

<p>Slide 1</p>	<p style="text-align: center;"><b>Clinical Trials</b></p> <p style="text-align: center;"><b>Design and Analysis</b></p> <p style="text-align: center;">Nick Holford Dept Pharmacology &amp; Clinical Pharmacology University of Auckland, New Zealand</p>	<p>Clinical trials are essential experiments for learning and confirming the clinical benefits and adverse effects of drugs. The conclusions drawn from a clinical trial will depend on both the design of the trial and how it is analyzed.</p>
<p>Slide 2</p>	<p style="text-align: center;"><b>Objectives</b></p> <ul style="list-style-type: none"> <li>➤ Learn the ABCS of clinical trial design</li> <li>➤ Understand the 2 main types of question that are asked by clinical trials</li> <li>➤ Know what power of a trial design means</li> <li>➤ Appreciate the pros and cons of the intention to treat analysis perspective</li> </ul> <p><small>©NHG Holford, 2021. all rights reserved.</small></p>	
<p>Slide 3</p>	<p style="text-align: center;"><b>Clinical Trial Design</b> <b>ABCS</b></p> <ul style="list-style-type: none"> <li>➤ <b>A</b>ssignment</li> <li>➤ <b>B</b>linding</li> <li>➤ <b>C</b>omparison</li> <li>➤ <b>S</b>equence</li> </ul> <p><small>©NHG Holford, 2021. all rights reserved.</small></p>	<p>There are 4 major elements in the design of a clinical trial. Each has an effect on the way trials are designed and interpreted.</p>

## Assignment

- First Come, First Served
  
- Randomized
  - » Balanced
  - » Stratified
    - E.g. Sex, Previous Stroke

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The assignment process is used to determine which subjects get which treatment.

The “First Come, First Served” assignment process covers a range of possibilities that will typically introduce bias e.g. giving active treatment to subjects seen in the morning and placebo to those seen in the afternoon, or alternating between active and placebo treatment. The main source of bias from this process is the loss of blinding. The investigator can guess which subjects are getting different treatments even if he/she is blinded to the actual assignment.

A randomized assignment process is considered the best method of deciding which subjects get which treatment. A list of random numbers is used to decide on treatments e.g. if a random number is drawn from a uniform distribution between 0 and 1 then active treatment might be assigned if the number is  $<0.5$  and placebo if it is  $\geq 0.5$ .

In order to ensure balanced allocation of treatments the number of subjects to be randomized is decided ahead of time and a balanced list of treatments is drawn up. This list is then randomly permuted and subjects drawn in turn from the permuted list. This ensures that the desired balance e.g. 50% in each of two treatment groups, is not affected by the randomization process.

If different sub-groups might have different responses it is common to stratify the randomization sequence. Separate sequences are drawn up for each sub-group e.g. one list for males and one for females.

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## Blinding

- Open
- Single Blind
- Double Blind
  - » Double Dummy
- Triple Blind ?

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Blinding is used to reduce bias. Bias can arise from both the investigator's and subject's expectation of the treatment effect.

Open trials are unblinded. They are still commonly used for marketing purposes but have little scientific merit.

Single blind trials mean the investigator will know the treatment but the subject does not.

Double blind trials mean both the investigator and subject are not aware of the treatment.

Double dummy trials are used when two physically different treatments are compared e.g. tablet and inhaler treatments for asthma.

e.g. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. The Lancet. 2021;397(10278):971-84.

Triple blind trials may occur if the randomization sequence is lost or misinterpreted – this means that nobody ever knows what treatment was given.

Blinded trials often become unblinded if the treatment has very prominent beneficial effects or adverse effects. This is very hard to prevent or adjust for in the analysis.

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## Comparison

- Active
  - » Dose Control (RDCT)
  - » Concentration Control (RCCT)
  - » Biomarker Control (RBCT)
- Inactive ("Placebo")
- Standard Treatment
  - » Non-Inferiority
  - » Add-On

RxCT = Randomized 'x' Controlled Trial

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Good experimental science uses a control group to account for factors that might influence the outcome that are not experimentally assigned.

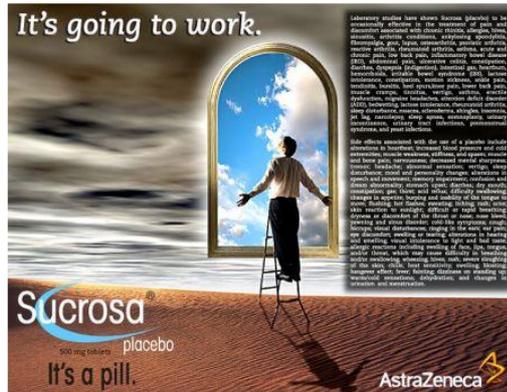
Within an active treatment arm it is usually desirable to learn about the relationship between intensity of treatment and outcome. The within active treatment control that is most widely used is the dose control i.e. there are two or more different doses arms in the active treatment group e.g. 100 mg, 200mg, 300mg.

Concentration control can be used to reduce the influence of random differences in pharmacokinetics. By measuring concentration and individualizing the dose to reach desired target concentrations e.g. 10 mg/L, 20 mg/L, 30 mg/L, then the concentration effect relationship can be discovered. Finally, if there is a biomarker (e.g. cholesterol concentration) that reflects the effect of the drug it can be used to control the intensity of treatment and reduce

		<p>both pharmacokinetic and pharmacodynamic variability. Subjects are randomized to one or more target biomarker levels and the dose is adjusted to reach the target biomarker effect.</p> <p>From a scientific perspective the best treatment control is to use an inactive substance. If there is genuine uncertainty about the effect of the active treatment then it is usually considered ethical to randomize to inactive (the ethical principle of ' equipoise ').</p> <p>However, if there is a standard treatment that would always be used because it is known to be effective then investigation of a new treatment may be in comparison with the standard treatment. This kind of trial is sometimes designed to show that the new treatment is no worse than the standard treatment – a non-inferiority trial.</p> <p>If the active treatment and the standard treatment is given to all subjects then this would be considered an add-on trial design i.e. it looks for the effect of the new treatment in addition to the standard treatment. The control group would receive an inactive as well as the standard treatment.</p> <p>Hale et al (1998) and Shaffer et al (2002) are examples of target concentration intervention trials used to determine the exposure-response relationship.</p> <p>Hale M, Nicholls A, Bullingham R, Hene R, Hoitsman A, Squifflet J, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther. 1998;64:672-83.  Shaffer CL, Gal P, Ransom JL, Carlos RQ, Smith MS, Davey AM, et al. Effect of age and birth weight on indomethacin pharmacodynamics in neonates treated for patent ductus arteriosus. Crit Care Med. 2002;30(2):343-8.</p>
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## The Placebo Effect – True or False?

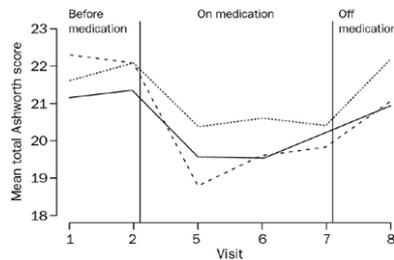


Is this a genuine advertisement?  
True or False?

<http://www.theonion.com/article/fda-approves-sale-of-prescription-placebo-1606>

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## Which is the Active Drug?



Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003;362:1517-26

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The importance of a placebo control is shown in this study which tried to determine if cannabis is helpful in treating the symptoms of multiple sclerosis. Dashed line is pure THC. Dotted line is cannabis extract. Solid line is placebo.

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## Sequence

- Parallel
- Crossover
- Titration
  - » Forced
  - » Flexible

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The sequence of treatments can influence what is learned from a trial and the kind of bias that can arise.

The parallel design has different treatments assigned to different groups of subjects. It is a good design for finding out the answer to the simple 'Does the drug work?' question but gives unclear answers to learning questions that ask about the shape of the dose response relationship of what dose is needed to achieve a particular effect.

A crossover design uses two or more treatments in each subject. This allows individual dose response curves to be observed and the true shape of the dose response relationship can be determined.

The crossover design may also have an advantage in terms of statistical power. If it assumed that within subject variability is small then fewer subjects need to be studied to detect a treatment effect.

		<p>There are several disadvantages of the crossover design. There may be a treatment carryover effect e.g. due to a drug with a long half-life. This would bias the response seen in a placebo treatment period that followed an active treatment period. If there is some systematic difference between periods e.g. the first treatment is given in the winter and the second treatment is given in the summer, then there may be a period effect that influences the response. Because each subject is asked to take several treatments there is a higher risk of dropout and loss of information from that subject.</p> <p>Titration designs are a special kind of crossover design. These may involve giving a fixed sequence of doses ('forced titration') to each subject to learn about the dose response relationship. A more realistic titration design ('flexible titration') involves starting with a low dose and if the subject responds the dose is kept constant. The dose is only increased if the desired response is not reached.</p>
Slide 10	<p style="text-align: center;"><b>Analysis</b></p> <p>➤ What is the question?</p> <ul style="list-style-type: none"> <li>» Does it work? <ul style="list-style-type: none"> <li>– Yes/No/Maybe</li> </ul> </li> <li>» How well does it work? <ul style="list-style-type: none"> <li>– Continuous scale answer</li> </ul> </li> </ul> <p><small>©EMG Health, 2021. All rights reserved.</small></p>	<p>The question to be answered by a clinical trial will influence both the design and the analysis.</p> <p>There are 2 kinds of question:</p> <ul style="list-style-type: none"> <li>• Confirming questions have yes/no answers and are used to test a hypothesis e.g. Does the drug lower blood pressure?</li> <li>• Learning questions have how much answers and are used to quantify the size of an effect e.g. what dose is needed to lower blood pressure by 5 mm/Hg?</li> </ul>

<p>Slide 11</p>	<h2 style="text-align: center;">Does It Work?</h2> <ul style="list-style-type: none"> <li>➤ Simple Comparison <ul style="list-style-type: none"> <li>» Active vs Control</li> </ul> </li>   <li>➤ Method <ul style="list-style-type: none"> <li>» Hypothesis testing <ul style="list-style-type: none"> <li>- t-test (two groups)</li> <li>- ANOVA (several groups)</li> <li>- Log rank test (survival)</li> </ul> </li> </ul> </li> </ul> <p style="font-size: small;">©NHG Hofstad, 2021 all rights reserved.</p>	<p>Analysis procedures for testing hypotheses include the t-test for comparing 2 groups an Analysis of Variance (ANOVA) if there are several treatment groups. If the endpoint of the trial is an event such as death then a survival analysis is performed and might use the log-rank test to evaluate the hypothesis that survival is changed by the treatment.</p>
<p>Slide 12</p>	<h2 style="text-align: center;">How Well Does It Work?</h2> <ul style="list-style-type: none"> <li>➤ Size of Response <ul style="list-style-type: none"> <li>» CL, V</li> <li>» Emax, C50</li> </ul> </li>   <li>➤ Method <ul style="list-style-type: none"> <li>» Pharmacokinetic model</li> <li>» Pharmacodynamic model</li> </ul> </li> </ul> <p style="font-size: small;">©NHG Hofstad, 2021 all rights reserved.</p>	<p>The application of pharmacological principles can be used to determine the answer to 'how much' questions. The 4 basic properties of a drug, clearance, volume of distribution, maximum effect, and dose (or concentration) producing 50% of the maximum can be used to predict the answer to 'how much' questions. The trial is designed to estimate the values of these parameters using pharmacokinetic and pharmacodynamic models.</p>
<p>Slide 13</p>	<h2 style="text-align: center;">Model Based Analysis</h2> <ul style="list-style-type: none"> <li>➤ Models <ul style="list-style-type: none"> <li>» PK, PD, PKPD</li> </ul> </li> <li>➤ Execution <ul style="list-style-type: none"> <li>» Adherence</li> <li>» Dropouts</li> </ul> </li> <li>➤ Covariates <ul style="list-style-type: none"> <li>» Renal function, size, sex</li> </ul> </li> </ul> <p style="font-size: small;">©NHG Hofstad, 2021 all rights reserved.</p>	<p>Model based analysis procedures can be more informative than simple hypothesis tests. A model can be used to account for unplanned trial execution differences e.g. subjects may dropout or may not take the treatment as prescribed (adherence failure). The influence of subject demographic features can also be used to learn about why treatment differences exist between subjects and to identify ways to individualize drug treatment.</p>

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## Power Analysis

- Is this trial design reasonable?
  - » What is the size of the effect?
  - » What is the variability in the response?
  - » What is the desired P-value? e.g. 0.05
  - » What is the desired Power? e.g. 0.80
  
- Usually only tests number of subjects

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Power analysis is used to determine the likelihood that a clinical trial will detect a drug effect when the drug effect really exists.

Because of the random variability in a trial e.g. due to differences between subjects and measurement error, a drug may really work but the effect may be lost in the noise.

A power analysis takes into account the size of the expected treatment effect, the expected size of the variability in response and the statistical criterion used to judge if the null hypothesis should be rejected. This criterion is usually expressed the probability of accepting that the drug works when in fact it does not ('the null hypothesis').

A target power is usually greater than 0.8 (often described as 80% power). This means that given the assumptions about the size of effect, variability of response and statistical criterion the probability of rejecting the null hypothesis will be 0.8. This kind of power analysis is a sensible idea if you are planning to invest several million dollars in a clinical trial.

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## Analysis Perspective

- Intention to Treat
  - » "use effectiveness"
  - » pharmacoeconomic perspective
  
- As Treated
  - » "method effectiveness"
  - » development science perspective

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There are 2 perspectives that can be considered when analysing a clinical trial. The intention to treat analysis only considers the treatment assignment. It does not take into account information about whether the subject actually took the treatment. This inevitably means that the size of the treatment effect will be underestimated if some subjects do not take the active treatment they were assigned or if a placebo subject takes an active treatment. The intention to treat perspective is useful for making pharmacoeconomic decisions where the cost of the drug has to be paid whether or not it is actually taken.

The as treated analysis perspective will take into account information about what the subject actually took for their treatment. It will be less likely to have the underestimation bias that is associated with the intention to treat approach. It is therefore more suitable for making scientific decisions.

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## Further Reading

### ➤ Drug Discovery and Development

[https://en.wikipedia.org/wiki/Drug\\_development](https://en.wikipedia.org/wiki/Drug_development)

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Wikipedia provides a useful overview of the role of the pharmaceutical industry in society.

[https://en.wikipedia.org/wiki/Drug\\_development](https://en.wikipedia.org/wiki/Drug_development)