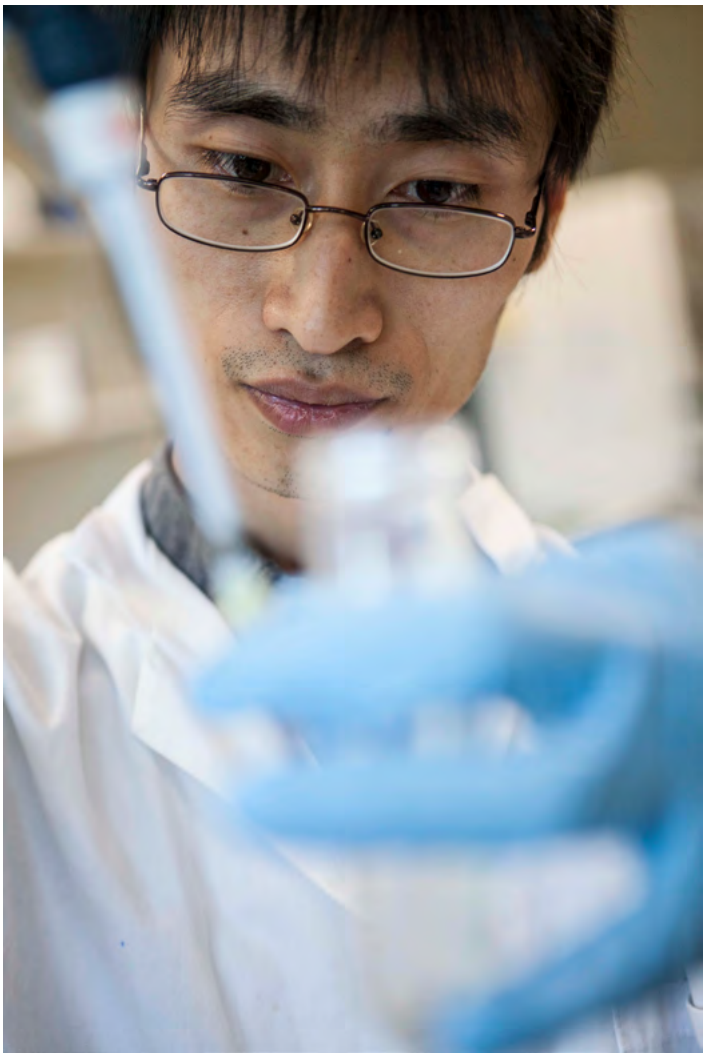
# The UK MND Research Institute



mnda
motor neurone disease
association

MY
NAME'5
DODDIE
foundation

MND
Scotland
Supporting people affected by Motor Neurone Disease

January 2021

## MND: a therapeutic opportunity

Motor neuron disease (MND) is a devastating neurodegenerative disease in which progressive motor neuron loss leads to increasing paralysis and disability. The average life expectancy of someone with MND from diagnosis is just 18 months. It is one of the most common age-related neurodegenerative diseases, with a lifetime risk of 1 in 300, and the most common of mid-life.

Despite the fact that the number of people newly diagnosed with MND each year is similar to the number diagnosed with multiple sclerosis, MND appears far less common because it dramatically shortens life. However, MND is attracting unprecedented interest from industry as the neurodegenerative disease most likely to deliver effective therapies in the near future. There is therefore an urgent need for a coordinated approach to accelerate drug development and clinical trials.

## The UK: leader and innovator in MND research

Investment now will capitalize on and energize the established UK infrastructure and world leading MND clinical and research innovations. The major barriers to finding a cure for MND have been understanding of the underlying biology of MND, the need to engage pharmaceutical industry interest, and money.

Understanding of MND has accelerated in the last 5 years and there is an opportunity for the UK to capitalize on that new knowledge, bringing in major industrial investment around the new pathways, drug targets and ensuring cutting-edge therapies are delivered first to people living with MND in the UK. With UK government support of £50 million, the UK MND Research Institute will ultimately be able to leverage inward investment from industry for every new drug in the pipeline, given that the typical costs of drug development are in excess of £500 million per drug; this initial development could be kickstarted in the 5-year timeframe. Without investment, industry will look to other partners in Europe and the US.

Interest from leading pharmaceutical companies indicates the current high regard and competitive advantage of the UK MND research community and demonstrate their strong appetite to partner with a UK MND Research Institute. Once established, these partnerships will develop beyond MND and bring investment opportunities around the drug development pathway more broadly.

There are many reasons for the collective optimism that we are on the verge of making MND a treatable disease:

- The massive upsurge in international research output in the last decade, which has driven MND to the forefront of neurodegenerative disease research
- The identification of multiple therapeutic targets and the generation of novel laboratory models for target validation and preclinical testing
- The only licensed treatment (riluzole) shown to modify disease trajectory in any age-related neurodegenerative disease, indicating that MND is a tractable disease
- Identification of the genetic basis for a significant proportion of cases, placing MND at the forefront of gene therapy strategies for neurodegeneration, and building on successful treatment development for SMA, a childhood motor neuron disease
- Near 100% diagnostic accuracy ensuring research results are truly representative
- New and innovative measures of disease trajectory and stratification methodologies
- Emerging biomarkers to aid early diagnosis, improve prognostic accuracy and determine treatment efficacy
- The opportunity for preventative strategies in inherited forms of MND
- The creation of novel trial platforms, permitting faster and cheaper trials
- A tightly knit, and highly collaborative community of scientists, clinicians and charities with international reach, all focused on the single common goal of finding a cure.

Paradoxically, the rapid and relentless progression that distinguishes MND from its neurological counterparts also makes it an ideal exemplar for age-related neurodegeneration, permitting more rapid and efficient clinical trials to be performed. A therapeutic breakthrough in MND will have positive consequences for other conditions, including dementias and Parkinson's disease.

## The need for a dedicated MND Research Institute

The UK has a longstanding record as a world leader in MND research in both basic and clinical science. The time is right to build on the inherent strengths of the UK MND research community to create the strong foundations for a sustainable translational research programme, to drive new discoveries from bench to bedside.

As a neurodegenerative disease, MND currently features as a condition listed under the auspices of the UK Dementia Research Institute (UK DRI) but it is principally a disease of the motor system rather than a dementia. Moreover, the UK DRI is predominantly focused on upstream disease pathogenesis and target discovery, whereas for MND, the identification in recent years of the majority of inherited causative genes has provided a greater level of insight into disease pathogenesis. These discoveries are generating viable therapeutic targets that offer **significant** and **immediate** opportunity to translate this knowledge for patient benefit.

MND requires a bespoke research pathway to catalyse the drug development pipeline, supplying candidates to a dedicated clinical trial platform which seeks to test new treatments quickly and efficiently. A philosophy of continuous improvement is needed, notably by seeking to maximize the knowledge gained from every trial, whether the investigative treatment is found to be effective or not, to increase the likelihood of future success.

A UK MND Research Institute would achieve these aims, through an organized network of centres of excellence. The goal is to generate synergy and sustainability through funding the right research and the right people, building on existing infrastructure and resources. At its core, it will draw together several world-class institutes where an extensive interdisciplinary 'critical mass' combining basic, clinical and healthcare research has already been generated. These institutes will work in partnership with an extensive network of specialist MND clinics with a strong record of recruitment to clinical research studies and supported by the country's leading MND charities.

## Patient-led and patient-focused

The proposal to develop a collaborative MND Research Institute has been initiated by patients and comes with the full support of the leading MND charities in the UK. It fulfils and will continue to emphasize the Government's INVOLVE agenda of ensuring patient and public involvement in research. The goal of giving everyone diagnosed with MND the opportunity to take part in research and clinical trials is consistent with the Government's INCLUDE agenda to ensure equality for all in access to research. In particular, it addresses the point that people with MND have a high healthcare burden that is not matched by the volume of research designed for the group. We will utilize the strength and networks of the MND charities to ensure that public involvement guides all aspects of this plan.

## What the MND Research Institute would do

### The MND Research Institute has three principal aims

### Aim 1.

**Create a drug discovery and development programme** which will deliver a continuous stream of new targeted medicines for testing in clinical trials.

MND is one of the fastest moving fields in neurological disease research, catalysed by the ongoing discovery of numerous causative genes and the identification of novel disease- associated pathways through 'wet' and 'dry' biology, and accompanied by a plethora of emerging *in vivo* and *in vitro* models for target discovery and preclinical drug development.

Following a workshop in spring 2020, comprising key opinion leaders from academia, industry, funding agencies and patient associations, the UK Medicines Discovery Catapult has drawn up a nine-month plan to develop a Roadmap to improve collaboration and accelerate drug discovery for MND. Given the leading role for MND in the development of gene therapy strategies for neurodegenerative disease, the UK Cell and Gene Therapy Catapult has been invited into the partnership, in order to incorporate the broadest spectrum of opportunity for therapy development.

This initiative is divided into three distinct workplans:

- Develop guidance on use of preclinical models and how to access them
- Agree criteria for minimum evidence required to take an asset to the clinic
- Establish a precompetitive consortium approach to MND drug discovery

The Roadmap will be informed by an unbiased data-driven approach, complemented by expert consensus, providing the guidance for a collaborative drug development funding programme. The aim is then to generate an investment portfolio of promising targets, led by the new MND research institute, through establishing precompetitive academic-industry partnerships, incorporating the right expertise and the right models at the right time. The 'preclinical package' of

evidence generated will stimulate further investment to drive development seamlessly from lab to clinic via an established trials network ready to receive novel therapeutic candidates for testing.

## Aim 2.

**Deliver a sustainable UK MND trials platform** for rapid and efficient clinical trials.

The bottleneck in drug testing for MND is not in patient recruitment; people with MND are desperate for treatments and keen to take part in trials. The issue is the inefficient infrastructure for setting up trials of all phases. However, the UK offers great advantages to the pharmaceutical industry: a single payer NHS system, a demonstrable collaborative environment, a single national governance approvals system, and innovation in developing trial endpoints.

A cornerstone to solving this issue is already being established. The MND clinical research community has enthusiastically embraced innovative 'multi-arm' trial design from the field of cancer. The UK-wide MND-SMART and international TRICALS-MAGNET MND trial platforms follow a master protocol that serves as a template for multiple individual trials to be harmonized in their eligibility criteria, study management and clinical endpoints, improving the speed and efficiency of academic and industry-led therapeutic trials. Through use of a shared placebo arm, these platforms will also increase the proportion of patients in each trial who obtain the active treatment.

Historically, fewer than 10% of people with MND have been eligible for trials due to restrictive inclusion criteria. The new platforms vastly extend the opportunity of trial participation to 60-90% of the patient population, with the potential for rapid and efficient recruitment through a comprehensive population-based patient registry.

Moreover, an estimated 90% of people with MND receive a component of their care via a network of dedicated multidisciplinary MND clinics. A number of these clinics have successfully integrated clinical research with day-to-day operational clinical management, including the recent incorporation of novel telehealth-based approaches to monitor patients during the pandemic.

These opportunities will be extended to ensure many more centres can serve as a primary resource for therapeutic trials, facilitating rapid recruitment and reducing patient burden and drop-out though more extensive geographical spread and incorporation of appropriate technology. We know we have motivated patients and dedicated clinical research teams – in 2018/19, 16% of all participants in a neurodegeneration clinical research study were recruited to MND studies.

## Aim 3.

Implement a rigorous clinical research programme to fully understand the disease and patients' experience, while maximising the knowledge generated from each trial, resulting in continuous improvement and new learning, regardless of the trial outcome. In other words, we design the drugs, test the drugs and then learn from each trial, feeding that learning back, so that every iteration we improve.

MND is a heterogeneous disease, with multiple factors involved in disease initiation and trajectory. As a result, a single universal therapy is highly unlikely. What is needed is a personalized, "precision medicine" approach, based on an in-depth understanding of how the pathological processes at play within each affected person link with their clinical symptoms. Considerable inroads have been made in recent years in genotype-phenotype correlation, disease stratification, prognostic modelling and the identification of surrogate markers, including imaging, neurophysiological, spinal fluid and blood biomarkers.

Historically, cost and practicality have restricted any added value to be gained through nested studies in drug trials. To ensure we can truly augment the value of each trial regardless of outcome, the MND Research Institute will:

- Create an accompanying biobank, serving as a world-leading resource for the identification of novel markers and facilitating their incorporation into everyday clinical practice;
- Develop and validate novel patient-reported outcome measures, reflecting the real-world priorities of patients and caregivers;
- Create accurate prognostic models and reduce the need for placebos through the use of statistical models, improved endpoints, and surrogate markers.

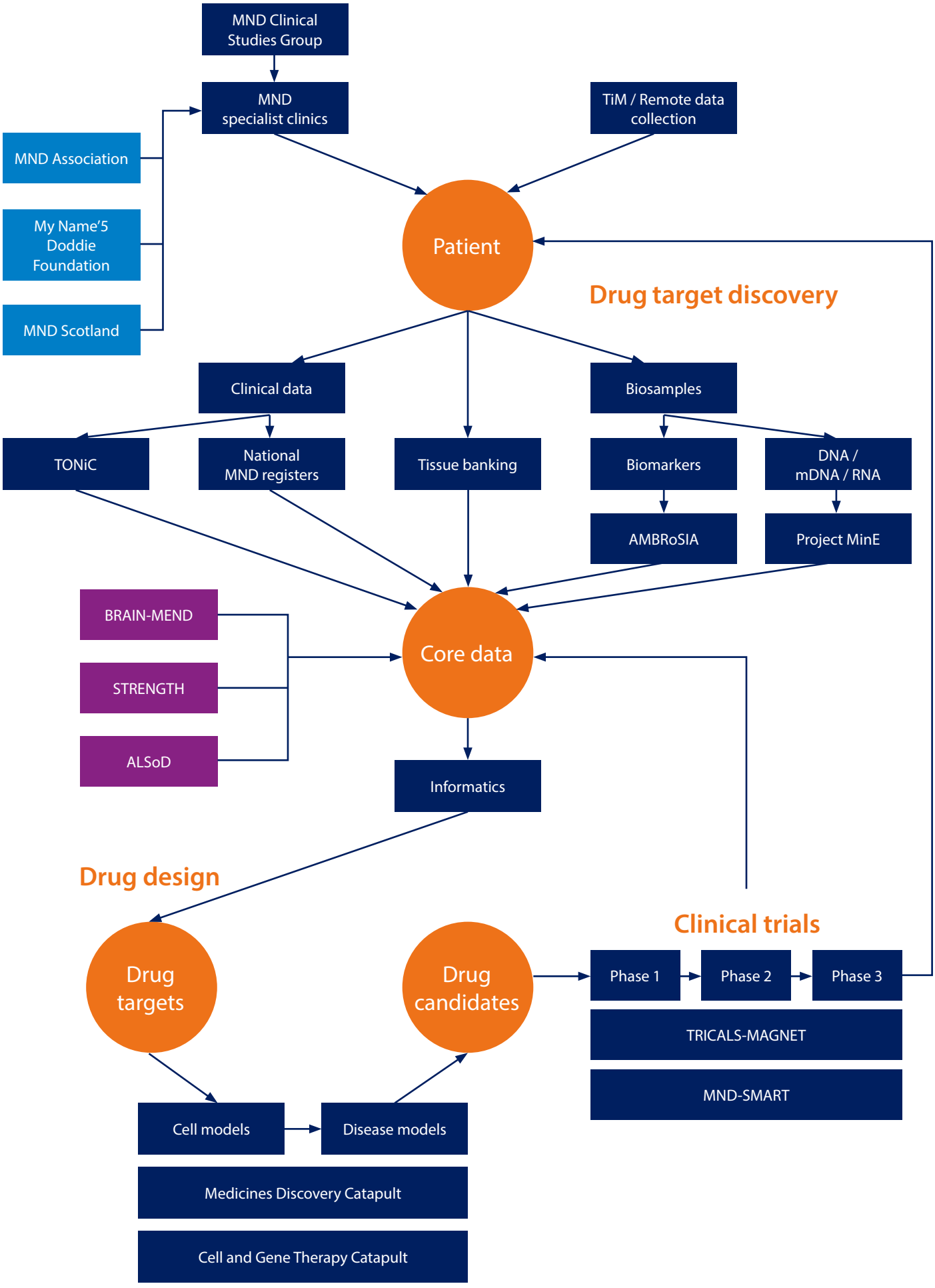



*Figure 1. Potential connections and relationships of UK MND research infrastructure components.*

## Key infrastructure components

| | |
|---|---|
| **Data and samples** | The MND Research Institute will require co-ordinated collection of clinical, epidemiological and psychosocial information, supplemented by biosampling and tissue banking, with harmonisation of data and samples in a linked repository. Much of the groundwork is already in place, with globally compliant standard operating procedures, databases and clinical questionnaires. |
| **A national MND register** | The MND Research Institute will benefit from significant work already underway to create a register that seeks to identify every person diagnosed with MND in the country. Building on the success of the longstanding **Scottish MND Register** which covers 100% of Scotland, a complementary **MND Register for England, Wales and Northern Ireland** is in development and currently covers 60% of the rest of the UK by geography. Continued development of a UK-wide register will not only improve timely, co-ordinated support for people with MND and the assessment of the impact of care, but will also serve as a primary recruitment tool for clinical studies, including trials. |
| **Remote data collection** | TiM on MyPathway (telehealth in MND) is a digitally enabled care system that was launched into the NHS in 2020. TiM enables remote collection of real-time, real-world data from people with MND and their carers. This remote capture enables care to be responsive, but also enables outcome data for clinical trials to be collected remotely.<br><br>Historically as few as 10% of people with MND have taken part in clinical trials for complex reasons which include the burden of taking part. The TiM system will reduce the burden and make it easier for individuals to participate in clinical trials. |
| **Biosampling** | **AMBRoSIA** (A Multicentre Biomarker Resource in ALS) is the UK's largest MND biobanking initiative, collecting multiple biosamples (blood, urine, cerebrospinal fluid, skin) and detailed data from several hundred people living with MND at regular timepoints through the course of their disease.<br><br>Samples and data are collected, processed and stored to rigorous standard operating procedures and harmonized with European and other international cohorts, permitting large scale collaboration and rapid validation of novel biomarker candidates. |
| **Tissue banking** | A proportion of people with MND seek to donate their brain and spinal cord tissue, muscle, or skin cells, predominately through the **UK Brain Banks Network:** an MRC-led initiative to establish a co-ordinated resource, working to common standards of operation and technical protocols, to provide *post mortem* tissue samples to the research community. |
| **Patient reported outcomes** | The TONiC (Trajectories of Outcome in Neurological Conditions) initiative is the world's largest study of the physical and psychosocial factors that impact on quality of life in MND, informing the development of more sensitive and accurate Patient Reported Outcome Measures for use in clinical research and healthcare provision. |

| | |
|---|---|
| **Trial infrastructure and networks** | The UK MND community is primed to capitalize on the accelerating momentum in the search for a cure for MND with unique infrastructure and networks with a strong track record of collaboration and leadership in the field.<br><br>Within the UK, MND commercial and academic-led clinical trials are supported where possible by the government's NIHR Clinical Research Network (CRN) and reviewed monthly by a UK Clinical Studies Group. We have extensive expertise going back to the first successful trial in MND for riluzole in 1994. We have learnt that national coordination and networking are essential for efficient recruitment. |
| **Multi-arm trial platforms** | The UK-wide **MND-SMART** and international **TRICALS-MAGNET** trial platforms were developed in response to the huge unmet need of large-scale, coordinated trials for MND, with broad eligibility criteria, targeted treatments, and learning from each study. They hold promise to dramatically accelerate the speed at which an effective treatment will be found. |
| **MND specialist clinics / care centres** | Around 90% of people with MND receive medical care and support from 25 specialist multidisciplinary MND clinics. These centres of excellence serve as a highly effective network for clinical care and research studies. |
| **The UK MND Clinical Studies Group** | Comprising award-winning and leading MND clinicians, clinical researchers and patient representatives, the MND Clinical Studies Group promotes research opportunities, facilitates recruitment to studies and monitors study setup, recruitment and retention rates, enhancing both the quality and quantity of MND research in the UK and providing people with MND more opportunity to participate in research. |
| **TRICALS** | A new international MND clinical trials consortium, co-led by the UK, has been created to identify the best ways to classify types of MND for targeted treatments, to develop biomarkers to shorten trials, to harness remote assessment tools, to develop better outcome measures for trials, and to harmonize MND trial design internationally, to find the right treatment for the right patient at the right time. |
| **Target validation and preclinical development** | The explosion of new disease models including induced pluripotent stem cells from patients, combined with innovative AI techniques, has highlighted common disease pathways and generated multiple novel therapeutic targets.<br><br>Working with the Catapult Centres, the MND Research Institute will combine informatics with expert consensus to determine the models and assays best placed to predict clinical outcome and to progress candidates to the clinic. This process will set the standard for a preclinical drug development programme which will catalyse collaboration between academia and industry. |
| **DNA and cell lines** | The MND Association's **UK MND Collections**, the *2019 UK Biobank of the Year*, contains an extensive collection of several thousand DNA samples and cell lines from people with MND and unaffected controls. Together with the **AMBRoSIA** biobank, this resource plays a fundamental role in the identification of genetic causes and new disease pathways, as well as facilitating early stage therapeutic compound screening. |

| | |
|---|---|
| **Genetic Data** | **Project MinE**, the 2020 *Healey Innovations Prize* winner is an international whole genome sequencing consortium, co-founded by UK investigators. Researchers have access to whole genome and methylomics data from over 14,000 people with ALS and matched controls (including 2,200 samples from the UK MND Collections) as part of the world's largest disease-specific gene hunting initiative, involving scientists, funding bodies and patient associations from 20 countries across the world.<br><br>**ALSoD**, the ALS Online Genetics Database, is a repository of ALS gene variations identified since the first discovery in 1994, with corresponding clinical information and linked to publications and other relevant databases. |
| **Other Global Research Consortia** | The Joint Programme on Neurodegeneration **STRENGTH** and **BRAIN-MEND** programmes are UK-led international consortia that aim to understand the genetic, epigenetic and environmental factors influencing MND risk, phenotype and survival, and the relationship of complex neurodegenerative diseases such as MND, but including dementias and parkinsonian syndromes, with each other. |
| **Catapult Centres** | The Medicines Discovery Catapult and Cell and Gene Therapy Catapult were established by Innovate UK to promote medical research and development through business-led collaboration and exploit commercial market opportunities. The extensive knowledge and connections of the Catapults seamlessly complements the specialist expertise in pathogenesis and treatment within the MND research community. |

## Deliverables

- A coordinated pipeline of work in MND, from patient, through basic science to drug discovery and back to the patient.
- Everyone diagnosed with MND offered the chance to take part in a clinical trial
- Information from any study maximized (learn from every study)
- Validation of emerging biomarkers, investigation of new biomarkers
- New Patient Reported Outcomes, including remote outcomes and the inclusion of new technology
- At least four pharmaceutical industry partners by year 5
- At least four new clinical trials in setup or recruiting by year 3
- A national register for the whole UK by year 3
- 20-fold increase in patients recruited to studies by year 3
- 10 novel compounds prioritized from pipeline into late preclinical/early phase studies
- 8 academic-industry partnerships
- Educational exchanges in place between academia and industry

# Impact Summary

## Patients

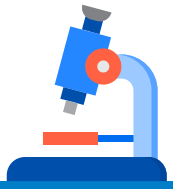
New treatments, hope, empowerment through active participation in research

## Government, charities and other research funders

More effective use of resources as funders and facilitators, with coordinated research pipelines, minimizing duplication, ensuring successful translation of findings from preclinical studies to first in human, or from Phase 2 to Phase 3

## Pharmaceutical organisations/Industry

State-of-the-art system for running efficient, cheaper trials, with better outcome measures



## Researchers

Access to resources, harmonized research programmes, more effective research, collaboration, expertise

## UK

Enhances and cements its already world-leading position in MND research

## UK economy

Inward investment from pharmaceutical industry, job creation

**Motor Neurone Disease Association**
Francis Crick House
6 Summerhouse Road
Moulton Park
Northampton
NN3 6BJ

Tel: 01604 250505
Email: campaigns@mndassociation.org
**www.mndassociation.org**

**/mndassociation**
**@mndassoc**

**MND Scotland**
2nd Floor
City View
6 Eagle Street
Glasgow
G4 9XA

Tel: 0141 332 3903
Email: info@mndscotland.org.uk
**www.mndscotland.org.uk**

**/mndscotland**
**@mndscotland**

**My Name'5 Doddie Foundation**
c/o Gilson Gray LLP,
29 Rutland Square
Edinburgh
EH1 2BW

Email: info@myname5doddie.co.uk
**www.myname5doddie.co.uk**

**/MNDoddie5**
**@MNDoddie5**