mnda
motor neurone disease association

Research

Clinical trials

Information Sheet D

This information sheet explains what clinical trials are, how they are organised, and discusses some of the issues involved in taking part in a trial. It also contains basic information on how drugs are approved after clinical trials.

For more detailed information on drug licensing and early access to medicines, please see **Information Sheet H: Accessing unapproved drugs**.

The content is split into the following sections:

Disclaimer: *Please note that information provided in this information sheet is based on a review of the currently available literature. This information sheet was written by MND Association staff who are not clinicians, so any information provided in this sheet should not be considered clinical advice. You should always discuss potential treatments with your clinician.*

This symbol is used to highlight **our other publications**. To find out how to access these, see *Further information* at the end of this sheet.

What do the words and abbreviations mean?

ALS Functional Rating Scale (ALSFRS or ALSFRS-R):	A rating scale used by doctors to assess progression and severity of MND.
Double blinded study:	A study in which neither the participant nor the researcher know whether a person is receiving the treatment drug or placebo.
Early Access to Medicines Scheme (EAMS):	The UK scheme for accessing medicines that have not yet been licensed.
Medicines and Healthcare products Regulatory Agency (MHRA):	The UK agency that evaluates medicinal products and grants marketing approval.
National Institute for Health and Care Excellence (NICE):	The UK public body that publishes evidence-based guidance on effective ways to prevent, diagnose and treat ill health.
Off-label:	The use of a licensed drug in a different way than stated in its licence (e.g., for a different condition).
Open label:	A phase at the end of a clinical trial when all participants are offered the trial drug.
Orphan disease:	A chronic or life-threatening disease that is considered a 'rare' disease.
Orphan drug status:	A status given to a drug to provide guidance and support throughout its development process.
Placebo:	An inactive compound ('dummy drug') given to half of participants in most clinical trials.
Phase I, II, III, IV:	Stages of clinical trials to test a drug's safety, route of delivery, dosage, and effectiveness.
Randomisation:	Random assignment to a treatment or placebo group in a clinical trial.

1: An overview of drug development

A drug's journey from initial development in the lab to routine use in treating patients is a very long one - involving many stages and taking many years. Patients only get involved in the last stage of testing, before a drug is licensed for general use in treating a disease. These final stages of testing are known as a clinical trial.

The earlier stages involve laboratory studies and testing in cell and animal models. These are needed to provide the best possible assurance that the drug will be safe for people to take and to see whether it might be effective. This is the pre-clinical stage.

2: What is a clinical trial and why is it necessary?

Clinical trials are research studies in human volunteers that determine whether potential treatments are safe and effective. It is extremely important to establish whether any side effects of a new drug are more threatening than the disease it is designed to treat. It is also necessary to prove, beyond reasonable doubt, that the drug is beneficial. The only fool proof way of doing this is by monitoring the effects of the drug in a group of patients and comparing the progress of these patients with the progress of a similar group not taking the drug.

How do clinical trials proceed?

Traditionally, clinical trials are divided into four phases. However, with increasingly complex trial designs the distinction between Phase II and Phase III trials often becomes blurred.

Phase I examines the **safety of the potential new treatment**, often in just a few (5 – 20) people. In many cases, this phase involves healthy volunteers rather than patients. Participants are monitored for adverse reactions or side effects; if any appear that are judged too dangerous, the drug will not advance to further clinical trial phases.

Phase II determines the **optimal dose size, timing of doses and drug delivery route** (e.g., by mouth, or injection) for the next phase of testing. Although Phase II may provide some indication of the drug's ability to treat the disease, the numbers of patients involved in this phase is too small for such findings to be relied upon.

Phase III aims to show whether the **drug has a beneficial effect on patients**. This stage of testing will usually involve hundreds of patients, which is enough to allow a reliable assessment of the drug's effectiveness. Phase III results will determine whether a drug is approved for use to treat a disease.

Phase IV occurs after the drug has been approved for sale. With the drug in general use, further data can be gathered on its **effects in an extremely large number of people** over an extended period of time.

Clinical trial design

Trials must be conducted in such a way that the experimental drug undergoes the most rigorous testing possible. Well conducted Phase II and Phase III trials are usually placebo controlled, randomised, and double blind.

Placebo-controlled
Some of the trial participants are given an inactive 'dummy drug' instead of the trial drug - this is called 'placebo'. A trial of a new treatment must ensure that any beneficial effects seen are entirely down to the trial drug and not due to the power of positive thinking, the extra attention from medical staff that comes with participating in a trial, or any other factor. The group of patients taking the placebo are known as the control group and are used for comparison to give a true picture of the effects of the trial treatment.

Randomisation
Participants in trials are often assigned to a treatment group (either trial drug or placebo) at random. This is usually done by computer and it is similar to drawing numbers from a hat. It prevents bias occurring in choosing which patients get which treatment.

Double blinding
In a double blind trial, neither the researchers nor the patients know who is taking the trial drug and who is taking the placebo. This prevents unintentional bias creeping in when participants are reporting how they feel or when researchers are looking at data from the trial. However, a central trial co-ordinating centre does know who is taking the trial drug and can make this information available very quickly if a patient suffers a possible side effect.

As we know more about the need to design individualised treatments, DNA testing and biomarkers are increasingly incorporated into the design of clinical trials.

At the beginning of the trial, the researchers will define outcome measures. These are the measurements or assessments that are used in the trial to determine whether the trial drug is safe and / or effective. For example, muscle strength may be an outcome measure used to show whether a trial treatment is of benefit in MND. Rating scales are also often used to measure trial outcome. These scales assess various aspects of life with MND, such as ability to move, ability to carry out day-to-day activities and problems with eating or breathing. The ALS Functional Rating Scale (ALSFRS-R) is an example of a scale often used in MND clinical trials.

Occasionally, at the end of the study period, participants on both the active drug and the placebo have the opportunity to take the active drug. This is usually while other participants are still within their original study period or while the results of the study are being analysed (not everyone taking the drug will start on the study on the same day – the recruitment period can be over a few months). This is usually known as an 'open label' phase of the study.

3: Who can participate in a clinical trial?

All clinical trials have strict guidelines about who can take part. Factors that allow someone to participate in a clinical trial are called 'inclusion criteria' while factors preventing someone from participating are called 'exclusion criteria'. These criteria usually include factors such as age, type and stage of disease, previous or current treatments and other medical conditions. Inclusion / exclusion criteria are essential to ensure that the trial produces reliable results and to help maintain participant safety.

Many willing trial participants may find that they do not meet the criteria for taking part. Others may find that there is no trial centre near to where they live or that the researchers already have all the participants they need. Although this is disappointing, it is important to remember that trials are experiments, not treatments. The fact that they are happening at all is still very positive.

If I am eligible to take part in a trial, how do I decide if I want to?

If you are thinking of taking part in a clinical trial, it is extremely important that you are given all the information you need to make your decision. The research team running the trial will explain the trial to you and will provide information sheets giving details of the trial's purpose, duration and procedures as well as any risks or potential benefits of taking part. Being given all the necessary information and agreeing to take part in the study is known as giving 'informed consent'.

Any questions you have should be answered. Even after you have given informed consent and have agreed to participate, you are free to withdraw from the trial at any time.

Some of the potential **benefits** of taking part in clinical trials include:

- Being able to do something positive and help others by contributing to research.
- The additional expert medical attention received during the trial.
- The possibility that the trial treatment is more successful at treating the disease than existing treatment(s).

Some of the **risks or drawbacks** include:

- Unpleasant and possibly serious side effects of the trial treatment.
- Having to commit time to following trial procedures, travel etc.
- The possibility that the trial treatment will be ineffective or even detrimental.
- The possibility that you may not be given the trial treatment because you are in the placebo group (see section on clinical trial design page 3).

Before you decide to participate, consider asking yourself the following questions:

- Who will I be doing this for?
- How might this trial affect my daily life?
- Do I want to risk being on the placebo?
- Do I understand why there needs to be a placebo group?
- Will my carer and I be able to travel to the centre for each visit demanded by the study protocol?
- Can I make the commitment to the trial in terms of time, energy and finances?
- Could I cope with the disappointment of having to drop out because the trial treatment produced dangerous or unpleasant side effects?

Should you decide that you do not want to take part in a clinical trial or if you do not fit the inclusion criteria, there are other ways in which you could participate in research.

Research studies looking at symptom management or monitoring disease progression are listed at **www.ukctg.nihr.ac.uk**.

More information is available at **www.mndassociation.org/takepartinresearch**.

4: Design of clinical trials in the future

Platform trials

The use of 'platform trials' is becoming widely accepted as a more efficient way of testing new therapies. Unlike traditional clinical trials, platform trials evaluate several treatments against a common control group. The design has pre-specified rules, such as regular testing of participants to assess disease progression that allows ineffective treatments to be dropped, and flexibility so that new treatments or interventions can be added during the trial. This means that more people will be treated with a trial drug and results may be available more quickly.

Platform trials can find beneficial treatments with fewer patients, fewer patient failures, less time and with greater probability of success than the traditional two-arm method of clinical trials.

Biomarkers

Another important feature of modern clinical trials is the incorporation of a biomarker element. A biomarker is a measurable indicator of a condition found in blood, urine and cerebrospinal fluid, that can be evaluated to examine normal biological processes, progression of disease and pharmacologic responses to a therapeutic intervention. Identifying reliable biomarkers of MND will lead to a speedier diagnosis and a dependable method of prognosis.

Drug repurposing
More and more often, drugs that are already licensed to treat a specific condition are being tested for their effectiveness to treat other diseases. This is called drug repurposing and, because safety in humans has already been established, Phase 1 of a trial may be bypassed completely making the overall duration of clinical testing shorter.

5: Treatment trials in MND research

A number of clinical trials of potential new treatments for MND have been completed and some are still in progress. So far only one drug, riluzole, has been proven to have enough of an impact on the disease to warrant its licensing for general use. The National Institute for Health and Clinical Excellence (NICE) approved the use of riluzole, through the NHS, in the UK to treat most cases of MND.

For further information about riluzole, see Information sheet 5A – Riluzole.

People with MND and their carers play the most important role in the successful completion of a clinical trial; without their support and commitment these trials could not be carried out. The MND Association can provide information on specific trials as well as fund UK-based trials that require additional funding. When trials include patients in the UK, we will liaise with drug companies to ensure that the needs of people with MND are considered when designing and carrying out trials.

6: Current clinical trials in MND

For an up-to-date list of MND clinical trials taking place in the UK please visit our website **www.mndassociation.org/treatment-trials**. Updates on recently completed clinical trials will also be listed on this page.

There are many trials currently underway around the world. For a complete list, see **www.clinicaltrials.gov**, which gives updated information on clinical trials. Once on the site's home page, enter the search term 'amyotrophic lateral sclerosis' to see a list of trials currently recruiting or underway. Most of the trials are however located in the USA and will not necessarily be recruiting participants from abroad. For an overview of UK trials, visit the **NIHR Trials Gateway** (**www.ukctg.nihr.ac.uk**).

7: How do drugs get approved for use in the UK?

Licensing

If a drug has been shown to be effective in Phase III trial(s), the company behind the drug can apply for a licence for the treatment. In the UK, this is administered through the Medicines and Healthcare products Regulatory Agency (MHRA) and in Europe, via

the European Medicines Agency (EMA).

A licence is granted based on the evidence gained from well-designed clinical trials showing the drug's safety and effectiveness. Before the newly licensed drugs can be prescribed within the NHS, the drug needs to be approved by the National Institute for Health and Care Excellence (NICE) in England and Wales, the Scottish Medicines Consortium (SMC) in Scotland and the Department of Health (DoH) in Northern Ireland. The NHS is legally obliged to fund medicines recommended by these bodies, usually within 90 days of receipt of recommendation.

Orphan drug status

Drugs that are intended to treat rare diseases sometimes receive orphan drug status. This status aims to encourage the development of treatments for rare diseases by introducing incentives for companies wishing to undertake their development.

Orphan drug status is an administrative procedure. It considers the nature and rarity of a particular disease. It does not review the effectiveness of a potential drug.

For further information about orphan drug status, see Information sheet H – *Accessing unapproved drugs.*

8: Other routes for accessing trial drugs or those not yet licensed

In some instances, it might be possible to access drugs that are undergoing, or have completed, the clinical trials process but that have not received a full licence from the relevant authority. This is usually completion of Phase III, but potentially Phase II if the results were exceptionally positive.

Strict criteria need to be met to access unlicensed drugs; the drug needs be safe and to have rigorously shown a significant effect in slowing MND progression or treating specific symptoms. No other satisfactory treatments should be available for the disease.

Early Access to Medicines Scheme (EAMS)

This UK scheme, launched in 2015, was introduced to make it possible for promising unlicensed drugs or treatments to be made available to patients sooner.

These medicines may be part of ongoing research, so there is a chance the medication could have some unknown side effects. The full results from the Phase II or III trials of the medicine may not yet be known at this stage.

The scheme requires drug companies with promising compounds to undergo a two-

stage evaluation process: (1) application for designation as a 'Promising Innovative Medicine', and (2) the EAMS 'Scientific Opinion' of available data.

Since its launch in 2014, the EAMS system has awarded 20 licences, the majority of which have been for cancer treatments, and currently **none for MND**.

Off label use

Sometimes a medicine may be licensed for one condition, but could have the potential to be used to treat other conditions or illnesses. This is referred to as off-label use. An unlicensed medication may be prescribed by doctors if they think it is likely to be effective for their patient and if any benefits outweigh potential side-effects or risks.

Doctors will still need to gather evidence about the treatment and consult with other doctors to get their opinions on it before it could be recommended to a patient. If the patient consents to the treatment, positive and negative effects of the medication are recorded on the medical innovation register to inform other doctors about it. In the future, this could benefit other patients and inform future clinical trials.

For further information about routes to access unlicensed drugs, see Information sheet H – *Accessing unapproved drugs*.

9: How do I find out more?

Useful organisations

We do not necessarily endorse any of the following organisations but have included them to help you begin your search for further information.

The contact details are correct at the time of publishing but may change between revisions. If you need help to find an organisation, contact the Research Development Team (see *Further information* at the end of this sheet for details).

Clinical trials database
Web-based resource to provide easy access to information on clinical trials worldwide.

Website: **www.clinicaltrials.gov**

European Medicines Agency (EMA)
The European Union (EU) agency that evaluates medicinal products and grants marketing approval.

Email: via their website contact page
Website: **www.ema.europa.eu**

Food and Drug Administration (FDA)

The US agency that evaluates medicinal products and grants marketing approval.

Email: via their website contact page
Website : **www.fda.gov**

Medicines and Healthcare products Regulatory Agency (MHRA)

The UK agency that evaluates medicinal products and grants marketing approval.

Address: 10 South Collonade, Canary Wharf, London, E14 4PU
Email: info@mhra.gov.uk
Website: **www.gov.uk/mhra**

National Institute for Health and Care Excellence (NICE)

The UK public body that publishes evidence-based guidance on effective ways to prevent, diagnose and treat ill health.

Address: London office: 2nd Floor, 2 Redman Place, London, E20 1JQ
Manchester office: Level 1A, City Tower, Piccadilly Plaza, M1 4BT
Email: nice@nice.org.uk
Website: **www.nice.org.uk**

NIHR Be Part of Research

The UK's National institute for Health Research (NIHR) website aims to help people make informed choices about taking part in clinical trials.

Website: **www.bepartofresearch.nihr.ac.uk**

Further information

You may find these information sheets from the MND Association helpful:

H – *Accessing unapproved drugs*
5A – *Riluzole*

We also provide the following guides:

Living with motor neurone disease – our main guide to help you manage the impact of the disease

Caring and MND: support for you – comprehensive information for unpaid or family carers, who support someone living with MND

Caring and MND: quick guide – the summary version of our information for carers

You can download most of our publications from our website at **www.mndassociation.org/publications** or order in print from the MND Connect helpline, who can provide further information and support.

MND Connect can also help locate external services and providers, and introduce you to our services as available, including your local branch, group, Association visitor or service development manager.

MND Connect
Telephone: 0808 802 6262
Email: mndconnect@mndassociation.org

Research Development Team
Telephone: 01604 611 880
Email: research@mndassociation.org

MND Association website and online forum
Website: **www.mndassociation.org**
Online forum: **http://forum.mndassociation.org** or through the website

We welcome your views

Your feedback is really important to us, as it helps improve our information for the benefit of people living with MND and those who care for them. If you would like to provide feedback on any of our information sheets, you can access an online form at: **www.surveymonkey.co.uk/r/infosheets_research**

You can request a paper version of the form or provide direct feedback by email: research@mndassociation.org.

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