Drug development and clinical trials

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

Stages of drug development and clinical trials

- Drug Discovery
- Preclinical Development
- Phase I trials
- Phase II trials
- Phase III trials
- Phase IV studies
- For clinical trials
- For marketing
- Regulatory approval
- Marketing approval

For clinical trials

For marketing

Regulatory approval
### 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

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

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

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
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

Parallel Group Trial

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

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
**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

**Ethical aspects**

- Ethical committees review the trial protocol, patient information sheet and informed consent form, and oversee 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

**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
Statistical aspects

- Sample size calculation
  - Statistical procedures for estimating the numbers of subjects needed to achieve 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

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

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