Phase I and phase II trials: summary of common designs

Phase I trials

The purpose of phase I trials is to characterise the properties of the drug in humans such that subsequent trials may use a dose and schedule of that drug that is most likely to be safe and efficacious. Phase I trials typically evaluate:

- route of administration
- pharmacokinetics and pharmacodynamics
- side effects
- distribution of the compound throughout the body
- acceptable dose range to use in subsequent studies
- toxicity and tolerance
- optimal determination of the maximum tolerated dose (MTD)

The sample size required typically ranges from 20 to 100 people.

Types of phase I studies: classical studies

These use a dose escalation design in which the dose is escalated to the maximum tolerated dose. The MTD is usually declared at the dose below which a third of patients were observed to have unacceptable toxicity.

Example

Simple dose escalation designs are often used for Phase I trials. Variations of the above design exist, but the above design provides a general broad overview of how a typical dose-escalation design is conducted. With the above trial design the MTD is dosing level one step below the final dose administered.

Types of phase I studies: specialty trials

- vaccines: immunogenicity is a key endpoint of interest
- devices and procedures: feasibility and safety. some historical regulatory differences in development plan.
- genetically modified organisms (GMOs): safety, sometimes issue of product replication (transfection)

Phase II trials

The purpose of phase II trials is to establish sufficient evidence to justify conduct of a phase III trial. Evidence includes:

- feasibility of treatment
- efficacy of treatment
- safety of treatment

They may have a broader population or single arm, or be a pilot study.

Design of phase II trials

A phase II study may be designed as a single-arm study or a randomised (controlled) study, typically with two arms. In a randomised study, some patients are allocated to receive the intervention and others to receive a placebo or the standard intervention. The sample size required is typically 100–300 people. They are designed to estimate an ‘effect size’ albeit with liberal confidence intervals (leading to lower power and precision than a phase III study).

Statistical rules on stopping the trial are required because of potential inactivity or excess toxicity due to the intervention.

Typical 2-arm simple parallel design

Randomised phase II trials may be conducted with multiple arms but without specific standard control. The purpose may be to determine the optimal schedule and dose.

Some study designs may combine phase I and phase II, and test both efficacy and toxicity.

Contact the Outreach team (trials@ctc.usyd.edu.au) or go to the CTC website (www.ctc.usyd.edu.au/our-research/ctc-outreach.aspx) for further advice.