



### **An EXPERIMENTAL medicine Route To Success in ALS (EXPERTS-ALS)**

EXPERTS-ALS is a ground-breaking project that will provide a platform to test drugs rapidly for their potential to slow the progression of Amyotrophic Lateral Sclerosis (ALS, the commonest form of Motor Neuron Disease) in people living with ALS. This will be done at a pace and scale not previously possible. Although EXPERTS-ALS cannot prove that a drug does or does not have long-term benefit in MND, it will quickly identify the most promising candidate drugs to go forward into the larger clinical trials needed to test this.

#### What is 'experimental medicine'?

Experimental medicine refers to investigations undertaken in humans (rather than laboratory cells or animal models), to look for early evidence of benefits in terms of slowing disease and to identify the biochemical mechanisms underlying MND.

#### Who is funding it?

This is an £8m investment in MND research by the National Institute for Health & Care Research (NIHR) through the Department of Health and Social Care (DHSC). Patient charities MND Association, My Name's Doddie Foundation, MND Scotland, and medical research charity LifeArc intend to provide additional support to extend the study to five years and support additional lab research.

#### Who is running it?

Professor Martin Turner (University of Oxford) and Professor Chris McDermott (University of Sheffield) are jointly leading this. They are consultant neurologists who have been working in MND care and research for 20 years. There is a large team of other people, which will extend the involvement to 11 MND centres spread across the UK. EXPERTS-ALS is a flagship project of the UK MND Research Institute (UK

MNDRI) and brings together the scientific expertise from within the NIHR Biomedical Research Centres (BRCs) and the Dementia Research Institute (DRI) around the UK.

#### What are the problems that EXPERTS-ALS is aiming to solve?

1. There is currently no highly effective disease slowing therapy for MND.
2. Using measures of disability, it is very difficult to tell if people with MND in a drug trial are getting worse more slowly i.e. whether there is a benefit of taking the drug. It needs so-called Phase 3 studies, using at least 200 patients and run over a total of 2-3 years to be certain. The success rate of those studies has been very low, and part of the reason may be that the drug candidates have often been chosen based mainly on effects seen in laboratory models of MND.
3. There are many candidate drugs emerging from laboratories, but it has not been previously possible to test them quickly using a simple human readout to prioritise the most likely to benefit people with MND.
4. At present, many people diagnosed with MND will not have the opportunity to take part in any drug study, or only one of the longer Phase 3 trials at most, during their remaining lifetime.
5. There was a need to harness the collective expertise of the BRCs across the UK in MND research, with a programme of training to maintain the UK's leadership in this field.

#### Is this a short-cut around standard drug trials?

No. There is no substitute for randomised-controlled trials (RCTs), which also need to have a placebo ('dummy pill') arm to prove the benefit of any drug beyond doubt. Such Phase 3 studies are expensive and time-consuming. The EXPERTS-ALS platform can be used to prioritise the choice of drug according to signals of likely human benefit, which can be detected in small groups of patients in less than 6 months. EXPERTS-ALS will help to ensure the drugs with the highest chance of success go into the Phase 3 studies.

#### How does the study work in broad terms?

1. At the point of diagnosis, people with MND will be offered the opportunity to take one of three drugs being tested at any one time. Initially these will be so-called 'repurposed' drugs i.e. medicines already licensed for use in other diseases, but with some laboratory data suggesting possible benefit in MND.
2. The individual's blood level of a marker called neurofilament light chain (NFL) will be measured at regular intervals over the next 3-6 months with continuous monitoring of the overall group level. Blood NFL level represents the most promising biomarker in MND to date. In healthy brain states this marker should be essentially undetectable. The NFL level at the time of diagnosis of MND is strongly associated with the rate of disability progression (higher is faster, lower is slower) and tends to stay the same for an individual throughout their disease course. It therefore seems intuitive to want to try to reduce the NFL level as much as possible in those with MND.
3. If the overall group NFL level for each drug is not changing significantly, or if it is rising, then the drug will be assumed as not slowing disease activity to any

large degree and so of lower priority. However, if the group NFL level is found to be significantly falling (i.e. potentially slowing disease activity), then that drug will be prioritised for one of the larger Phase 3 trial platforms such as MND-SMART, so that its potential as a treatment for MND can be tested properly.

Will EXPERTS-ALS be open to everyone living with MND?

No. Some people's MND progresses at a significantly slower pace than average. Although good for those individuals, their blood NFL marker may not be high enough to be able to detect a significant change in response to the drug being tested. Some people may also be intolerant of some of the drugs being tested.

When will it get started for patients?

EXPERTS-ALS is the largest logistical undertaking of its kind in MND in the UK. Everyone involved is committed to getting it set up as soon as possible, with first dosing of patients hoped to be from Summer 2024. Because we will not start until next summer, we are not registering interest at this point but will begin this process next year.

Are there other trials I can get involved with now?

There are a number of clinical trials recruiting throughout the UK. Information is available at the following place:

<https://www.mndcsg.org.uk/clinical-research/what-and-where>

<https://www.mndassociation.org/research/clinical-trials/treatment-trials>