



Drug and Clinical Trials

Medications used to treat a disease are based on the results of laboratory and clinic-based research studies, or trials. Drugs are first developed in the laboratory using technological methods and animal model testing to see if the treatment has an effect on the disease process. Treatments that show promise then need to be studied on actual patients with the disease in a clinical setting to test for **drug delivery efficiency** (i.e., what is the best way to give the medicine?), **safety** (i.e., how well is it tolerated and at what dosage?), and **efficacy** (i.e., is the drug actually changing the expected course of the disease in patients receiving the drug as compared to others who are not and to what degree is there a difference?). While not all clinical trials are successful at turning out a new, acceptable treatment, they nevertheless help to answer research questions and move research in a forward direction.

Treatments that have shown positive results in mice very often do not translate to humans. For example the antibiotic minocycline was effective in prolonging life expectancy in experimental mice but results from human trials indicated that it might in fact be harmful to some of those participating in the trials. Recent clinical and research thinking has turned from seeing everyone with MND as potential participants in drug trials to realising that different people have different pathologies underlying their MND. Some pathologies, such as the flail arm syndrome that afflicts some younger men

affected by ALS, are likely to be due to similar causes in each person with that form of the disease and so, as a group, they should be more likely to respond to a particular positive treatment than a group made up of volunteers representing all the different sub-types of MND. This has been described as “Stratifying” the patients who volunteer to take part in trials and it is hoped that “stratification” resulting from better understanding of the underlying cause of the different MNDs might show that some drugs previously tested and discarded are useful for particular sub-groups of people with MND.

Clinical trials are subject to stringent research protocols for the protection of human subjects. From time to time there may be an opportunity for you to participate in a trial. To learn more about the clinical trial process, ask your neurologist for up-to-date information on what clinical studies are currently being conducted to help us better understand how to treat ALS. A database of worldwide clinical trial information can be found through the World Federation of Neurology at www.wfnals.org.

What is the procedure when new treatments emerge from the laboratory ready for testing on humans?

Clinical trials are designed to answer some fundamental questions:

- Does a treatment work on humans?

MND Scotland is the working name of the Scottish Motor Neurone Disease Association, the only charity funding research and providing care and information for those affected by MND in Scotland.

- How effective is a treatment?
- Is a treatment safe?
- What are the side effects?
- How efficiently does it prevent or improve symptoms?
- What dosage levels should be administered?

The standard model adopted when a new treatment is tested follows three consecutive stages known as Phases I, II and III.

Any therapy, which is on the brink of the first small-scale human trials, will have already undergone a long period of development and testing in the laboratory. When scientists believe their work is ready and the potential treatment has been successful in alleviating the symptoms of animal models, they publish their results.

Phase I Trials

Phase I trials are pilot studies. They are the first time a new treatment is administered to humans. Their purpose is to determine how safe the treatment is, and whether it is tolerated and behaves in the way predicted by all the previous experimental investigations. Initial doses are the lowest possible consistent with obtaining the required information but may gradually be raised to the required dosage level. The number of participants at this stage is very small. All those who are asked to join a trial are protected by regulations governing their participation. They must be fully informed and have had ample opportunity to ask questions and to think about their decision. All participants are free to leave a trial at any time without giving a reason, or can refuse to join it in the first place without jeopardising any other treatment they should be receiving.

They have to sign a lengthy consent form confirming that all this has been made clear to them. Clinical trials have to be exceptionally carefully set up and controlled and run. Only then will there be broad agreement amongst clinicians and scientists based on reliable information.

Phase II Trials

These can start if Phase I results are satisfactory. They are the first in which the disorder is actually properly treated. Different dosages may be given to different patient groups to establish whether the treatment is suitable for further study or should be abandoned. Patient numbers in these trials are usually small.

Phase III Trials

In the final clinical trials, the treatment is likely to be compared with an inactive medication called a placebo and possibly with another standard treatment already used for the disorder under investigation.

Patients are allocated randomly to one of the groups and during the trials neither the doctor nor the patient knows which preparation is being given. This is known as a double blind trial. Phase III usually involves much larger numbers of patients so that the results can be analysed statistically. Sometimes we hear of amazing breakthroughs in other countries whose standards may be different to the UK.

Usually trials are conducted to internationally approved standards, which mean these are transferable between countries, though there may still be differences of opinion between the

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regulatory boards of different countries. If a condition is severe enough and the treatment looks very promising, Phase III trials might be accelerated to make the treatment available to doctors quickly.

It is pointless to administer any therapy unless it works. Prescribing treatments, which turn out not to have any effect raises false hopes and causes patients to lose faith in future therapies. Even if the substance is useless and harmless, it may interact badly with other drugs. If the substance can relieve symptoms, it is important to establish correct dosages and regimens scientifically rather than through guesswork. And if a treatment (albeit useless) is already being prescribed alternative trials for other useful potential treatments may not go forward.

Understandably, many people with life-threatening or severe disorders have concerns about how soon a treatment would become widely available. The timescales for trials are very variable. For example, if the new treatment were an antibiotic for a urinary tract infection, a positive result would be apparent in each patient within a few days as the infection was eradicated, so each phase of the trials would be relatively short-term.

However, for progressive disorders such as MND the trial may last for more than a year with each patient and involve long-term follow up to ensure that any effects are of lasting value. The authorities do take into account the severity of the condition when sanctioning trials and treatment licences. They recognise that the more severe a condition is, the more urgently awaited the treatment, and the more acceptable any side effects.

Chemotherapy for cancer has considerable side effects and risks but chemotherapy is common practice in view of the alternatives if the condition goes untreated. Similar considerations may apply to treatments for MND.

Having been successful in clinical trials a drug is not automatically cleared for use. Different countries have different procedures by which a drug is licensed for use and the availability of a drug in one country does not mean it is universally accepted or available. In the UK, where the NHS absorbs the vast majority of prescription costs, any new drugs have also to be approved for use by the NHS even after the drug has been licensed and is available on private prescription.

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