# Project title: Virtual clinical trial populations in motor neuron disease

**Project reference: DT4H_04_2023**

**1st supervisor: Prof. Ammar Al-Chalabi – Department of Basic and Clinical Neuroscience**

**2nd supervisor: Dr Alfredo Iacoangeli - Department of Biostatistics and Health Informatics**

## Aim of the project

Motor neuron disease kills 1 in 300 people by progressive paralysis and is one of the most feared diagnoses. There is considerable debate around the ethics of using placebo arms in clinical trials in a fatal disease like this, and modelling the rate of symptom progression is crucial for trial design. The aims of this project are therefore:

1. To generate virtual placebo populations modelled on known clinical trial populations using multiple methods
2. To test the behaviour of the virtual populations in real data from completed clinical trials – would they have yielded the same results?
3. To explore the use of placebo populations in trial design, both at the modelling stage for power calculation, which is heavily dependent on "events" such as death, and as an adjunct to actual placebo trial arms
4. To model these virtual placebo populations targeting survival, clinical function, clinical stage and other end points.

## Project description

Motor neuron disease (MND, ALS) is a neurodegenerative disease in which the nerve cells controlling voluntary movement are progressively lost. The result is a spreading and worsening weakness that leads to complete paralysis, with 50% of people dead within two years because the breathing muscles have been affected. MND kills 1 in every 300 people, making it as common as multiple sclerosis in the UK, but the high rate of death means it appears rare. There is no cure, and the only treatment currently available in the UK is Riluzole, which slows the disease almost imperceptibly. Our understanding of what causes MND is rapidly improving, and as a result there are many new potential treatments that need to be tested in clinical trials. To be accepted as valid evidence for licensing a new therapy, a clinical trial needs to give some people a placebo, rather than the active drug.

In a disease that is inevitably fatal, like MND, the use of placebo leads to ethical concerns, and the field has responded by shortening trials and randomizing more people to treatment arms than placebo arms. These changes make it more difficult to detect a treatment effect however, and other approaches are needed. One option is to model MND to generate virtual populations that have the same characteristics as real trial participants. This modelling would allow more accurate prediction of the effects of different clinical trial

designs, could be used to predict the potential results of a trial even if everyone were on active therapy (no placebo), and might be used to supplement real trial populations to reduce the need for large numbers of people on placebo.

This project aims to generate virtual MND patients using various methods, comparing their properties with real MND populations. The methods will include simulation, database manipulation, artificial intelligence and other approaches. Real clinical trial data will be used to test the behaviour of the virtual populations, assessing the strengths and drawbacks of each approach. The final method will use a combination of all successful techniques to produce a robust, high performing virtual MND population, suitable for trial design and analysis.

The project would suit a candidate with knowledge of simulation, artificial intelligence or machine learning. An understanding of biology or clinical trials would be helpful but is not essential. Similarly, familiarity with basic statistics would be a benefit, but any statistical methods needed can be taught during the PhD programme. The project is a collaboration between the Department of Basic and Clinical Neuroscience and the Department of Bioinformatics.

A graphic of a brain made of machine parts representing a virtual patient with a brain disease.