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Drug development and clinical trials

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Learning goals

- Appreciate how drug development and clinical trials generate critical information for prescribers
- Understand the drug development process
- Know the 4 phases of clinical trials
- Define key clinical trial terminology
- Understand the roles of ethical and regulatory review

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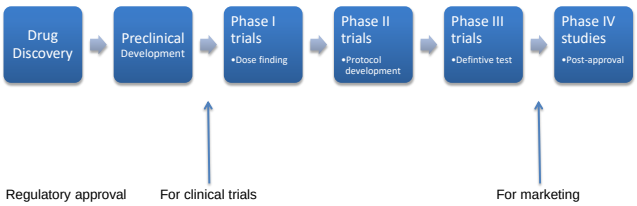
Stages of drug development and clinical trials



Slide 4	**Drug Discovery** **Target Identification** • Molecular target for drug – eg. enzyme **Lead finding** • Find compounds with desired pharmacological activity – eg inhibition of target enzyme **Lead optimisation** • Improve dose potency, selectivity and pharmacokinetic properties	
Slide 5	**Preclinical development** **Establish basic pharmacology, pharmacokinetics, toxicological profile and human starting dose of drug using animal and in vitro systems** • In vitro studies – eg. mutagenicity, metabolism • Animal studies – Toxicology eg. acute, subacute, chronic, carcinogenicity, reproductive – Pharmacokinetics **Establish clinical dose form and manufacturing processes**	
Slide 6	**Phases of clinical trials** • Phase I – find doses for clinical testing • Phase II – establish treatment protocols • Phase III – definitive comparison to standard care • Phase IV – post-marketing confirmation of safety and efficacy	

Slide 7	**Phase I clinical trials** • Objective – Find doses for further clinical evaluation based on safety, tolerability and pharmacology • Participants – Normal healthy volunteers (20 to 50 subjects) • Treatment – Dose ranging • Design – Prospective; sequential cohort; ascending dose	
Slide 8	**Phase II clinical trials** • Objective – Therapeutic exploration to establish treatment protocol • Participants – Patients (homogenous group; 30 to 300 subjects) • Treatment – Standard dose, treatment schedule concomitant medicines • Design – Prospective; single group; open-label	
Slide 9	**Phase III clinical trials** • Objective – Definitive confirmation of efficacy and safety compared to standard care • Participants – Patients (homogenous group; 300 to 3000 subjects) • Treatment – Standard dose, treatment schedule concomitant medicines • Design – Prospective; parallel group; randomised; double-blind; initial-to-treat analysis	

Slide 10	**Phase IV clinical studies** • Objective – Confirmation of safety and effectiveness in the general population • Participants – Patients treated in the setting of routine care • Treatment – Not under the control of the researcher • Design – Retrospective; observational; cohort study	
Slide 11	**Prospective versus retrospective** • Prospective study design – Study groups, participants, interventions, endpoints and procedures are defined before the study is done • Retrospective study design – Endpoints reached before the study questions are defined – Study groups defined after data collection – More prone to bias and confounding than prospective studies	
Slide 12	**Controlled trials** • Where study treatment is compared to something else • Control group does not receive study treatment but usually the standard treatment • Controls – Placebo – Active treatment – Historical	

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Randomisation

- An unbiased method for allocating participants to one or more treatment groups
- Assignment of treatment group by chance
- Avoids selection bias
- Controls confounding variables
- Achieves equal distribution of potential confounding variables between different study groups

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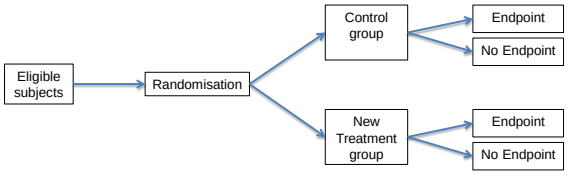
Parallel Group Trial

- Two or more groups compared simultaneously
- Each subject is assigned to one treatment group for duration of study



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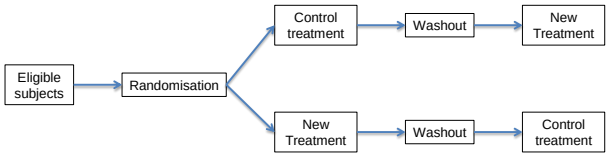
Cross-Over Trial

- Each subject receives all treatments in random sequence, acting as their own control
- Statistical powerful but prone to carry over and time dependent effects



Slide 16	**Blinding** • Refers to awareness or otherwise if the people involved in the trial of the treatment assignment to individual participants • Open label – The researcher and subject knows the assigned treatment • Single blind – The researcher knows the assigned treatment but the subject does not • Double blind – Neither the researcher nor the subject know the assigned treatment • Controls for placebo effects and observer expectations	
Slide 17	**Ethical aspects** • Ethical committees review the trial protocol, patient information sheet and informed consent form, and over see the conduct of the study • Participants are fully informed about the trial and give written consent • Ethical trials only answer important clinical questions and test interventions not known to be inferior to each other	
Slide 18	**Regulatory aspects** • Clinical trials often done to gain regulatory approval for marketing • Regulatory approval also required for clinical trials of unregistered medicines and new indications for registered medicines • Review of trial protocol and all preclinical and clinical data (Investigators Brochure) • Good Clinical Practice (GCP) quality standards	

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Statistical aspects

- Sample size calculation
  - Statistical procedures for estimating the numbers of subjects needed to achieve to trial objective based on the magnitude of effect to be detected, confidence intervals and probabilities of false positive and false negative trial results
- Analysis
  - Statistical procedures for determining study results
  - "Intention-to-treat analysis" – all patients remain in assigned group regardless of their actual treatment

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Drug Development Case Study – Anaplastic Lymphoma Kinase (ALK) inhibitors for treating ALK gene fusion positive lung cancer

Discovery	**2007**	**Identification of ALK fusion genes in lung cancer**	**1**
Preclinical development	2008	Development of potent and selective small MW inhibitors of Anaplastic Lymphoma Kinase	2
Phase I/II trials	2010	Single arm clinical trials showed high tumour response rates in ALK-positive lung cancer patients	3
Phase III trials	2013	Randomised controlled trials confirmed improved efficacy compared to standard chemotherapy	4
Regulatory approval	2015	Medsafe approves first ALK inhibitor drugs (but not PHARMAC funded until Dec 2019)	
Phase IV	2019	First population-based observational study of ALK lung cancer in NZ (2 yr survival 85 vs 6.7% ALKi treated or not)	5

1. Soda M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448(7153):561-U3.
2. Cui JJ., et al. Structure Based Drug Design of Crizotinib (PF-02341066), a Potent and Selective Dual Inhibitor of Mesenchymal-Epithelial Transition Factor (c-MET) Kinase and Anaplastic Lymphoma Kinase (ALK). J Med Chem. 2011;54(18):6342-63.
3. Kwak EL, et al. Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer. N Engl J Med. 2010;363(18):1693-703.
4. Shaw AT, et al. Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer. N Engl J Med. 2013;368(25):2385-94.
5. McKeage MJ, et al. Screening for ALK gene rearrangements in NSCLC in NZ. Internal Medicine Journal.2020; doi:10.1111/imj.14435

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Short answer question example

An engineering student friend is thinking about participating as a paid volunteer in a phase I clinical trial of a new medicine being developed for treating dementia. They ask your advice and give you the Trial Patient Information Sheet to read. They ask you the following questions.

1) What are the main objectives of Phase I clinical trials?
2) The Patient Information Sheet states that it is a sequential cohort, ascending dose, open-label trial. What do those terms mean?
3) How could your friend's participation in this trial contribute to knowledge ultimately required by prescribers of this medicine?