26.08.21

Multiple System Atrophy Trust Research Strategy

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Foreword

Multiple system atrophy (MSA) is an incurable, rapidly progressive neurodegenerative disease, the cause of which is unknown. Clinical detection of MSA is challenging because symptoms in its earlier stages may overlap with other related conditions such as Parkinson's disease, and there is no definitive test that can prove the diagnosis. MSA is a life-limiting condition, and treatments to improve symptoms are often poorly effective. Better understanding of the underlying causes of MSA, its symptoms and clinical progression has the potential to lead to effective treatments to help people with MSA as well as a potential cure for this devastating condition.

The MSA Trust is dedicated to funding research into the causes, potential cure and treatment of MSA. The MSA Trust has continued to grow and increase its funding and has spent £2,200,000 in research funding over the past 21 years. This funding is supported by generous donations from our supporters, so it is critical that we invest in research likely to meet these aims. This Research Strategy outlines the research priorities of the MSA Trust and how these are informed by global work on MSA research. In it we discuss our current active research grants, and our clinical research training programme designed to develop the next generation of clinical academics in MSA. This document follows on from our initial research strategy from 2014 and subsequent revisions in 2017 and 2019.

As a clinician involved in specialist care of people with MSA, I see the impact of this condition on their quality of life. As an academic researcher I have been involved in several research studies seeking to better understand the symptoms, progression and treatment of MSA, and have received research grant support from the Trust. I understand the importance of basic scientific and clinical research in improving our understanding of the underlying causes, clinical course and potential treatments for MSA. As a Trustee and Chair of the MSA Trust Scientific Advisory Panel I aim to ensure we continue to fund research that is of critical importance to helping people living with the impact of MSA.

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Scientific Advisory Panel

The MSA Trust is the main UK funder of research into Multiple System Atrophy (MSA). It is therefore critically important to ensure we are funding the best research and making the best use of the donations and other funding we receive. To this end, we have revised our award process to make sure it is compliant with the criteria for research standards of the Association of Medical Research Charities (AMRC).

As part of this process, we have set up an independent Scientific Advisory Panel (SAP):
Dr Christopher Kobylecki (Chair)
Dr Louise Wiblin
Professor Marios Hadjivassiliou
Professor Janice Holton
Professor John Hardy
Nicola Blake
John Telford

The membership of the SAP includes experts in clinical and research aspects of MSA, and people whose lives have been affected by MSA. The SAP members meet for the following tasks:

- Draw on their scientific, clinical and personal experience and knowledge in the field of MSA to determine research priorities that are pertinent to finding the cause and cure of MSA.
- Fund and promote research that leads to new understanding and treatments and improves clinical care of people with MSA, by reviewing research grant applications. This is done with the aid of peer review by national and international experts in MSA, who comment on the relative merits of our grant applications. The SAP is then able to make a final decision based on the peer review scores and further discussion of the grant applications.
- Review the results of MSA research and advise on key topics related to research relevant to people with MSA.
- To ensure priorities remain current and in line with the Global MSA Research Roadmap and programs are delivered within agreed criteria.

The MSA Trust are very grateful for the time given by the scientific advisory panel to ensure the research awarded funding continues to innovate and support the underlying principles of the Trust to find the cause and ultimately the cure for multiple system atrophy

Global Multiple System Atrophy Research

In 2014 and again in 2018 an international group of experts in MSA met to identify research priorities to improve understanding, diagnosis and treatment of MSA; Recommendations of the Global Multiple System Atrophy Research Roadmap Meeting were published (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5772155/).

Nine topic areas were defined; as indicated below. Working groups for each priority were formed and priority-ranked research recommendations developed.

- Pathogenesis
- Pre-clinical modelling
- Target development
- Phenotype
- Clinical outcome measures
- Imaging Biomarkers
- Non-imaging Biomarkers
- Treatments and Trials
- Patient Advocacy

The timetable for achieving these objectives was agreed upon at the Roadmap meeting and it is reviewed every two years at the MSA Global research meeting. (https://cdn-links.lww.com/permalink/wnl/a/wnl_2017_11_07_walsh_1_sdc1.pdf).
The international meeting in 2020 was cancelled due to the Pandemic, however MSA Trust continue to use the road map and its research strategy to develop its research priorities.

MSA Trust research priorities align with these global priorities, and additionally are informed by the expertise and knowledge of the SAP, current knowledge, and most recent developments of MSA research and identified research priorities of our members and people affected by MSA.

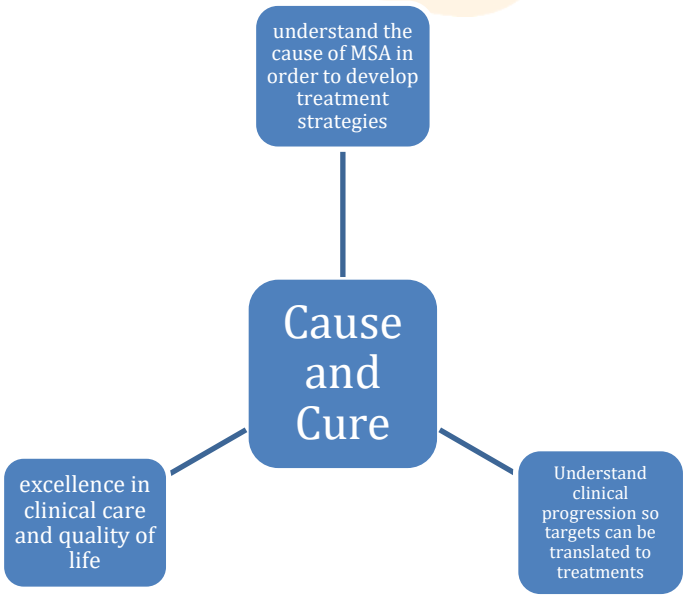
MSA Trust research priorities will be regularly reviewed and revised by SAP in order to best reflect the relevant and necessary research priorities within the field of MSA research, and of our members. A review is made before each funding call, it will include a review of research evidence since the last priorities were set and any changes can be made in the light of new findings. A record of this is conveyed to all interested parties through our research hub on the website.

All processes are compliant with the Association of Medical Charities recommendations and policies, details to be found here. Funding is awarded in open competition compliant with appropriate guidelines. Details of grant application process, outcomes and results are published on the MSA Trust website research pages and available upon request. We ask researchers to make their research available and accessible both to the scientific community and also in lay-terms. We observe all UK financial regulations with regard to the processing of funds raised for research and report to the Charities Commission yearly as required.

MSA Trust Research Priorities

To give clarity, MSA research can be viewed as falling into three related domains; the research priorities identified in the Global MSA Research Roadmap can usefully be grouped under these domains:

1) **Finding the cause of MSA**. The cause of MSA is still unknown, despite advances made in this area, and further research is needed to understand the cause of MSA. This is essential to identifying potential therapeutic targets in order to develop effective treatments for the condition.
   (Global MSA Research Road Map Working groups, 1-3, pre-clinical)
2) **Understanding clinical progression of MSA**. Further understanding the natural history of MSA and how it develops and progresses will aid the translation of scientific discoveries into potential therapeutic treatments for people with MSA. The identification of a biological or neuroimaging biomarker in MSA will allow for earlier diagnosis and more timely entry into clinical studies of potential therapies. A network of 'research ready' people with MSA will allow for clinical trials to be conducted efficiently and successfully when potential therapies need to be tested in real-world settings.
   (Global MSA Research Road Map working groups, 4-7, phenotype, outcome measures and biomarkers)
3) **Developing an evidence base to inform and improve clinical care for people with MSA.** Lack of a definitive test or biomarker for MSA often leads to delayed diagnosis of MSA, and the rarity of the condition and lack of evidence or clinical guidelines to inform best practice means that standards of care are variable from area to area. We want to support research that improves the experience and clinical care of people with MSA, in line with priorities identified by people affected by MSA. While prevention or cure of MSA remains the ultimate goal, MSA greatly affects quality of life and many symptoms of MSA are disabling and difficult to manage effectively. We will engage with members of the MSA community to understand priorities for research.
   (Global MSA Research Roadmap working groups 8,9, treatment and trials and patient advocacy)



We achieve this by:

- **Funding research via our MSA Trust grant award programme** – the MSA Trust has to date contributed £2.2 million to research funding and continues to put out funding calls for further research.
- **Clinical research training programme** – we aim to develop clinicians of the future by funding MSA Research Fellowships. The first fellowship has been successfully completed and a second fellow commences in post in September 2021.
- **Collaboration** with other organisations such as pharmaceutical industry, the academic community, other third-sector organisations, the NIHR and the NHS and members of the MSA community.

MSA Trust Grant Award Programme

Our current research grant awards from 2020 are addressing the key objectives set out in our research strategy as follows:

- Dr Maria Xilouri's work (University of Athens, Greece) aims at understanding the ways in which toxic proteins are removed from the brain, and how this may not be working effectively in MSA. Alpha-synuclein protein building up in the brain cells is thought to be a critical cause of brain cell death in MSA. Dr Xilouri's team are examining the process of autophagy, a key mechanism to dispose of unwanted proteins, in animal models and post mortem brain tissue of people with MSA. Understanding how this process works, or fails to work, in MSA has the potential to identify treatments to modify a potential important underlying cause of brain cell death.
- Dr Conceição Bettencourt (UCL, UK) is examining post mortem brain tissue from people with MSA who donated their brains to the Queen Square Brain Bank, an important resource for research in neurodegenerative diseases. DNA, the genetic material found in all cells in the body, undergoes modification (including methylation) which may affect the expression of genes in different cell types. It has been shown that methylation of DNA is altered in neurodegenerative disorders, and the team are examining this process in the brains of people with MSA compared to healthy control participants and those with conditions such as Parkinson's disease. Methylation is a reversible process, so identifying how it is altered in the brains of people with MSA could identify a way to slow down or alter the progression of damage to brain regions in this condition.
- Dr Christos Proukakis (UCL, UK) is examining the role of somatic mutations, which occur in DNA in cells during life. This can alter the expression of genes in different body regions and cell types and can contribute to disease. Some cells in the brains of people with MSA have a somatic mutation leading to an extra copy of the gene for alpha-synuclein, the protein that is thought to drive cell death in MSA. The project aims to examine this process in more detail in post mortem brain tissue from people with both main types of MSA, in different cell types and brain regions. If they are able to identify significant changes in somatic mutations in people with MSA, it would bring greater understanding of how this process contributes to neurodegeneration and whether it could be modified.
- PROSPECT-M-UK study. This grant awarded to Professor Henry Houlden of UCL aims to discover biomarkers associated with progression in MSA. Biomarkers are a measure (from clinical scores, blood tests, or brain scans) that can be associated with clinical features of a condition like MSA. The PROSPECT study (see below) has already recruited a large cohort of people with MSA including samples of blood and spinal fluid as well as clinical information and scores. This grant is aimed at supporting the recruitment of additional people to be followed up over time, to better determine how changes in these markers relate to clinical features. In addition, novel ways to monitor disease like skin biopsies are being investigated. As new clinical trials in MSA become a reality (see below information on the Exenatide trial), having a cohort of people with well-defined markers to support their diagnosis and progression will greatly help us conduct trials to develop disease-modifying treatments in MSA.

The next MSA Trust grant award programme will open in September 2021, full details are available on the website.

Clinical Training Research Programme

Many of the key developments in MSA research have been led by clinician scientists with a good understanding of the clinical problems that face people with this disabling condition. This allows productive collaborations with basic scientists and other researchers to improve our understanding of what MSA is, how and why it progresses and how we can identify potential treatments. The MSA Trust firmly believe that supporting the development of the next generation of clinician scientists in this area is critical to the success of research in MSA.

The MSA Trust has been pleased to co-fund the Sir Roger Bannister Clinical Research Training Fellowship programme with the Association of British Neurologists (ABN). The Fellowship is named after Sir Roger Bannister CH CBE FRCP, a clinical neurologist and former Chair of the MSA Trust Research Committee and MSA Trust Patron. Sir Roger was dedicated over the course of his career in neurology to understanding autonomic failure, one of the key clinical features of MSA.

Our research training fellowship offers the opportunity to undertake research training addressing an aspect of cause, prevention and treatment of MSA. Typically working alongside experienced clinical and research mentors with an track record of academic excellence in the field of MSA, the post allows the Fellow to develop their experience of both research and clinical aspects of MSA.

Our first Research Fellow, Dr Viorica Chelban, has worked alongside Professor Henry Houlden at UCL. She has been a key player in many research studies, including developing biomarkers in MSA and improving our understanding of genetic contributions to MSA. She is a leader on the PROSPECT-M-UK study (see below). She is an investigator on the MSA Exenatide study (see below). In addition she has contributed to the clinical care of people with MSA in the UCL service and more widely.

In April 2021, the Trustees approved funding of the second research Fellow and Dr Yee Yen Goh was appointed to work in Professor Henry Houlden's team at the Institute of Neurology, University College London. Dr Goh will be supporting and continuing the work of Dr Chelban in identifying biomarkers in MSA.

Collaboration

Support for research teams to develop our understanding of MSA is critical to achieving our objectives of identifying a cure or disease-modifying treatment for this condition. However, we understand the importance of new symptomatic treatments for disabling aspects of the condition, given the many people living with MSA. Pharmaceutical companies play a key role in developing, testing and delivering these therapies, and the MSA Trust is committed to collaboration to help this process. We also engage with academic researchers, other charities, the NHS, the NIHR, MSA Trust members and people affected by MSA. Examples of engagement include:

- The SEQUOIA and REDWOOD clinical research studies (Theravance Biopharma) are examining the effect of the drug ampreloxetine for symptoms of postural hypotension (low blood pressure on standing) in people with MSA. These symptoms could include lightheadedness, blackouts or pain in the neck and shoulders, and are often very disabling for people with MSA. Existing treatments do not always work well for this symptom and may have significant side-effects. The SEQUOIA and REDWOOD studies are double-blind placebo-controlled, which means neither the participant nor investigator are aware whether they are taking the active drug or a “dummy” placebo tablet. The effectiveness of the treatment will be compared between active and placebo treatments using a questionnaire of symptoms of postural hypotension. Participants will have the opportunity to enter longer REDWOOD study and receive the treatment long-term once the SEQUOIA study ends. The MSA Trust have supported recruitment to these studies by publishing information about the study on their website, as well as helping to raise awareness of symptoms of postural hypotension amongst people living with MSA, their carers and health professionals. They have also contributed to a sub-study, thought to be the first of it’s kind that specifically looks at carer burden when caring for a person with neurogenic orthostatic hypotension.

- The Exenatide study is a trial of a diabetes drug carried out at UCL and led by Professor Henry Houlden and Professor Tom Foltynie. Exenatide has been shown to have potential to slow down progression in people with Parkinson’s disease, and is being tested for the first time in people with MSA. The study is an open-label study in which people with MSA are randomized to receive exenatide or standard care over 48 weeks. The MSA Trust has supported this study by publicising it and providing contact details for people interested in taking part and supporting participation.

- The MSA Trust is proud to support the PROSPECT-M-UK study, which aims to establish biomarkers of progression in atypical parkinsonian syndromes, including MSA as well as progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). The study includes a *natural history* cohort, who are being followed up regularly over three or more years at seven core centres in the UK with a dedicated MSA clinical service. Participants are examined for using scores for MSA symptoms and have cognitive assessments at each visit. In addition, participants give blood samples, and a smaller number of people undergo lumbar puncture and MRI brain scans to try and identify features on these investigations that could help with diagnosis or monitoring of these conditions.
  In addition, a *cross-sectional* cohort of the PROSPECT-M-UK study involves people with MSA and other conditions donating a one-off blood sample at

hospital or their GP practice and filling in questionnaires about their condition. A new *longitudinal* cohort of the study are being followed up in similar detail to the natural history cohort, but over the course of one year.
This study aims to better characterize how conditions like MSA progress over time, and what markers may help us identify people likely to progress at different rates. These markers include clinical scores, findings on brain scans, or tests of blood or spinal fluid. PROSPECT has already led to high-profile publications in several neurology journals, including a description of the natural history cohort that included MSA patients. Further work is ongoing on the participants with MSA to determine markers associated with rates of disease progression.

In 2019 the MSA Trust undertook a needs survey of people with MSA and their carers. Findings from this survey were used to form the basis of our Information and Services strategy, in order to meet the needs of our members. We will be doing a further survey of our members in 2022 and we will ask them about research and research priorities, which will further be used to inform research priorities in future funding calls. We will also aim to form a focus group regarding research priorities and the results of this will be fed back to the Scientific advisory panel in due course.

The MSA Trust are committed to developing collaborative partnerships with other organisations involved in neurodegenerative research to increase research capacity, share resources and raise the profile of MSA. Examples of such collaborations include being non-commercial partners of the National Institute for Health Research and a member of the Association of Medical research Charities.

MSA Trust Research Policies

1. The Policies and practices of the biennial grant call and grant review are available on the website. These consist of:
    - Research Grant Process
    - The Pre-proposal application form
    - The Grant Call
    - Short biographies of SAP
    - Grant Terms and conditions
    - The Peer Review Process
    - Conflict of Interest Policy

2. Research using animals

Multiple System Atrophy Trust Statement on the use of animal tissue and/or live animals in MSA Research:

There is an urgent need for ongoing research to find the cause and hopefully a cure for the life ending disease that is multiple system atrophy (MSA). We believe the use of animals in research is essential to understanding MSA and enabling research to find a cure.

MSA trust will only fund and support research involving animals when no realistic alternatives are available and that any institution preparing to research using animals can demonstrate they comply with the rigorous laws that safeguard the welfare of animals used in research both here in the UK and across the EU. As with all funded research there must be a clear potential benefit to people with MSA.

MSA Trust's policy is to act responsibly, sensitively and in compliance with both the letter and the spirit of the law in funding any such project which may involve the use of animal tissue and/or live animals.

The Trust requires that any application for funding for a project which involves the use of animals must include review by an animal care and use committee within the host institution.

The following conditions for any such project are to apply at all times:

1. *The use of animals must be absolutely necessary.*
2. *The potential benefits to MSA patients must outweigh the cost to animals.*
3. *There must be full justification for the animal species and methods used.*
4. *There must be a clear indication of what the outcome of the research will be.*

It is recognised that there are non-animal methods, such as studies of post-mortem human tissue, computer modelling, studies of patients and populations, which may be of benefit (sometimes in conjunction with animals) and should be considered in the planning of any research project submitted to the Trust for funding.

Adopted by Trustee Board, June 2014, reviewed 2021.

As a member if the AMRC we expect researchers applying for research funding to follow the guidance set out by the AMRC with regards to use of animals in research. More information can be found at https://www.amrc.org.uk/position-statement-on-the-use-of-animals-in-research

MSA Trust also recommends researchers considering using animals in research look at the NC3Rs website for further information and guidance (www.nc3rs.org.uk).

All grant holders using animals must implement the principles in the cross-funder guidance Responsibility in the Use of Animals in Bioscience Research (www.nc3rs.org.uk/responsibility).

Grant holders using non-human primates must comply with the NC3Rs guidelines Primate Accommodation, Care and Use (www.nc3rs.org.uk/primatesguidelines).

Grant holders should make use of the ARRIVE guidelines (www.nc3rs.org.uk/ARRIVE) when designing their experiments, and ensure that they report animal-based studies in accordance with the ARRIVE guidelines as far as possible, taking into account the specific editorial policies of the journal concerned.

We ask that researchers that propose the use of animals in their work complete the additional page regarding use of animals in their work when they submit funding applications.

3. Multiple System Atrophy Trust Policy:
Stem Cell Research:

The Trustees of the Multiple System Atrophy Trust recognise that the issues surrounding embryonic stem cell research and therapeutic cloning give rise to serious ethical and moral questions. In principle, however, they are prepared to fund projects which may involve stem cell research provided it has been satisfactorily demonstrated to them that such research is legal and has both a sound scientific basis and the potential to lead to viable treatments and/or a cure for MSA.

Adopted by Trustee Board June 2014.

Background information on regulation of stem cell research in the UK

The UK has a well-established regulatory framework for stem cell research. Embryonic stem cell research is allowed subject to a licence from the Human Fertilisation and Embryology Authority (HFEA). Licences are granted only if the HFEA is satisfied that any proposed use of embryos is absolutely necessary for the purposes of the research. Licenced research can only take place on embryos created in vitro - embryos that have developed from eggs fertilised outside the body. Licensed research can only take place on embryos up to 14 days. Stem cells are isolated from the blastocyst much sooner than this – at five to six days. Embryos that are used must have been donated with appropriate consent or have been created by non-reproductive cloning.

Further details are outlined in the Human Fertilisation and Embryology Act (1990) and the subsequent Human Fertilisation and Embryology (Research Purposes) Regulations 2001.