

Proposal for a UK Motor Neurone Disease (MND)

Translational Research Institute

July 2021

*Our ambition is to realise significant, effective and life changing treatments for MND
by the end of this decade (2030)*



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1. Message from the United to End MND Coalition

Research into motor neurone disease (MND) has reached a critical juncture. We are now on the cusp of treatments that could halt the progress of this horrific disease.

We are calling on the government for a wholly new investment of £50m over five years to bring forward these treatments and establish the UK's leadership in this area of research. This would be combined with ongoing commitments from the MND charities and other stakeholders to create a funding pot towards £100m for this new, groundbreaking and timely venture.

MND is a devastating neurodegenerative disease which leads to paralysis and, ultimately, death. It is not rare – one in every 300 people will develop MND in their lifetime. About 200,000 of the current UK population will die of MND unless effective treatments are found.

With new dedicated stimulus funding of £50m over five years, an MND Translational Research Institute will:

- Create a drug discovery programme delivering a continuous stream of new targeted medicines for testing in clinical trials, with a pioneering approach that will have wider applications.
- Develop an innovative UK trials platform to deliver rapid and efficient clinical trials that will attract pharmaceutical clients.
- Leverage inward investment from industry for every new drug in the pipeline. Investment and skills development will take place across the UK.
- Facilitate savings in health and social care, welfare benefits and equipment costs.
- Accelerate treatment across all neurological diseases including dementia and Parkinson's disease.

This proposal has been developed with the backing of global pharmaceutical companies, with letters of support from Biogen, GlaxoSmithKline, Novartis, Eli Lilly and PrecisionLife, illustrating the potential for growth and inward investment given the UK's leadership in MND research.

Now is the time to make this investment in MND research. We can bring an end to this disease and establish the UK as the leading player in the extremely valuable global field of neurological disease research.

2. Background

A diagnosis of MND is a death sentence. Patients will lose the ability to walk, use their arms and hands, speak, eat and ultimately breathe. A third of people die within a year of diagnosis, and typically survival is no longer than 2 or 3 years post diagnosis.

MND is not rare as it is often perceived. One in every 300 people will develop MND in their lifetime, about the same as multiple sclerosis (MS). Yet only 5000 remain alive at any one time, such is the severe prognosis.

About 200,000 of the current UK population, many in the prime of life, will die of MND unless effective treatments are found.

MND is, perhaps, the unmet need disease of all diseases.

The exciting potential of MND research

Despite limited investment, MND is now one of the fastest moving sectors in UK health and biomedical research. Current trials hold real promise of a licensed treatment in just 2-3 years for some forms of MND with the appropriate level of investment.

There are many reasons for optimism that we are on the cusp of making MND a treatable disease, including:

- 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.
- Identification of the genetic basis for a proportion of cases, placing MND at the forefront of gene therapy strategies for neurodegeneration, and building on the recently successful treatment development for spinal muscular atrophy (SMA), a childhood motor neurone disease.
- Emerging biomarkers to aid early diagnosis, improve prognostic accuracy and determine treatment efficacy.

- The creation of novel trial platforms, permitting faster and cheaper trials.

MND research has great potential to support and advance research into the more common neurodegenerative diseases such as the dementias. The sheer rapidity of MND progression and diagnostic precision makes it easier to pioneer and trial treatments in a realistic time frame. These treatments can then go on to accelerate progress in dementia.

There has never been a better opportunity to harness unprecedented advances in science, medicine and technology that will not only make MND a treatable condition but also accelerate treatment strategies across all neurological diseases.

Current funding model

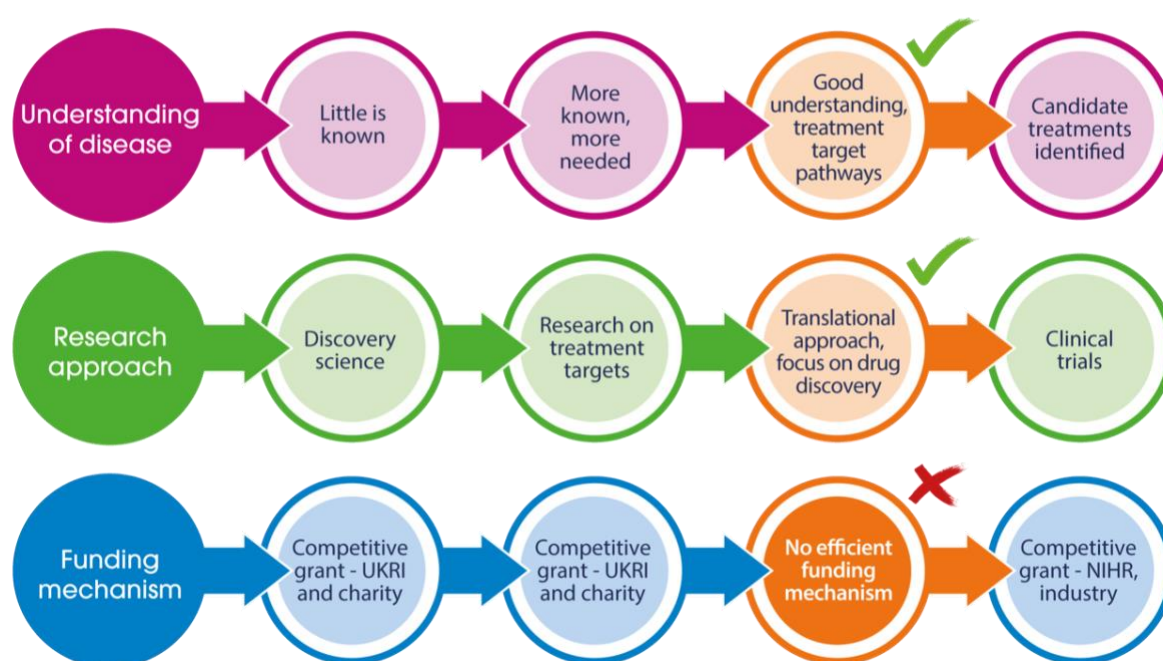
The UK Government has provided vital research and development funding through the National Institute for Health Research (NIHR) and UK Research and Innovation (UKRI). In recent years that has been up to £5m* annually for targeted MND research. Alongside this, MND charities invest over £5m every year.

*Note: In answers to both oral and written questions in Parliament over the last two years, significantly higher figures than this have been presented in response to enquiries on MND research spend. Such figures unfortunately represent the wider spending in neurodegenerative disease as a whole rather than targeted MND research. We would be delighted to discuss the basis of such figures and why targeted funding is so crucial.

This financial support by Government for MND research was for a time also supplemented by the proceeds from the Ice Bucket Challenge in 2014, with £7m raised through public donations. This singular fundraising phenomenon enabled disease research to reach a tipping point that has now led to the disease being *translational* ready i.e. turning scientific discoveries into treatments.

However, this progress has not yet led to the realisation of potential life changing treatments that can be delivered to patients. Is it this funding model that is now ultimately failing MND research?

Figure 1: The evolving needs of disease research



There are significant and fundamental complexities^[fig1] within the existing funding systems that are posing challenges to a translational ready disease, including but not limited to the following:

- Funding is applied through open and competitive grant calls to the government funding councils. This functions very well when scientific research in an area is in its early stages. However, coordinating a truly national approach to capitalise on the burgeoning progress for MND cannot be achieved through such a structure because of the fragmented nature of funding.
- NIHR funding is not designed to fund animal testing or animal tissue-based research, which is still a vital necessity for human disease exploration and MND research.
- NIHR funding is aligned to the latter stages of the translational pathway, e.g. clinical trials and applied healthcare.
- UKRI funding is aligned to the early stages of the translational pathway, e.g. basic, but vital, core science.
- Within the NIHR the 'pillars' of programme funding can be restrictive, e.g. grant duration, funding limits and application opportunities.

- In particular, project grants associated with vital infrastructure and integrated components (e.g. DNA Bank, MND Register, any project that collects patient data and samples) have a limited grant duration. As such, on termination, these key entities are subject to ongoing funding challenges.
- The process of grant calls, applying and actual allocation is very slow, can consume excessive researcher time and often takes several years to complete. It does not allow for an iterative process whereby discovery is immediately fed into a developed and innovative approach.

Because MND research is now firmly at a translational point, there is no effective and efficient funding source, and hence the reason for this spending review application.

The result is that despite significant government expenditure on neurodegenerative disease research, still only about £5m is spent yearly on **targeted** MND research from the Department of Health and Social Care (DHSC) and the Department for Business, Energy & Industrial Strategy (BEIS). A significant boost is required to maintain the impetus that the Ice Bucket Challenge donations once enabled.

MND research strategy needs to move beyond using single centres or small collaborations to answer narrow research questions, towards a large-scale, coordinated approach, tackling every aspect of the translational pathway with the multidisciplinary expertise available nationally to rapidly find and develop new, effective therapies for MND. The search for new therapies requires a truly multidisciplinary, pan-national approach spanning the entire translational pathway.

3. The UK Government's agenda for science and research

The Government has set out an ambitious agenda to cement the UK's status as a science superpower. In the [UK Research and Development Roadmap \[1\]](#), the Government sets out a once-in-a-generation opportunity to strengthen our global position in research. This report sets out challenges, including how to fund 'truly transformational opportunities', and introduces an objective of taking 'bigger bets' such as the funding of new institutes in genuinely transformational areas of science and research. The Department of Health and Social Care has an objective to support research to maximise health and economic productivity with part of this being to ensure the UK remains the leader in genomics.

UK leadership in MND research

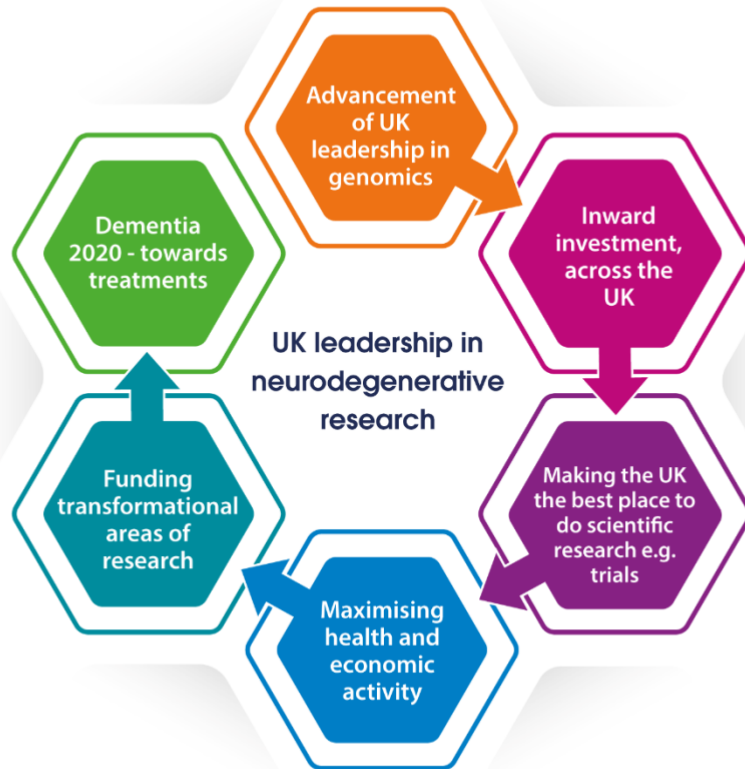
The field of neurodegenerative disease research, in particular the accelerating drive to find effective treatments for MND, has now the potential to be the next major leap forward for UK medical science with UK world leading genomics technology at the centre. Understanding of MND has accelerated in the last five years and there is an opportunity for the UK to capitalise on this new knowledge. However, research has reached a point where a step change in approach is required. The current principle of funding individual research projects will not bring about this transformation.

A new MND Translational Research Institute has the potential to establish a new arena of leadership for UK science, with significant opportunities for inward investment, growth and highly skilled jobs. It also allows the development of new templates for the funding of innovative science, creating new opportunities in neurological research and beyond. This is in line with the UK Government's strategic objectives.

MND's importance for dementia

Moreover, MND is a 'gateway disease', offering a unique opportunity to develop treatments that in turn create new possibilities for treatments for dementia, Parkinson's and other diseases. This supports the Government's objective to make the UK a world leader in dementia research, set out in the [Prime Minister's Challenge on Dementia 2020 \[2\]](#). Part of this is the pledge to double dementia research spending over the next decade through the delivery of a 'dementia moonshot.' MND, the most common neurodegenerative disease of middle age, is well placed to deliver concrete progress for these wider research objectives.

Figure 2: Leadership in neurodegenerative research and UK Government Strategy



4. The case for investment - the UK MND Translational Research Institute

Objectives

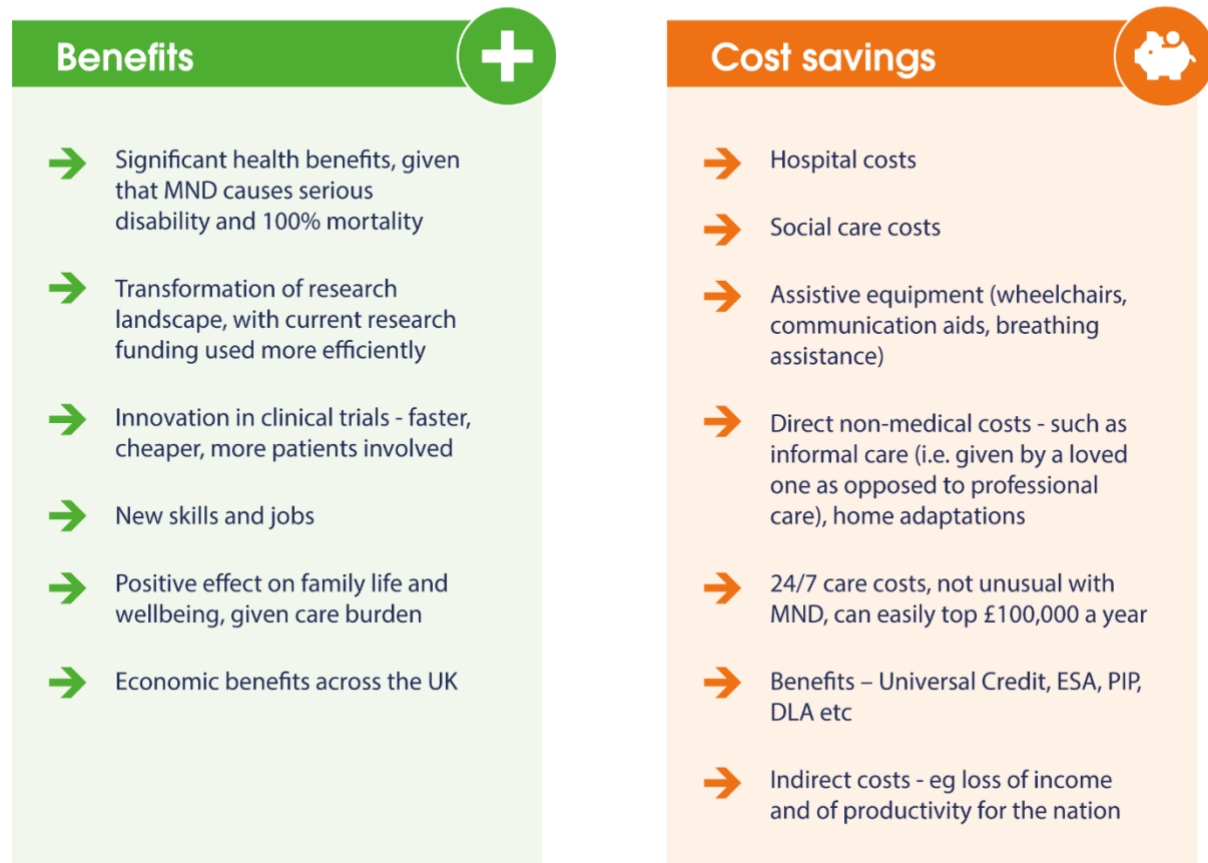
The overall strategic objective of the Institute is to transform and accelerate the research landscape for MND that would support an ambition of *bringing significant effective treatments to the MND community before the decade is out*.

To achieve this, the MND Translational Research Institute will enable:

- An enhanced multi-centre and multidisciplinary approach, with all the leading MND research centres in the UK.
- Accelerated drug discovery, coordinating research and facilitating innovation with a single aim of bringing treatments to the clinic.
- A novel approach to clinical trials, which will allow quicker and cheaper trials, ensure that we learn from every patient, and aim to offer every patient a place on a trial.
- A single point to engage with industry to attract new investment into the UK around new pathways.
- Supporting the government's levelling-up agenda, with centres involved from across the UK.
- A coordinated approach to skills development, job opportunities and manufacturing growth.

These are the very challenges the Government is seeking to address across the research landscape. The MND Translational Research Institute offers the potential to find new solutions.

Summary of benefits and cost savings



Benefits

The proposed virtual institute will transform the current research landscape for MND and neurological diseases. Funding for the research institute will allow new infrastructure shared between the UK centres of excellence - Kings College London, the Sheffield Institute for Translational Neuroscience (SITraN), the University of Edinburgh, the University of Oxford and University College London. Existing research funding will be used more efficiently and will in turn attract industry investment.

The Institute will innovate with new methods of conducting trials. This will act as a case study and model for other diseases / sectors, benefiting in particular research into dementia. An innovative trial platform will attract industry as well as accelerate the scientific process. It will also transform the patient experience. Currently, only about 10% of patients have the opportunity to participate in a trial - our aim is that all patients should have that chance as part of their essential medical care.

The creation of new infrastructure along with inward investment will create new skilled jobs and protect existing jobs. New research fellowships along with overall increased activity will drive development and growth in employment. This growth will be spread across the UK. This skills development will have benefits in turn for neurological research more broadly, and the UK's position in leading that.

There will be benefits to the UK economy, but above all, the health and family benefits will be truly significant. MND brings such serious, crippling and progressive disability, making for a disproportionate financial and humanitarian burden.

The consequences of a disease which takes the patient and, in most cases, their partner, out of the labour market in the prime of their lives are brutal, but often hidden.

Cost savings

With so many therapists from different disciplines involved because of MND's multi-system effects on the body, there are considerable cost pressures on the NHS and social services. This is in addition to the significant level of burden on the individual and family that is quite unlike any other disease.

These costs include:

- Direct medical and social care costs - including hospital costs, health and social care costs in the community, and assistive equipment (wheelchairs, communication aids, breathing assistance).
- Direct non-medical costs – e.g. informal care (i.e. given by family and friends as opposed to professional care), home adaptations, assistive equipment and formal care costs.
- 24/7 care costs, not unusual with MND, can easily top £100,000 a year.
- Increase in welfare spending – Universal Credit, Employment and Support Allowance (ESA), Personal Independence Payment (PIP), Disability Living Allowance (DLA) etc.
- Indirect costs – e.g. loss of income and of productivity for the nation. MND is the most common neurodegenerative disease of middle age often hitting people in the prime of their lives.

Combining these direct medical and non-medical costs reveals the extensive financial burden on the state and individual(s) as this study [3] in 2014 on the economic burden of MND in Germany illustrates.

The mean annual total cost of MND was €78,000 per patient while the lifetime cost per patient was estimated at €250,000. The total yearly burden for the German nation was more than €500m

(The incidence, prevalence and disease severity of MND in Germany and the UK is comparable).

These burdens are both a constant and growing cost, with a sadly revolving door of patients who essentially live now in 2021 with the same life prognosis as 25 years ago, with over 50% dying within 2 years.

Research has further shown that keeping patients stable earlier in the disease, through the development of treatments and earlier diagnosis, is economically very attractive [4] as the costs for late stage MND can be more than nine times as expensive as the early stages.

In this most comprehensive health utility and cost study on MND in the UK, the average 3-month NHS cost of £1,889 [4] is significantly higher than estimates for some other neurodegenerative conditions (e.g. £529 for patients with Parkinson's).[4]

5. Options and proposal

MND research is now at a critical juncture. Funding individual projects and limited collaboration has taken us to the point where treatments are feasible. The next stage now requires a bold and innovative approach to enable the UK to take advantage of this historic opportunity. We are calling for strategic, ring fenced, additional targeted funding of £50m over five years.

What will success look like?

People with MND and their families are daily, and unsurprisingly, demanding urgency and real hope from their interactions with their healthcare professionals. The proposed virtual institute will address this directly by:

1. Maintaining relentless progress urgency through ensuring a continuous pipeline of treatment candidates, with at least 10 novel drug compounds prioritised into pre-clinical/early phase human studies by year 5.
2. The deployment of an innovative new on-demand clinical trials platform, which dramatically increases the number of patients (at any disease stage) being offered a place in a clinical trial with at least 4 new trials in full operation by year 3.
3. Learning rapidly from each and every trial, successful or not, through newly developed biomarkers with at least 2 emerging biomarkers by year 5, part of a new national biobank of data and samples.
4. Driving nothing short of a total revolution in the consultant/patient discussion. The offer of a trial of a treatment will be an expectation from the very first consultation upon diagnosis as opposed to the exception. It will be part of every patient's care plan.

Innovation

Consortium partners have already driven many MND research innovations, including leadership of international consortia such as Project MinE, which aims to understand the genetic basis for MND and is now the largest single disease whole genome sequencing project in the world. Further innovation in the field of genetics will be a target, including use of genetics for stratification and precision medicine. Trial design will be a focus, including for example, the use of remote monitoring for increased efficiency.

Options

The ambitions of the Institute quite simply demand a radical new approach. Considering feasibility, affordability and fitness for purpose (given the current state of progress), what are the options for the MND research community going forward?

- **Business as usual:** our scientists continue to compete for grants and continue to work mainly in silos with collaboration happening informally and on specific projects.
- **Do minimum:** limited additional funding is provided to MND research, through a one-time national flexible Life Sciences grant process (as yet undefined) across the DHSC and BEIS. Collaboration is still likely to be largely informal and not transformative.
- **The formation of a virtual Research Institute (this proposal):** A strategic, ring fenced, stimulus funded government collaboration across UK centres of excellence with the aim of accelerated drug discovery, an innovative trials platform and a single point of contact for industry. Optional capabilities can be considered to not only find effective treatments but to expand to prevention and accelerate wider neurodegenerative disease research.

The status quo, along with these other options is depicted in the following red, amber, green (RAG) chart.

Note: The current 'business as usual' (BAU) model for funding MND research can be envisaged as three-tiered, primarily led by MND charities who contribute over £5m yearly for targeted MND research. The UK government currently grants circa £5m yearly in open competition grants to the research community. In addition, there is UK Government funding in general neurological disease research.

Table 1: RAG high-level analysis of funding options

	BAU NIHR & UKRI grants	Do minimum Limited national grant	UKMNDTRI Ring fenced funded Institute Optional packages example	UKMNDTRI Ring fenced funded Institute Core packages
CSFS - Summary				
<i>Innovative trial platform</i>		Indeterminate		
<i>New trials</i>	New trials continue under existing model.	Indeterminate	New platform promotes trials	New platform promotes additional trials
<i>Biomarkers</i>	Emerging work will continue	Indeterminate		
<i>Novel compounds</i>		Indeterminate		
<i>Prevention/Non Motor Symptoms</i>	Outside scope	Outside scope	Challenging	Outside scope
Strategic fit				
Benefits optimisation (costs/benefits)	Model not fit for purpose for MND	Indeterminate	Challenging	
Potential achievability		Indeterminate	Challenging	
Supply-side capacity & capability	N/A	Indeterminate	Resource intensive	
Potential affordability	N/A	Indeterminate		
Summary	Discounted – non strategic			

Only dedicated funding for MND research combined with a fully integrated approach across UK institutions - an MND Translational Research Institute - will deliver the innovation needed. In particular, it would provide:

- pathways across the whole of the lifecycle of life sciences.
- increasing dramatically the number of UK patients offered a place on a treatment clinical trial. Currently only 10% of patients diagnosed are offered such a place due to technology limited inclusion criteria, resources and the sheer lack of trials.
- innovative disease progression measurement techniques supplemented with emerging biomarkers. The UK is positioned well with many building blocks already in place and innovative and groundbreaking scientists active in the field.
- significant industry involvement and investment. There is significant backing from industry for our plans for an ‘on-demand’ clinical trials platform along with a drug discovery programme.

With these elements in place, the proposed MND virtual research institute is an investment that will solidify an achievable ambition:

To realise significant effective and life changing treatments for MND by the end of this decade (2030)

6. Delivery of the MND Translational Research Institute

The Institute will bring together all key stakeholders in MND research:

Patients; the major UK charities that support research into MND, including the MND Association, MND Scotland and the My Name's Doddie Foundation; the main UK MND research centres - King's College London, the Sheffield Institute for Translational Neuroscience, the University of Oxford, University College London, and the University of Edinburgh; and industry partners.

The overall strategy is to move beyond the idea of using single centres or small collaborations to answer narrow research questions, to a large-scale, coordinated approach, tackling every aspect of the translational pathway with the multidisciplinary expertise available nationally to rapidly find and develop new, effective therapies for MND.

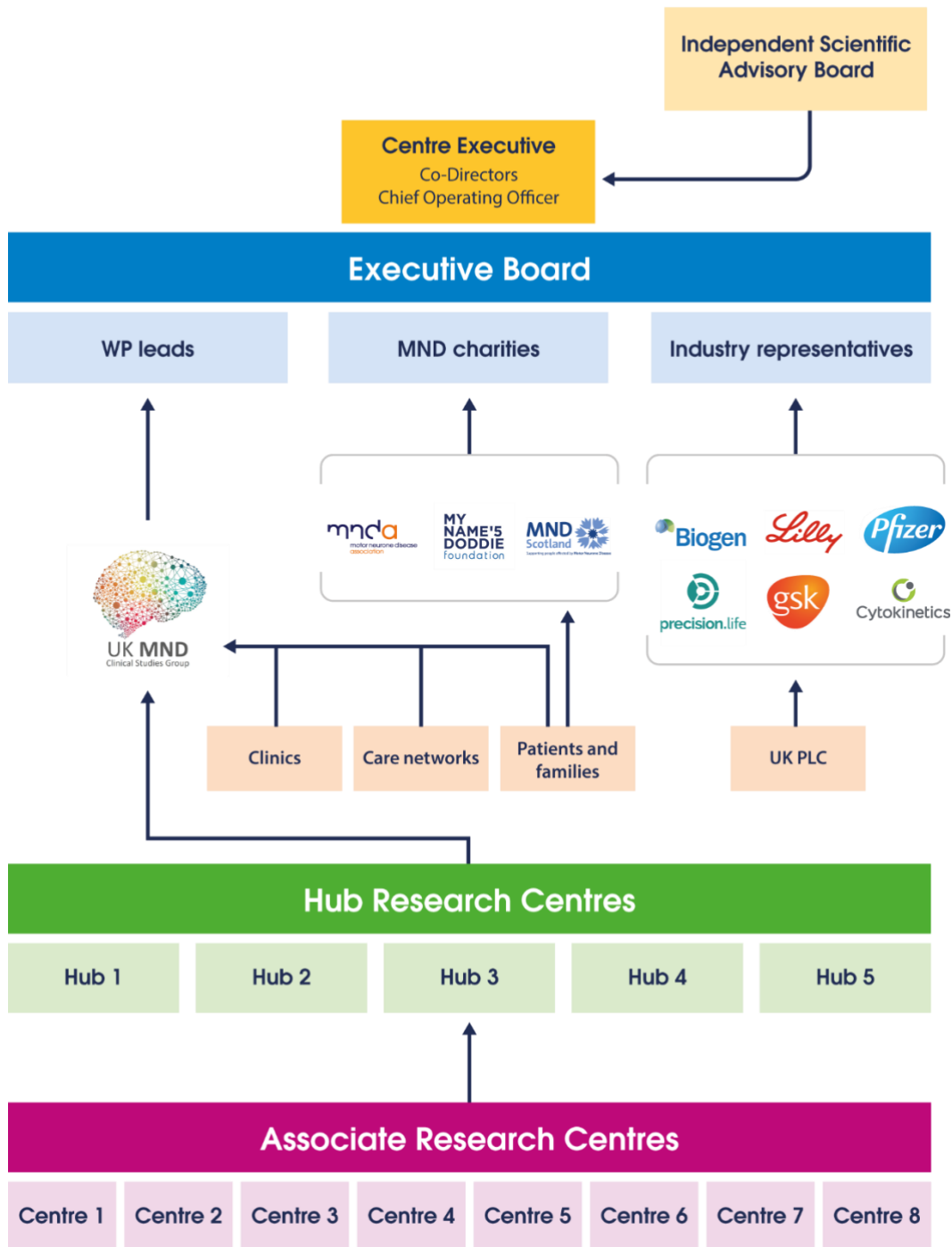
For MND in the UK, this is facilitated by the close existing relationships between people with MND and specialist Care Centres nationally. We will therefore identify relevant disease pathways by various methods, test and validate them in models, identifying the likely mechanism, and generate drug targets with likely interactors. These will then be resolved and tested in cell and animal models, followed by larger models for dose estimation and first in human studies, before Phase 2 and 3 clinical trials, feeding back clinical knowledge from each study participant, producing an efficient, national-scale pipeline for rapid throughput and testing of potential MND therapies.

Governance

The **Executive Board** (EB) will be the highest decision-making body in the Institute. Its main responsibility is to oversee the scientific and financial progress of the project activities towards its main objectives. The activities of the EB are based on agreed deliverables and associated milestones, within budgetary limits. The EB consists of one representative per project partner. The EB will be chaired by Prof. Ammar Al-Chalabi and Prof. Christopher McDermott.

Work Package Teams (WP Teams) will be responsible for an effective and efficient implementation of a specific work package (see below). The WP Teams consist of Work Package Leaders, leading investigators of the consortium partners who are active in that WP, and expert scientists or others in the area ("participants"). One WP Lead from each WP also takes a seat in the EB on behalf of the WP team members.

Figure 3: Governance structure of the Research Institute



The Institute consortium will seek regular advice from an independent **Scientific Advisory Board** (SAB). The Advisory Board will provide expert advice on the content, quality of the deliverables, ethical issues, general philosophy and direction

of the project, corrective measures in the content of the work if necessary and the dissemination and exploitation of project results.

Workplan

The main work packages will be:

- WP1. Clinical data collection (including bio samples)
- WP2. Biological data processing
- WP3. Drug target identification
- WP4. Drug target validation – cell models
- WP5. Drug target validation – model organisms
- WP6. Selection of compounds for human studies
- WP7. Preclinical/Early phase clinical studies
- WP8. Clinical trials infrastructure and platforms
- WP9. Maximisation of trial benefit (learn from every patient)
- WP10. Health Technology Appraisal (HTA) preparation and execution
- WP11. Management and Dissemination
- WP12. Training and Scholarships

Each WP will be led by at least two partners to maximise the cohesiveness and inclusive nature of the Institute.

Deliverables

No	Deliverables	Delivery month
1.1	Data dictionary and Standard Operating Procedures (SOPs) for every component	6
1.2	Integrated truly national MND registers	36
1.3	Accessible GDPR and Caldecott compliant platform for linked data storage	36
1.4	Linked research biobank	24

2.1	High performance computing infrastructure available for data storage and manipulation	24
2.2	New imaging data available for incorporation into registers	12
2.3	New neurophysiological data available for incorporation into registers	12
2.4	New biomarker data available for incorporation into registers	12
2.5	New genetic, epigenetic and transcriptomics data available for incorporation into registers	12
2.6	Registration and linkage of the new data in the national registers	24

3.1	A set of potential drug targets	24
3.2	Evidence available for filtering of promising targets into WP4	30
3.3	Report of further work needed for each potential target	36

4.1	Further required preparatory work, including structure solving and experimental approaches in cell lines for pathway identification where needed	36
4.2	Multiple drug testing assays across the same set of cell models representing a range of mutations and pathways	36
4.3	List of pathways and targets for validation in WP5	36
5.1	A range of assays employing animal models which recapitulate MND pathology and can be used to test the toxicity and effects of novel compounds using established biological readouts	36
5.2	A list of tractable drugs with dose ranges for further testing	36
5.3	Further disease mechanisms for investigation	24
6.1	Advisory board of key stakeholders and experts, with structure to enable selection of drugs for human studies	6
6.2	Protocol for drug repurposing, development, the use of tool molecules and strategies of medicinal chemistry and drug discovery programs	36
6.3	List of compounds to take to human early phase studies	12
7.1	Pharmacokinetic parameters in small animals	30
7.2	Novel formulations suitable for intranasal administration	36
7.3	GMP-grade pharmaceutical dosage forms for clinical use	42
8.1	A system for prioritization of drugs and selection of trial design from commercial and academic partners	12
8.2	Phase 2 studies setup and running	24
8.3	Phase 3 studies setup and running	36
8.4	Optimisation of trial designs	36
9.1	A set of stratification parameters useful for precision medicine approaches	24
9.2	A set of novel patient-reported outcome measures, clinical and biological outcomes for future trials	24
9.3	Systems for remote data capture to feed into future trials	36
9.4	A protocol for data sharing respecting confidentiality and data protection	24
10.1	A health economics analysis of MND as a baseline	24
10.2	Evidence in all three HTA domains for each new treatment developed, for presentation to NICE for Health Technology Assessment	60
11.1	Dissemination and knowledge exchange plan	3
11.2	Annual progress report	12 & 24
11.3	Final report	36
12.1	Completed PhD programmes at each centre	48
12.2	Completion of post-doctoral training programmes	48
12.3	Annual training courses for clinical trials and AHP staff	12

Timeline



Budget

A detailed plan is set out in the research funding proposal, but this will be allocated across the partners and associate centres over 5 years as follows:

Equipment and hardware: £8,000,000

New scientific and clinical staff posts: £30,000,000

Fellowships and PhDs: £2,000,000

Data collection and processing: £10,000,000

Research (including experimental work and drug development): £30,000,000

Clinical trials expenses excluding staff and equipment: £2,000,000

Health technology appraisal: £1,000,000

Total: £83,000,000

Funds would be allocated to work packages by the Executive Board and will be subject to oversight and reporting.

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