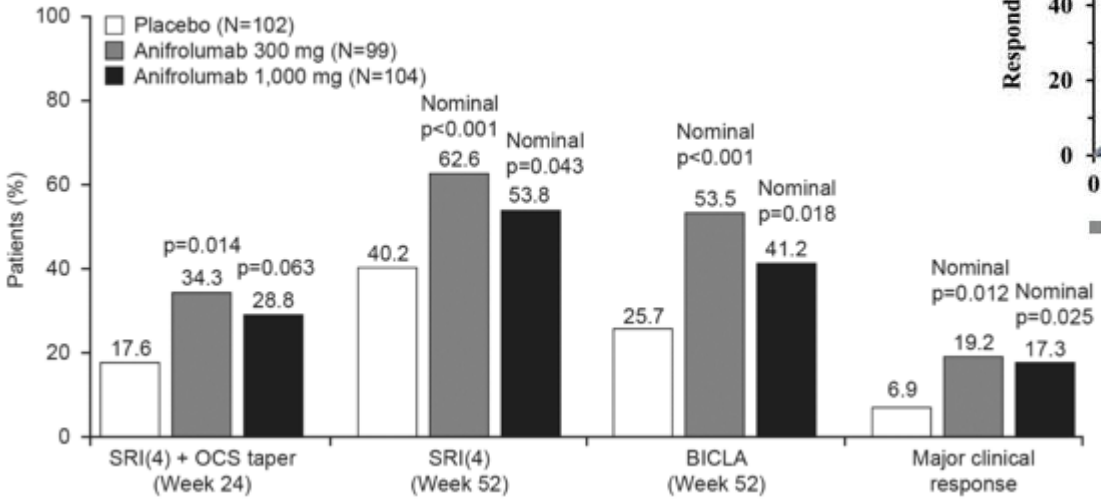
Not Missing at Random (NMAR)

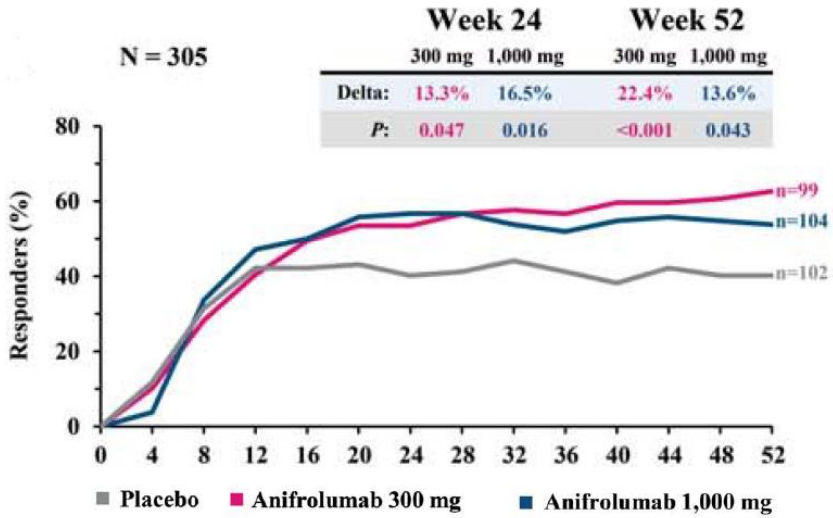
- Probability depends on variables that are incomplete

Clinical study report (CSR)

Includes ~200 tables, figures, listings:

- Population characteristics;
- Efficacy;
- Safety.





Transperancy and Regulation

ClinicalTrials.gov is a Web-based resource that provides the public with easy access to information on clinical studies on a wide range of diseases and conditions.

Big regulatory agencies:

- Food and Drug Administration (FDA)
- European Medicines Agency (EMA)

If the reviews by regulatory agencies show that the drug's benefits outweigh its known risks and the drug can be manufactured in a way that ensures a quality product, the drug is approved and can be marketed.

Conclusion

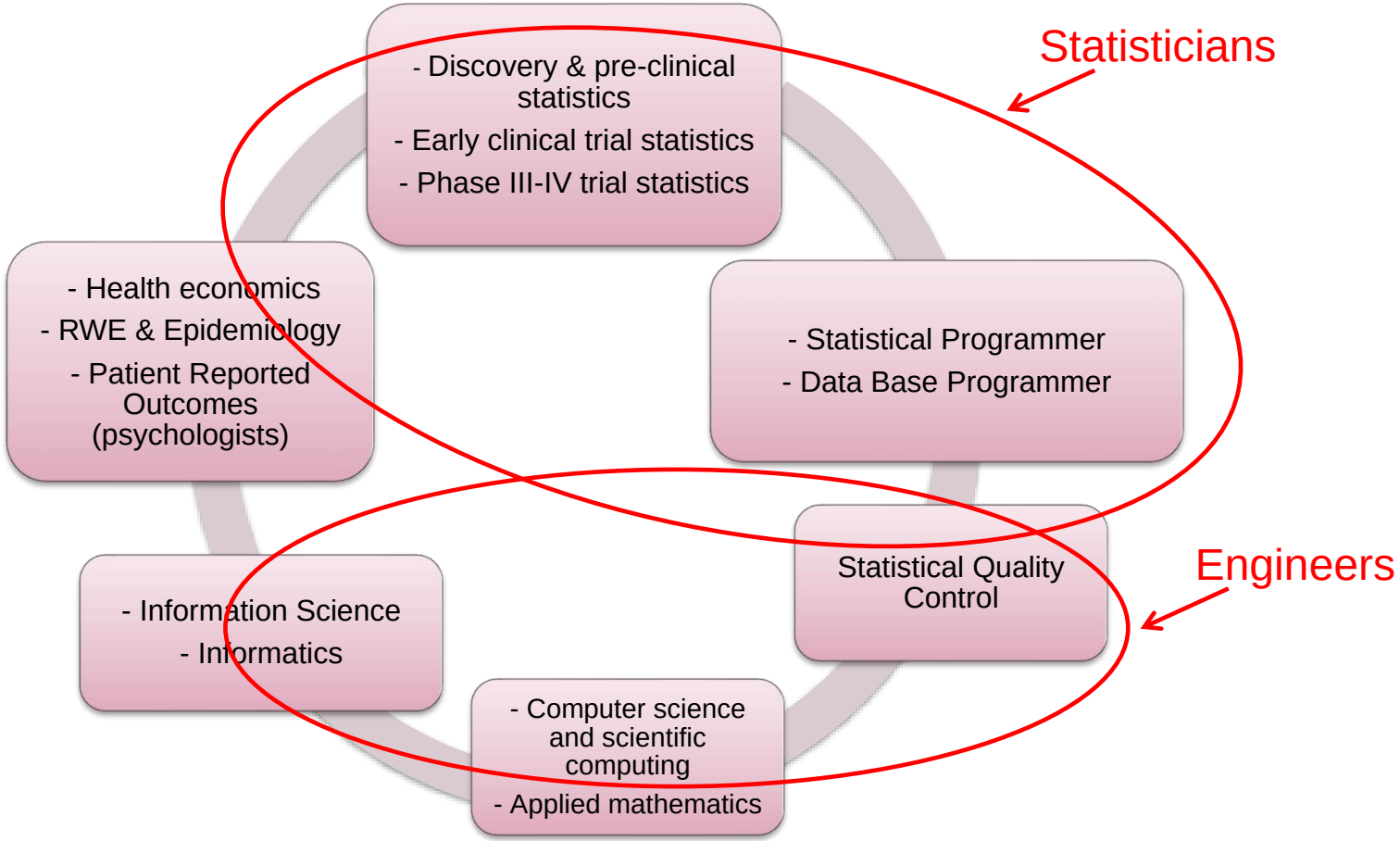
A biostatistician develops statistical methods and apply them to human health topics ultimately to improve human health.

Statistics aims to give answers about dependencies and inferences, but always states a measure of uncertainty.

Always space for exploration

Help save lives

Statistikområden och närliggande områden inom läkemedelsindustrin



Multiplicity Adjustment

N independet tests examined for statistical significance (due to multiple study objectives, multuple doses, etc.)

All null hypothses are true

The probability that at least one will be found statistically significant (reject the null hypohtesis) = $1-(1-\alpha)^N$ for given α level.

Bonferroni correction

- Test at $\alpha = \alpha_{FWER}/N$

Holm's correction

- Order the p-values from smallest to largest (i=1,…m).
- Each p_i is compared to $\alpha/(m-(i-1))$
- Stop if fail to reject for some i.

Benjamini and Hochberg's correction

- p-values are sorted in ascending order.
- Each p_i is compared to $\alpha(i/m)$
- Stopping rule

Hochberg and Hommel

- For multiple doses and objectives

More…

Interim Analysis and Futility Analysis

Great results:

Strategy for early stopping if an interim analysis reveals large differences between treatment groups.
- Saves time and resources
- Reduces study participants' exposure to the inferior treatment.

Interim futility analysis:

Stop the trial if chance of success at the final analysis be sufficiently small.
Key statistical considerations:

- When?
- What is the trigger value such that, if observed, the trial will be deemed futile?
- What will the savings be if futility is concluded?
- What is the probability futility will be concluded in error?
- What is the overall power of the trial with a futility analysis incorporated?