TRICALS PROJECTS TO IMPROVE CLINICAL TRIALS

TRICALS will have 3 different types of projects.

These include

- Infrastructural projects,
- targeted research projects
- clinical trials.

Infrastructural project

DEVELOPMENT OF A European Electronic Patient Registry and electronic CRF for Future Trials (In design phase)

The current models of clinical trial design are not suited to ALS, or other forms of rare disease.

We will develop a stand-alone, pan-European, patient-oriented, non-profit, clinical trial platform closely linked with European centres of Excellence.

This platform will combine work that has been undertaken by members of TRICALS, and will provide the engineering and infrastructure to support training modules for ALS Centres of Excellence in clinical trial enrolment, existing metrics, and new outcomes as they become available.

The platform will be underpinned by a real-time Electronic Patient Record (EPR) The EPR will be the central repository of all digital data.

The EPR will be enabled to capture data remotely (using patient reported outcome measures and home-based monitoring, while also taking into account all ethical, legal and privacy issues including compliance with European data protection regulation. The Platform will incorporate engineering to provide a Unique Patient Identifier for all patients consenting enrollment on the EPR. This Identifier will be used throughout the entire combined EPR and TRICALs platform, enabling transfer of patient data from the EPR directly to the trial platform for inclusion in clinical trials where appropriate

Objectives:

1. To design and develop a custom built, patient-oriented, Clinical Trials Platform for ALS as a foundation for other rare (neurological) diseases
2. To design and support training modules in clinical trial design and outcome measures for Centres of Excellence
3. To generate a flexible Clinical Report Form, suited to current and newly established outcome measures
4. To provide de-identified unique patient identifiers for all enrolled patients
5. To provide patient and caregiver portals (already developed by Sheffield)
6. To enable patients to self-enroll, and in do so provide permission to access their records and upload them to the EPR

Targeted Research Projects

1. LONGITUDINALS (In design phase)

Longitudinals will be designed as a clinical trial with a longitudinal follow-up of patients for 12 months after recruitment. In the 18-month recruitment period, we expect to enrol 400 ALS incident patients. The following measures of disease outcome will be considered: ALSFRS-R, MITOS and King's staging scales, respiratory function, BMI, cognitive status, and XX blood biomarkers (serum folate, uric acid, L-ferritin, PCR, Chitotriosidase, NOX2 enzyme activity, LDL/HDL ratio, creatine kinase, creatinine, albumin, vitamin D, neurofilament light and heavy chain). These measures will be covariated with patients' genetic status and lifetime exposures/food habits.

The standardized mean change of each measure over 6/12 months will be estimated using the change in the measure between each subject's Day 1 (Baseline visit) and Month 6/ Month 12 visits. In addition, we will re-estimate the standardized mean change by controlling for covariates including subject age, gender, onset site, symptom duration, body mass index (BMI), and riluzolo/edaravone use.

ANTICIPATED OUTPUT: The results of LONGITUDINALS will provide important evidence of the usefulness of a wide-ranging panel of biomarkers as potential in order to facilitate widespread clinical application of drug discovery efforts through efficient clinical trial design.

2. REVEALS (Currently underway)

To compare real world experience of current measurements of ventilatory function by evaluating (1) the impact of declining respiratory function on secretion management and (2) the frequency and impact of respiratory tract infection. These evaluations will be performed in collaboration with patients managed in ALS Centers in Europe (a) Each participating Centre will have an established population based disease Register, (b) Participating patients will have already committed to data collection on the European PROGENY site (managed by the University Medical Centre Utrecht (UMCU) group and (c) Centres will have committed to harmonization of approaches towards clinical measurement for clinical trial purposes as part of the Treatment Research Institute for Cure of ALS (TRICALS) initiative.

Study Objectives

1. Identify the rates of decline across a range of respiratory function constructs.
2. Examine the relationships between rates of decline in respiratory function measures and prognosis / life expectancy
3. Correlate rates of decline in respiratory function measures and the ALSFRS-R
4. Examine the respiratory tract infection morbidity rates
5. Examine the relationship between respiratory tract infection morbidity and respiratory function
6. Explore the potential relationships between other demographic characteristics, baseline variables, and outcome measures as defined above.

Design: Prospective Multi-Centre Longitudinal Study examining respiratory decline, mortality and morbidity for 18 months within a real-world population based setting.

Sample Size: 300 (60 per site, 5 sites) over 18 months

Recruitment: Patients will be approached by a gatekeeper at clinic. A patient information leaflet will be provided. Patients will have an opportunity to discuss the

study with the researcher and any questions will be answered. Patients will provide written informed consent and will be free to withdraw from the study at any time.

Outcome Measures: A range of valid and reliable outcome measures appropriate for use in ALS/MND will be used. ENCALS assessment protocols (ALSFRS-R, FVC, SVC, Peak Flow Assessment) will be followed where available and longitudinal data will be collected on PROGENY (an online database) as part of the TRICALS platform.

3. NEUROELECTRIC (Currently underway)

In ALS, Quantitative MRI and PET provide compelling evidence of widespread motor and extra-motor network change. MRI based studies can reliably distinguish *C9orf72* related ALS, and can characterized changes in **basal ganglia** and **cerebellum**, structures that until recently were not commonly considered as part of the ALS phenotype.
However, major limitations of MRI (both structural and functional) and PET include high cost and selection bias in favour of patients who are in the early stage of disease. Longitudinal studies are associated with high rates of attrition, particularly as the ND condition worsens.

These limitations provide considerable scope for innovation. This includes development of neurophysiology markers of disease subphenotype and disease progression using advanced signal analysis.

In clinical trials for ALS, such biomarkers (EMG-based MUNE, MUNIX and electrical impedence myography) have focused on the lower motor neuron and motor unit. Reliable measures of upper motor neuron dysfunction are not yet available for individual patient outcome measures, although early phase clinical trials of Retigabine have selected patients based on cortical threshold tracking using transcranial magnetic stimulation (TMS).

But we have never attempted to interrogate ALS as a disorder of integration of the motor network. This is now feasible as network activity can be picked up by neural signals recorded at rest and during targeted activations of specific networks using selected motor or non-motor tasks and/or stimuli. Joint recording and analysis of co-variability of patterns in the EMG/EEG **(**e.g. cortico-muscular coherence and directional network influences) during functional motor tasks can be used to interrogate this disrupted balance in multiple motor networks (including α - γ reweighting) due to cortical and spinal degeneration.

Early experiments during functional motor tasks can already distinguish differences between patients with primary lateral sclerosis (PLS), post-polio syndrome and controls. By extending this preliminary work to larger groups of patients will ALS we will aim to characterize and quantify the **disruption in motor networks that could be used as a future marker of disease progression.**

Additionally, time-series and spectral analysis of electroencephalogram (EEG) signals have shown that the alterations of functional/effective communication between brain regions can be reliably assessed both at rest and during non-motor functional tasks. **Novel analyses of the spectral patterns from high density crossectional and longitudinal EEG** has shown specific and reproducible regions of altered connectivity, with strongly increased EEG cortico-cortical coherence between parietal-frontal regions (in γ-band) and between bilateral motor regions (in θ-band) in ALS patients that persist in longitudinal analyses over 6 months.

By correlating these findings with 3T structural MR imaging from the same patients, focal disease-specific structural degeneration in motor areas and corticospinal tracts can be shown to parallel decreases in spectral power over motor areas. By contrast, extensively involved extra motor regions on MRI exhibit strong increased neural communication on spectral EEG.

This is the first time that multimodal analysis of structural and functional change using MRI and spectral EEG respectively has been done in ALS. It confirms the enormous potential of neuroelectric signalling as a method interrogate patterns of network disruption in ND. Development of this method could provide novel quantitative measures that reflects specific underlying pathology. These could in turn be used as a potential method of patient segregation, and potential quantitative clinical trial outcome measure.

4. Highway Towards Trial Readiness (In design phase)

Project: Test only the best

The will be an agreed framework and process for compound approval.

This will require a series (2-3) of 1-2 day workshop with key stakeholders (trialists, pharma, clinicians, scientists, regulatory bodies, CRO's, patient organisations).

Project: Harmony

The deliverable from this will be a SOPs in clinical trials for the harmonised delivery of interventions which effect outcome in ALS (NIV, Cough assist, gastrostomy, nutrition). This would go beyond simply when NIV is started but would also describe how efficacy is monitored of NIV for example.

Project: Take control

Develop a central co-ordination centre for which trials in development are registered. Co-ordination of control arm with harmonisation of inclusion criteria and trial visits assessments.

Hold a workshop to scope out how this would work. Invite key stakeholders (trialists, pharma, clinicians, scientists, regulatory bodies, CRO's, patient organisations).

Project: Ready to recuit

All TRICALS centres set up formal ALSFRS registers with ALSFRS conducted by certified individuals and with patients consented for data to be used in future studies. Centres aim to include all patients at diagnosis into the ALSFRS register. Patients contribute ALSFRS data at monthly intervals via remote capture (telephone, on-line etc). When new CTIMP's open subjects will all have ALSFRS trajectory data enabling patients to be selected who are progressing by at least 1 point. This ALSFRS data could also allow faster before and after slope change studies.

Cost: Centres may need some database support at each centre and some central co-ordination. Estimate 300K over 2 years.

Clinical Trials

Implementation and first TRICALS investigator-led studies of therapeutic agents. Protocols are already being developed for 3 Investigator Led studies. Details will be agreed in the coming months. The aim is to have these ready to enrol in mid- 2019.

1. LIGHTHOUSE 2
A repurposed drug that is currently used to treat HIV

2. ADORE
An oral form of edaravone

3. PRELUDE
A trial of lithium in patients with a particular genetic variant.