Statistical Issues in Drug Development

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Day 1 – 12th September 2023

Lecture 1

Control, randomisation and blinding. Why is concurrent control valuable? Trend effects, study effects, regression to the mean. Should patients in a clinical trial be representative? How are patients allocated to treatment? What is the point of randomisation? How is randomisation carried out? How are clinical trials blinded? What is the purpose of placebos? The double dummy technique. Double dummy loading. The TARGET study as an example(2). When is blinding inappropriate? Should we test blinding by asking patients if they can identify the treatment?

Lecture 2

The measurement of treatment effects. Scales commonly used. Why dichotomisation is a bad idea. Risk differences, relative risks, odds-ratios, hazard rates. The example of bioequivalence studies. The example of vaccine efficacy trials. Transferability of results. The Pfizer/BioNTech COVID vaccine efficacy trial as an example(3). Measures of uncertainty.

Lecture 3

The use of covariate information. Baselines. Placebo run-ins. Why change scores (also known as gain scores) are a bad idea. Why percentage change from baseline is an even worse idea. Stratification. Analysis of covariances. Why responder analysis should be avoided. Why personalised medicine is overhyped(4).

Lecture 4

Some examples and some lessons. The Lanarkshire Milk Experiment as a historical example(5, 6). What does it teach us about the value of concurrent control? The Shumaker and Metzler phenytoin study(7). What does it teach us about personal response? MTA/02: an example of a complex study(8).

Day 2 – 13th September 2023

Lecture 5

Determining the sample size. Basic idea. Using power. The meaning of clinically relevant differences. Effect of sample size on inference. P-values versus significance. Bayesian approaches. Assurance(9).

Lecture 6

Multi-centre trials. Recruitment. Issues regarding balancing numbers. Type II and Type III sums of squares. Fixed and random effects estimators. Results from individual centres. Effect reversals. Recovering inter-centre information. The Lanarkshire milk experiment revisited. The TARGET study(2).

Lecture 7

Cross-over Trials and n-of-1 Trials. Basic designs. Carry-over. The two-stage procedure and why it should not be used(10-12). Contralateral studies. N-of-1 trials. The Shumaker and Metzler(7) study revisited.

Lecture 8

Meta-analysis. History of weighting estimates. Airy(13). Glass(14). Fixed effects approaches. Random effects approaches. Publication bias. Use for using historical controls.

References

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