Slide 1	# Drug Development and Clinical Trials Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland New Zealand	
Slide 2	# Objectives • Distinguish drug discovery from drug development • Appreciate the time and cost involved • Learn the ABCS of clinical trial design • Appreciate the pros and cons of the intention to treat analysis perspective 	
Slide 3	# Clinical Drug Development Discovery Development General Use 	

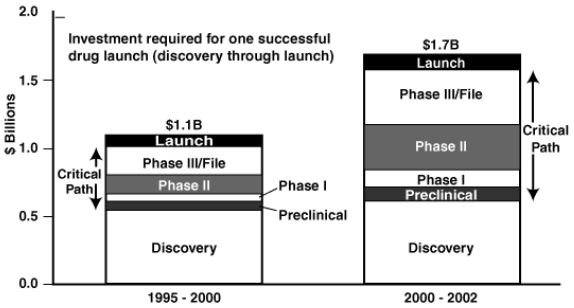
Slide 4

Long and Costly

- 10 years from Discovery to Market
- NZ$3,000,000,000 per drug (at least)
- 9 out of 10 that are tested in humans do not reach market
- Patent Protection Very Important to Drug Developers

Slide 5

Increased Cost in Phases II and III



SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm March 2004

Slide 6

World Wide Sales 2016

Rank	Product	Active Ingredient	Main Indications	Company	**2016 Revenue** (USD millions/year)
1	Humira	Adalimumab	Immunology (Organ Transplant, Arthritis etc.)	AbbVie Inc.	16,078
2	Harvoni	Ledipasvir/sofosbuvir	Infectious Diseases (HIV, Hepatitis etc.)	Gilead Sciences	9,081
3	Enbrel	Etanercept	Immunology (Organ Transplant, Arthritis etc.)	AmgenPfizer	8,875
4	Remicade	Infliximab	Immunology (Organ Transplant, Arthritis etc.)	Johnson & JohnsonMerck & Co.	8,234
5	MabtheraRituxan	Rituximab	Oncology	Roche	7,227
6	Revlimid	Lenalidomide	Oncology	Celgene	6,974
7	Avastin	Bevacizumab	Oncology	Roche	6,715
8	Herceptin	Trastuzumab	Oncology	Roche	6,714
9	Lantus	Insulin glargine	Diabetes	Sanofi	6,057
10	PrevnarPrevenar 13	Pneumococcal 7-Valent Conjugate	Anti-bacterial	Pfizer Inc.	5,718

https://en.wikipedia.org/wiki/List_of_largest_selling_pharmaceutical_products

Slide 7	**Phases of Drug Development** • Phase 0 » Predictions for Humans • Phase 1 » Tolerability • Phase 2 » Effectiveness • Phase 3 » Safety • Phase 4 » Post Marketing 	
Slide 8	**Biomarker/Surrogate/Outcome** • Biomarker » Readily measurable marker of response e.g. EEG response to anaesthetic induction agent • Surrogate » Biomarker used for Regulatory Approval e.g. Reduction in HIV viral load • Outcome » How the patient functions/feels/survives e.g. sex/pain/death 	
Slide 9	**Learn and Confirm** • Learn » Exploration of the unknown » Develop hypothesis/model • Confirm » Develop confidence » Test hypothesis/model 	

Slide 10	**Phase 0 [Non-Clinical] Predictions for Humans** • Data from non-human animals • Probable mechanism of action • Likely effective concentrations • Major routes of elimination • Oral Absorption properties 	
Slide 11	**Phase 1 Tolerability** • Start with very small doses • Slow increase • Stop when adverse effects noted • Learn » Single and multiple dose PK » Adverse effect PD? 	
Slide 12	**Phase 2 Effectiveness** • Phase 2A » “Proof of Concept” » YES/NO decision point • Phase 2B » Learn Dose response curve » Learn effective doses » Learn target concentration 	

Slide 13

Phase III Safety

- "Safety"
  - » Learn Adverse effects in target population
- Confirm effective dose(s)
  - » "Method Effectiveness"?
- Learn PD of Surrogate/Outcome
- Learn PK and PD covariates
  - » Age, Sex, Other Drugs…

Slide 14

Phase 4 Post-Marketing

- Confirm effective dose(s)
- Confirm common adverse events
- Learn uncommon adverse events
- Learn "Use Effectiveness"
- Learn Pharmacoeconomics

Slide 15

Alternative Medicines

- Herbal/Traditional Medicines
  - » Digoxin, morphine, aspirin, quinine
  - » Gossipol, artemesin, taxol
- Patent Protection Unlikely
  - » Uneconomic for full Drug Development
- Health Foods/Nutraceuticals
  - » No Claims No Testing No Good?
  - » St John's Wort -> Cardiac transplant rejection
  - » Black Cohosh -> Liver failure requiring transplant
  - » Bracken fern -> Carcinogenic
  - » 'Natural treatment' contains sildenafil et al.

"If its an alternative medicine then its not a medicine that is known to be safe and effective"

http://thinking-is-dangerous.blogspot.com/2008/01/complimentary-and-alternative-medicine.html (alternative medicine humbug)

Evans IA, Osman MA. Carcinogenicity of bracken and shikimic acid. Nature. 1974;250(464):348-9.

http://www.msnbc.msn.com/id/31088175/ (contaminants in 'natural' products)

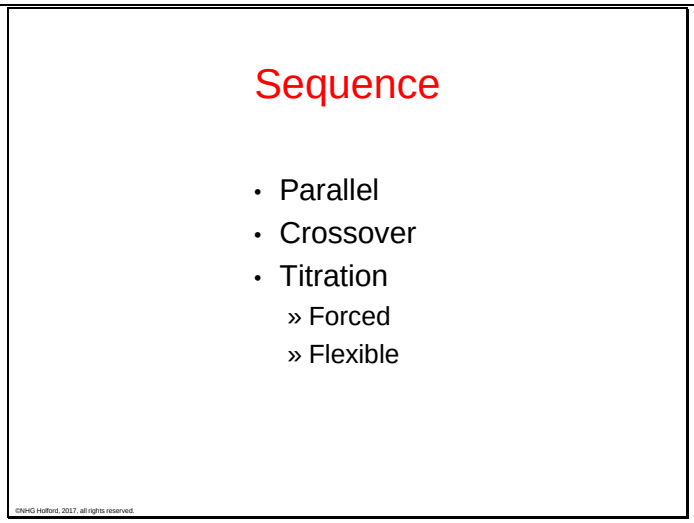
http://www.ncbi.nlm.nih.gov/pubmed/16006928 ('natural viagra')

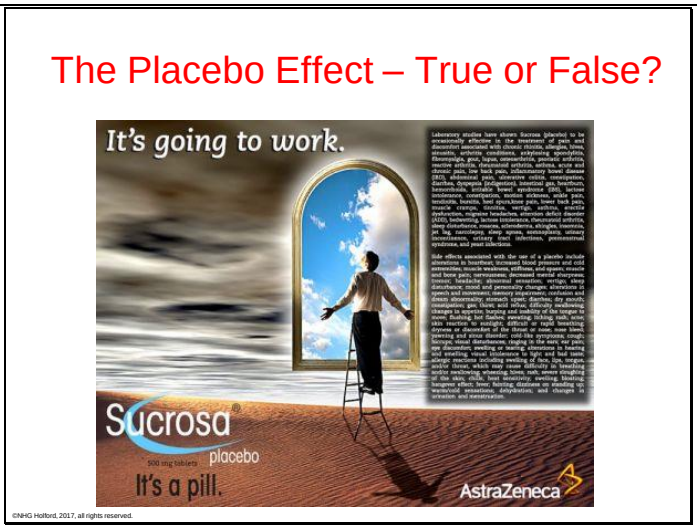
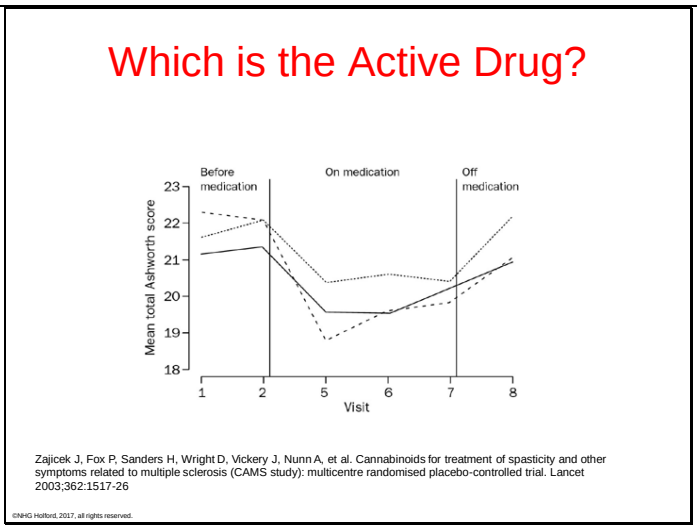
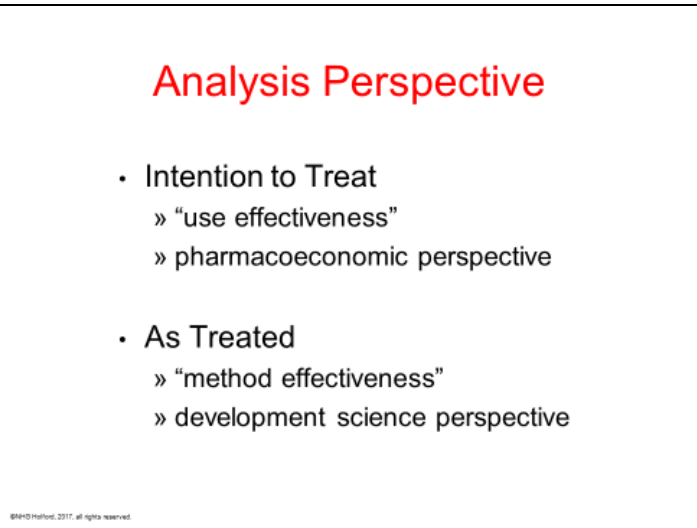
In a recent case report, a healthy 16-year-old girl reported symptoms of nausea, joint pain, and stomach pains. She was initially treated for a urinary tract infection, but after symptoms worsened she was diagnosed with hepatitis. She had been taking 3 cups of a Chinese **green tea** product that she ordered over the internet daily for

		the past 3 months. While the product was not tested for contamination, it is possible that undeclared ingredients could have caused the liver damage. Lugg ST, Braganza Menezes D, Gompertz S. Chinese green tea and acute hepatitis: a rare yet recurring theme. BMJ Case Rep. 2015 Sep 23;201 In a new scientific statement citing *Natural Medicines*, the American Heart Association (AHA) warns against the use of many supplements in people with heart failure. **St. John's wort**, **grapefruit juice**, **ginseng**, **hawthorn**, **danshen**, **black cohosh**, and **green tea** are among those discussed for their potential to cause significant interactions with commonly used heart failure medications. Other natural medicines, including **aconite**, **gossypol**, **licorice**, and **yohimbine** are noted for their potential to cause harmful cardiovascular effects, including high blood pressure and decreased heart rate. **Ephedra**, a banned substance in the US, is also warned against as it raises blood pressure, can stimulate the heart, and make chest pain and irregular heartbeat worse. For more details on specific drug interactions associated with these supplements, please review our scientific monographs on each product, or try our **interaction checker**. **References**: Page RL, O'Bryant CL, Cheng D, et al. Drugs that may cause or exacerbate heart failure. Circulation. 2016;CIR.0000000000000426.
Slide 16	Clinical Trial Design *ABCS* • Assignment • Blinding • Comparison • Sequence ©NHG Holford, 2017, all rights reserved.	There are 4 major elements in the design of a clinical trial. Each has an effect on the way trials are designed and interpreted.

Slide 17	# Assignment • First Come, First Served • Randomized » Balanced » Stratified E.g. Sex, Previous Stroke 	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 decided 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 >=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.
Slide 18	# Blinding • Open • Single Blind • Double Blind » Double Dummy • Triple Blind ? 	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. 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.

Slide 19	# Comparison • Active » Dose Control (RDCT) » Concentration Control (RCCT) » Biomarker Control (RBCT) • Placebo • Standard Treatment » Non-Inferiority » Add-On RxCT = Randomized 'x' Controlled Trial 	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 between subject 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 both pharmacokinetic and pharmacodynamic variability. Subjects are randomize to one or more target biomarker levels and the dose is adjusted to reach the target biomarker effect. From a scientific perspective the best treatment control is to use a placebo i.e. an inactive substance. If there is genuine uncertainty about the effect of the active treatment then it is usually considered ethical to randomize to placebo (the ethical principle of 'equipoise'). 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. If 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. A placebo control group would receive the standard treatment.

Slide 20		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 sujects. 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. 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. 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.

Slide 21		Is this a genuine advertisement? True or False? http://www.theonion.com/article/fda-approves-sale-of-prescription-placebo-1606
Slide 22		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. 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.
Slide 23		There are perspective 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 of 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.