The different phases of clinical trials

What are clinical trial phases?

Clinical trials which test new treatments are split into a number of different stages, each with different aims. At the earliest stages the aim is to determine whether the treatment is safe for people, while at later stages they will be trying to find out how well the treatment works.

The phases of a clinical trial range from phase 0 to phase 4, a summary of each is in the table below.

Trial stage	Size of group involved	Aim	Rough timescale*
Phase 0	A group of up to ~20	To make sure the drug is safe for use in humans.	Can take up to ~14 months.
Phase 1	A group of ~20-50	Identify the optimum treatment dosage, side-effects and what happens to the drug when in the body.	Several months to a year.
Phase 2	A group of about, and sometimes above 100	Testing the optimum dosage of treatment, identify any more side-effects and see how well the drug is working.	Up to ~2 years.
Phase 3	A group of 100's to 1000's of people	Compare the new drug to any current treatments or a placebo.	Between 1 and 4 years.
Phase 4	Variable- can be a group of up to 100's or up to 1000's	Gain more information about the long-term benefits and side effects of the drug.	Several years.

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*Please note these timescales are only indicative. They represent time frames for trials testing drugs for all types of conditions, not only MND. Phases for individual trials may take longer or shorter amounts of time than noted above.

Phase 0

Normally the first stage of a clinical trial is phase 1, however, in some cases a phase 0 may be run. In phase 0 a small number of individuals will be given the drug to make sure it is not harmful and behaves how is expected from lab testing. In this phase only a very small dose of the drug is given to those involved.

In phase 0 the dosage will be too low to treat the disease or, usually, cause any side effect. But it will let the researchers learn about how the drug is behaving in the body and confirm if it is reaching the target site in the body.

Phase 1 (I)

In a phase 1 trial a small number of individuals will be recruited to take part. Often this stage of the trial involves slowly increasing the dosage of the drug. This is to determine what the optimum dosage is in terms of benefits vs side effects. This stage will also help the researchers to identify what side effects the drug has. This is an important stage in the clinical trial process. Determining the dosage to be used and it's potential side effects are crucial before testing to see if the drug works.

Again, at this stage the drug will not normally have any treatment effects on the disease.

Phase 2 (II)

This stage of the trial requires a larger group of participants. The individuals will receive the optimum dosage of the drug which was determined in phase 1. The aim is to determine if the drug works well enough on the disease to warrant being moved to a phase 3 trial for wider testing and analysis of impact. Other important information gathered at this stage includes tracking the known side effects as well as determining any other side effects which may arise from longer term use. This is important as it can help the researchers to gain an understanding of the range of potential side effects longer term, and how they can be managed.

In some cases, the phase 2 stage can be a randomised trial. This means that there would be 2 groups involved. The first would receive the drug being tested while the second will take a placebo or the existing treatment. This comparison can sometimes help the researchers get an initial idea of whether the new drug is

more or less effective than the current drug or no treatment.

Phase 3 (III)

Phase 3 trials are much larger than the previous stages and can involves thousands of participants (particularly in more common conditions). These trials are usually randomised, like some of the phase 2 trials. The main aim of phase 3 is to generate more evidence on whether the new drug is of benefit. It also provides further information on side effects, as well as whether the drug is having any impact on the participant's quality of life.

Some things which may be compared to the new drug in phase 3 are

- A placebo
- The current treatment for the disease
- Different doses of the new drug
- The frequency of administering the treatment
- Different ways of giving the drug (e.g., oral vs injection)

It is usually after the findings from phase 3 have been published that a drug which shows promise can be submitted for licensing by the manufacturer.

In Scotland, any new or repurposed drugs will have to be approved by the MHRA (Medicines and Healthcare Regulatory Authority) and the SMC (Scottish Medicines Consortium) if it is to be made available on the NHS. Often the drug will also have been approved by the EMA (European Medicines Agency) and EC (European Commission) who approve marketing licensing for Europe, and NICE (the National Institute for Health and Care Excellence), who determine patient access of licensed drugs via the NHS in England and Wales.

Phase 4 (IV)

Phase 4 trials are not always carried out. If they are done, then it is often after the drug has been shown to work and has been licensed. In a phase 4 trial the researchers want to understand better any new side effects that may occur from long term use, as well as how previously known side effects progress when the drug is used long term. They also want to monitor how well the drug is working over the long term and that it is use is still beneficial to the individuals. Since the drug is available, phase 4 trials give researchers the opportunity to analyse drugs effects in a much larger population than in the previous trial stages.

Platform Trials (usually phase 2/3)

In recent years, a new design of clinical trial has been developed in the USA, UK and Europe. The trial design was initially developed for rapid testing of cancer treatments and is now being adopted for testing treatments in neurodegenerative conditions, including motor neuron disease. It is designed to have more than one drug tested, often simultaneously (multi-arm platform trial), which means less time is wasted (e.g., starting up and shutting down individual drug trials).

Platform trials are generally considered to be phase 2/3 (II/III). This is because the trial design, rather than having a fixed time-point end, has check-in stages built in. This allows for the drug to be discontinued (and a new drug brought in for testing instead) or continued at each stage., It also has a placebo arm (where participants do not receive the drug being tested), which is required for a phase 3 trial and by the regulators. One advantage of the platform trial is that different drug arms often share a placebo arm, which reduces the number of people assigned to that group.

The Stage 1 check-in analysis on a platform trial generally assesses safety and tolerability of the drug. If it is considered to be safe and tolerated by most participants, then the drug will be continued.

The Stage 2 check-in analysis will assess whether the drug is showing signs of having a statistically significant benefit on disease progression. If it is not, then the drug will be discontinued. If it does appear to bring significant benefit, then the drug will be continued. If a drug arm is continued beyond Stage 2, people will remain on the drug and the trial will monitor survival compared to the placebo arm.

An example of a platform trial for MND is the MND-SMART trial, which now has 22 recruitment centres in all four UK nations.

Experimental Medicine Platform for drug prioritisation

Experimental medicine can cover a number of different types of initiative but is now occurring in the clinical trial space. The list of MND clinical trials that have failed to demonstrate a positive effect is long and has spanned decades. To try and improve the chances that an effective drug will be found, a new approach is being tried in the UK. It will be an experimental medicine 'pre-trial' platform.

EXPERTS-ALS, which should launch in Summer 2024, will test potential new drugs in people with MND and try to assess quickly whether they are likely to bring benefit to people with MND and should be tested in a large phase 3 trial.

What makes this approach different is that it will measure levels of neurofilament light chain (NFL) to see whether this changes as a result of the treatment being tested. NFL is not normally detectable in healthy people but can be picked up in those with MND, even at the point of diagnosis, and seems to be associated with how quickly a person's disease progresses (high levels usually mean more rapid progression). NFL remains elevated throughout the course of the disease, so it is hoped that a treatment which reduces NFL levels will also be slowing disease progression. This 'biomarker' approach has the added benefit that each person will be their own control, eliminating the need for a placebo (no treatment) group.

If a drug is identified that reduces NFL in a number of people with MND, then this can be prioritised for testing in a large phase 3 trial, which would monitor disease progression over a longer timeframe and have a placebo control arm so you can be sure any effect is genuine.