

PROJECT TRICALS

AN INTERNATIONAL COLLABORATION TO FIND EFFECTIVE TREATMENTS FOR AMYOTROPHIC LATERAL SCLEROSIS

BACKGROUND

Amyotrophic Lateral Sclerosis (ALS), also known as Motor Neurone Disease (MND) is a fatal neurodegenerative disease that strikes in midlife and kills one person every 2 days in Ireland. People with ALS experience rapidly progressive and ultimately fatal decline in their ability to move their muscles, to speak and to swallow. Half of those affected by ALS experience decline in their ability to process information and to manage their behaviour.

We now know that ALS overlaps with other more common brain conditions including dementia and schizophrenia.

THE CHALLENGE

There is no effective treatment for ALS. Despite huge investment over the years in animal models of ALS, we have not yet succeeded in translating successful treatments to humans. In the past 15 years, over 45 clinical trials of new treatments in human have failed, costing hundreds of millions of euro. This is because human ALS is more than one condition, but our clinical trials have not reflected this.

THE GOAL

It is time to move to a new precision-medicine based approach towards treatment.

To achieve this we need a radical change in how we engage in research. ALS is a human disease. We must shift the focus from animal research to human research. We will not find new treatments without working together and investing in the study of people with the disease.

European ALS Centres must join forces to capitalize on our individual strengths, and to build on new and creative approaches that enhance our collective scientific expertise. It is also imperative that we include those who are experiencing the disease first hand.

By working together as the **Treatment and Research Initiative to Cure ALS (TRICALS)**, we have a better chance of succeeding in our shared goal to find a treatment for ALS.

The objective of Project TRICALS is to have the right drug in the right dose, for the right patient at the right time.

EUROPEAN CENTRES THAT ARE PART OF PROJECT TRICALS

Centres of ALS research in Ireland, Holland, the UK, France, Belgium and Italy, working at the highest international level, have joined in the Project TRICALS campaign. Each centre has cutting edge skills and scientific expertise in ALS that will contribute to our goal of a precision medicine-based approach towards new treatments for AL/MND.

The Project TRICALS campaign will raise funds for specific research initiatives that will enhance and share this expertise across sites.

BUILDING ON SUCCESS: From Project MinE to Project TRICALS

An important obstacle to finding new treatments for ALS has been our incomplete understanding of genetic factors. **Project MinE** (www.projectmine.com) was designed to address this.

Project MinE is a crowd funded initiative, in which 13 partner countries have raised funds to support genome sequencing of DNA samples from their own population. Project MinE is achieving its goals by analysing the genetic code of 15,000 ALS patients and 7,500 healthy people in exquisite detail to discover every gene that contributes to ALS risk.

Having raised €1.6 million, the Irish arm of Project MinE based in Trinity College Dublin has contributed DNA samples of 700 ALS patients and 350 healthy participants to the project.

Project MinE has already made many important discoveries that are reshaping our understanding of ALS and has taught us that there are many subtypes with distinctive characteristics. Each subgroup of patients is likely to require a different treatment.

But Genetics is only part of the story. We also need to focus on how the disease manifests in individual patients. We need to combine our collective clinical studies with our new genetic insights to have a true Precision Medicine approach towards new treatments.

Project TRICALS will combine the genetic information from Project Mine with innovative approaches towards disease categorization, using shared methods developed by individual partners within the Project TRICALS consortium. These additional cutting-edge methods include novel approaches towards epidemiology, clinical assessment, neuropsychology and behavioural assessment, biochemical measures, MRI, and brain signal analysis and measurements of patient outcome.

European Researchers in Project TRICALS will combine all of these approaches to identify new ways for grouping patients into different clusters, and to develop new and more cost-effective ways of testing new drugs.

This will allow us to enroll groups of patients in new clinical trials that are specifically targeted towards their type of disease.

PROJECT TRICALS – HOW IRELAND WILL CONTRIBUTE

Ireland has excelled in patient categorization for many years.

Our work capitalizes on the natural research strengths within the Irish population (epidemiology and genetics) and scientific expertise within the ALS Research Group at Trinity College Dublin.

Our contribution will be in 7 thematic areas, outlined in detail in the attached Appendix:

- **Genetics**
- **Epidemiology**
- **Cognition**
- **Imaging**
- **Signal Analysis**
- **Outcome measures**
- **Patient and Caregiver Ecosystem**

APPENDIX

DETAILED OF THE IRISH RESEARCH CONTRIBUTION TO PROJECT TRICALS

THEME 1: GENOMICS: A CONTINUATION OF PROJECT TRICALS

The Irish ALS Research Group has a strong track record in genetics research, including the identification of a new causative gene in ALS in 2006, and contributions to 3 new genes in the past 18 months. Genetics research has developed considerably over the past 3 -5 years and requires highly trained statisticians and bio-informaticians to analyse the trillions of data points generated from genomic sequencing.

As part of the Project Mine initiative (www.projectMinE.com), we will continue to engage in detailed analysis of Irish ALS genetics, using state of the art bioinformatics technology, in collaboration with colleagues in the Smurfit Institute of Genetics TCD. (Funding for genomics has been generated from the Project Mine initiative)

Deliverables:

- Identification of new susceptibility genes in ALS
- Identification of genes that “travel together” (oligogenic inheritance)
- Identification of gene interactions that contribute to ALS
- Identification of new pathways for drug development
- Genetic Association between ALS and Schizophrenia
- Characterization of the genetic profile of the Irish population

5-year cost: This project is funded from Project MinE

THEME 2: A STUDY OF GENETIC AND ENVIRONMENTAL RISK FACTORS IN ALS

The Irish Register of ALS captures and verify all new patients who have consented to their inclusion on the Register. It is the longest running Register of its kind in the world, and is internationally recognized as a “gold standard”.

This resource permits continued collection of information about lifetime exposures from people with ALS and recruitment matched controls as part of our international collaboration with colleagues in Holland and Italy as part of the ENCALS network (www.ENCALS.com)

Each person with ALS is asked for detailed information about their employment and recreational history. We also collect information about family history, and we are currently exploring the hypothesis that those with a strong family history of other related neurological and neuropsychiatric conditions harbour susceptibility genes that may contribute to both ALS and other neurological/neuropsychiatric conditions. DNA is used to look for these “at risk” genes, and to determine how they interact with environmental exposures.

Deliverables from the theme:

- Continuation of the Irish Register, inclusion of high quality verified data, and regular quality control analysis.
- 2,300 individuals have been included on the Register to date. Family aggregation studies have shown that the familial rate of ALS in Ireland is 30%.
- Exposures that are likely to increase the risk of developing ALS include smoking, exposure to pesticides, and possibly exposure to certain sex hormones.
- Rapid selection of subgroups for enrolment in clinical trials.

5 year Cost: Register Manager: €80,000 per annum
Epidemiologist: €90,000 per annum
Statistician: €90,000 per annum

THEME 3: COGNITION and BEHAVIOUR

Using the Irish Register and population-based controls, we are characterizing the cognitive and behavioural profile of ALS patients in Ireland and are studying the neuropsychiatric and neurobehavioral conditions in families of people with ALS using a previously described semi-structured interview, chart review and death certification. All patients and controls provide a DNA sample as part of our study of genetic and environmental factors in ALS. Control kindreds are selected based on age, gender and educational status of the ALS patients, and undergo similar analyses. Index patients and first-degree relatives are invited to participate in a detailed study using a previously used standardized neuropsychological battery including extensive assessment of cognitive and behavioural status and social cognition, and neuroimaging using standardized structural and functional protocols. The aim of this work is to identify families that are likely to harbour genes that can contribute to both neurological and neuropsychiatric conditions.

DNA from these families is sequenced to identify previously unknown genes that contribute to disease susceptibility.

Deliverables

- Definition of cognitive and behavioural subtypes in ALS
- Improved stratification of clinical trials
- Improved targeting of drugs to patient sub-cohorts
- Characterization of the clinical, behavioural and cognitive sub-phenotypes of ALS

5 Year Cost: Senior Neuropsychologist: €100,000 per annum
Research Assistants: €100,000 per annum

THEME 5: ALS AS A NETWORK DISORDER: SIGNAL ANALYSIS THAT HARNESSES BRAINWAVES TO UNDERSTAND SUBPOPULATIONS OF ALS

There is evolving evidence that ALS is caused by disintegration of networks of nerves, rather than death of individual nerve cells. We believe that the failure of translation of drugs from animals to humans is likely due to the complexity of neural networks in humans, which are disrupted in diverse ways (disease heterogeneity).

The purpose of this research theme is to change how we look at ALS based on the dysfunction levels in several specific neural networks.

Work in Trinity College Dublin is at the forefront of this type of signal analysis in the brain of those with ALS. The theme leader is a Neural Engineer (Dr. Bahman Nassereloslami).

The group is developing novel and inexpensive ways to separate patient groups based on differential types of network disruption. We collect brain waves (EEG) during resting-state to identify which networks are disrupted. We then study networks by EEG during thinking tasks, and movement-related networks by activating the motor nerves within the brain by a non-invasive device (magnetic stimulation). We correlate these measures with results from neuropsychological tests of thinking and behaviour, and with changes in MRI, and will use these new tools as biomarkers that will help to separate patients into different subgroups, and that can be used to measure disease progression over time in clinical trials.

Deliverables

- Identification of early differences in brain networking – improving diagnoses
- Identification of subgroups with different patterns of network disruption that respond to different drugs
- Tracking disease progression in clinical trials and improving quantitative outcomes
- Finding better ways to measure thinking and behavioural changes by identifying the patterns of network disruption

Research Costs:

Senior Neural Engineer:	€ 120,000 per annum
Research Scientist	€ 60,000 per annum
Clinician Scientist:	€80,000 per annum

THEME 6: NEW OUTCOME MEASURES FOR CLINICAL TRIALS

This work is focused on the decreased functional ability in walking ability (gait) hand function (dexterity), swallowing, and speech that occurs in ALS. The theme leader (Dr. Meldrum, and main researcher (Dr. Murray) are both academic physiotherapists who have recently joined the ALS Research Group. Their theme relates to the development of better outcome measure for clinical trials.

The objective in clinical trials is to measure the effect of a compound on functional ability by determining whether it can slow down or stop the rate of neurological decline. But detection of meaningful change requires reliable quantitative outcome measurements, and most of scales used for clinical trials are semi-qualitative. This means they attribute a numerical value to a clinical assessment by an examiner. Because clinical examination can be very variable, conversion of the clinical findings to a rigid ordinal scale introduces problems with reliability and variance, which increases the risk of failure to identify a real effect of a new drug. Also, most scales do not provide a "clinical meaningfulness" measurement. We have no way of determining the real-life impact of a drug, because we cannot convert the numerical outcome measurement into how functions of everyday life. We are developing sensitive non-subjective tests to resolve the problems of variance in the outcome measure for ALS (the ALSFRS-R).

Deliverables

- Quantitative outcome measures using novel devices
- Better and more accurate outcome measures for clinical trials
- Definition of clinical meaningfulness of a drug.

Research Costs: **Senior Clinician Scientist (Physiotherapist):** €90,000 per annum
Research Scientist: €60,000 per annum
Research Engineer: €60,000 per annum

THEME 7: MULTIDISCIPLINARY CARE AND HEALTH SERVICES RESEARCH

We are tracking the patient journey from diagnosis to end of life to understand the entire cost from a financial perspective. We are also studying the effect of the illness on the family “ecosystem”, by engaging with patients and caregivers determine quality of life, caregiver burden and palliative care needs.

Along with physical decline, thinking and behaviour changes are significant factors that contribute to caregiver burden in ALS and there is evolving evidence that caregivers’ psychological status may also influence the mental and physical outcome of patients. However, the presence of cognitive/behavioural changes in ALS is often under-recognized by healthcare professionals and the burden of care associated with these changes is not addressed. We are investigating the consequences of cognitive and behavioural effects on caregiver burden in ALS

We achieve this through assessment of objective and subjective caregiver burden using both structured and semi-structured interview techniques. We are developing a rational approach to enable self-management of burden and develop guidelines for health care professionals to recognize cognitive and behavioural change in ALS and the associated burden for caregivers.

Deliverables

- Total Cost of ALS
- Whole illness model of ALS
- New tools to measure the impact of a new therapeutics on the patient journey, for the purposes of health technology assessment
- New interventions to limit caregiver burden

Research Costs: Senior Research Scientist: €90,000 per annum
Research Assistants (x3): €90,000 per annum
Health Economist: €60,000 per annum

TOTAL COSTS (including estimated annual increments)

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL €		
THEME 1	FUNDED							
THEME 2	260,000	270,000	280,000	290,000	300,000	1,400,000		
THEME 3	200,000	210,000	220,000	230,000	240,000	1,100,000		
THEME 4	260,000	270,000	280,000	290,000	300,000	1,400,000		
THEME 5	260,000	270,000	280,000	290,000	300,000	1,400,000		
THEME 6	210,000	220,000	230,000	240,000	250,000	1,150,000		
THEME 7	240,000	250,000	260,000	270,000	280,000	1,300,000		
RESEARCH MANAGER	90,000	95,000	100,000	105,000	110,000	500,000		
TOTAL	1,520,000	1,585,000	1,650,000	1,715,000	1,780,000	8,250,000		