Multiple System Atrophy Trust

Research Strategy

Feb 2025

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Contents

Foreword

Multiple system atrophy (MSA) is an incurable, rapidly progressive neurodegenerative disease of unknown cause. Over the last decades, significant advances in understanding the underlying pathophysiology and clinical course of MSA have occurred. However, symptom management in MSA remains very challenging and there is no proven way of stopping or slowing the disease progress. The diagnosis of MSA is difficult due to significant overlap in clinical features with other conditions such as Parkinson's disease and ataxia, and there is no definitive test that can prove the diagnosis.

Recent important developments in MSA have occurred and are likely to change the landscape when considering funding for research. Firstly, new clinical diagnostic criteria were published in 2022, aimed at enhancing our ability to accurately make a diagnosis, ideally earlier in the disease course. These include a category of "prodromal MSA" raising the intriguing possibility to identify the condition even earlier when it may be more susceptible to disease modification. Secondly, there has been extensive research on tests such as seed amplification assays which have promise to help determine the presence of alpha-synuclein accumulation in the brain that may help to differentiate MSA from PD. Finally, several large clinical trials for both disease modification and symptom management in MSA have taken place in recent years, demonstrating the feasibility to test new treatments in large cohorts of people living with MSA.

The MSA Trust is dedicated to funding research into the causes, potential cure and treatment of MSA. In addition, our recent strategy update proposes that we also focus on additional aspects, including developing better clinical care pathways, and understanding the mental health challenges faced by people living with MSA and those supporting them. The MSA Trust has continued to grow and increase its funding and has spent £3 million in research funding since its inception. This research strategy document builds on previous iterations, most recently in 2021, and demonstrates our responsiveness to the needs of people living with MSA. It is critical that we use the money raised for MSA research in a manner that addresses these priorities, and I am confident that we are moving in the right direction with this current version of our strategy.

I see the devastating impact on the quality of life of people living with MSA as a clinician and specialist in MSA. As an academic clinician I have been involved in large collaborative research studies and clinical trials in MSA and have received grant support from the MSA Trust. I understand the importance both of basic scientific and clinical research in meeting the objectives that we set out in this strategy document. 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 altering the course of this disease as well as mitigating the clinical impact on people living with MSA. I would also like to extend my sincere thanks to all the colleagues, professional and lay members, peer reviewers and staff of the MSA Trust who make up and support the running of the Scientific Advisory Panel, without whom we could not undertake this work.

Dr Christopher Kobylecki FRCP PhD
Consultant Neurologist and Honorary Senior Lecturer
Manchester Centre for Clinical Neurosciences, Northern Care Alliance NHS Foundation Trust, Salford, U.K.
University of Manchester, Manchester, U.K.
Trustee and Chair of Scientific Advisory Panel, MSA Trust

Our thanks are made to the following members of the wider consultation:

Dr Viorica Chelban
Dr Yee Yen Goh
Dr Joy Roach
Dr Caroline Simonet
Leah O’Brien
Research webinar members group Oct 2024 - Feb 2025
Scientific Advisory Panel members
Andy Barrick
Emma Rushton
Emma Saunders
Karen Walker
Nikki Webster

Scientific Advisory Panel

The MSA Trust is the main UK funder of research into Multiple System Atrophy (MSA). It is therefore critically important that we are funding the best research and making the best use of the donations and other funding we receive. To this end, we regularly review and revise our research grant award process and research strategy 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) currently comprising the following members:

Dr Christopher Kobylecki (Chair)
Consultant Neurologist, Manchester Centre for Clinical Neurosciences

Dr Kieren Allinson
Clinical Lead of Cambridge Brain Bank

Professor Kailash Bhatia
President-Elect of European Academy of Neurology

Nicola Blake
Lay member and co-founder of Manx MSA Trust

Professor Marios Hadjivassiliou
Consultant Neurologist, University of Sheffield and Director of the Sheffield Ataxia Centre

Professor Sir John Hardy
Chair of Molecular Biology of Neurological Disease, University College London Institute of Neurology

Dr Sean O'Riordan
Consultant Neurologist, St Vincents University Hospital, Dublin

Professor Jalesh Panicker
Head of Neuro-urolology, University College London Institute of Neurology

Ian Pickford
Lay member

John Telford
Lay member

Dr Louise Wiblin
Consultant Neurologist, University Hospitals Tees

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 experience of scientific, clinical and personal experience and knowledge in the field of MSA to determine research priorities that are pertinent to finding the cause of and cure for 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 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.
- Support in providing feedback to the MSA Community on research results, key findings and next steps.

The SAP is chaired by Dr Christopher Kobylecki, Consultant Neurologist at Manchester Centre for Clinical Neurosciences, Northern Care Alliance NHS Foundation Trust, Salford. Dr Kobylecki has experience of clinical and research aspects of MSA, running the regional service for people with MSA and other forms of atypical parkinsonism. He has published peer-reviewed papers on MSA. He has been involved in several research studies in MSA, including the ongoing PROSPECT-M-UK study.

Global MSA 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://pmc.ncbi.nlm.nih.gov/articles/PMC5772155/

Since that time there has been an increasing amount of international collaboration between researchers in MSA, other forms of synucleinopathies and neurodegenerative conditions. The MSA Trust holds a research symposium every year and selects a theme to explore and hear updates of developments in clinical support through treatments for people with MSA.

The nine topic areas from the global research roadmap have continued to influence the priorities for MSA Trust in developing their research strategy and reviewing every three years. These are included below:

- Pathogenesis
- Pre-clinical modelling
- Target development
- Phenotyping
- Clinical outcome measures
- Imaging biomarkers
- Non-imaging biomarkers
- Treatments and trials
- Patient advocacy

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

Our research priorities will be regularly reviewed and revised by SAP 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. This 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 the grant application process, outcomes and results are published on the MSA Trust website research pages and are available upon request. We ask researchers to make their research available and accessible both to the scientific community and in lay-terms. We observe all UK financial regulations regarding the processing of funds raised for research and report to the Charities Commission yearly as required.

MSA Trust Research Priorities

Previously our research funding programme has been focused on the following priority areas:

1. **Finding the cause of MSA**. The underlying cause of MSA remains unknown, although we increasingly have better knowledge of the processes underlying neurodegeneration. More understanding of the triggers and modifiers of this process will be critical to developing therapeutic targets, another key objective described below.
2. **Understanding clinical progression of MSA**. Detailed understanding of the clinical course of MSA at all stages is required to improve clinical care and develop trials of interventions to change the course of MSA. 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.
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 geographically. We want to support research that improves the experience and clinical care of people with MSA. While prevention or cure of MSA remains the ultimate goal, MSA greatly affects quality of life and understanding optimal pathways for clinical care is a high priority. We will engage with members of the MSA community to understand priorities for research in this area, as with others.

In addition to the above, our research funding programme will now also focus on the following priority areas:

4. **Disease Modification.** Research into disease modification in MSA remains critically important since there are currently no effective treatments that can alter its progression. Building on research which can unveil the underlying biological processes that drive the disease, allows further research to focus on disease modification which may identify new therapeutic targets. Such insights can pave the way for innovative approaches to treatment, moving beyond symptom management to modifying the disease itself, thereby helping those affected by the disease maintain independence for longer.
5. **Biomarker Identification.** The identification of reliable biomarkers for MSA allows for improved diagnostic accuracy in MSA and would allow for earlier detection when treatment may be most effective. Biomarkers may also provide objective measures to track disease progression and evaluate the effectiveness of new therapies in clinical trials. The recent publication of the 2022 MDS MSA Diagnostic Criteria included a "prodromal MSA" category for the first time, highlighting the importance of finding better biomarkers of this condition at a very early stage.
6. **Symptom Management.** MSA presents a range of debilitating symptoms, including autonomic and motor issues, which can severely affect daily functioning. Effective management strategies can help alleviate these symptoms, improve overall well-being, and enhance the ability to carry out everyday activities. Research focused on symptom management and control in MSA is therefore crucial because it directly impacts the quality of life of those living with MSA and their wider support network. Additionally, understanding symptom control can guide better support and treatment options for those affected by this complex disease.

7. **Mental Health and Quality of Life**. MSA profoundly affects not only physical functioning but also emotional well-being of both those affected by MSA and their families. Individuals with MSA often experience anxiety, depression, and social isolation due to the challenges posed by their symptoms. Understanding the mental health needs of MSA patients and their caregivers has the potential to develop comprehensive care approaches, integrating psychological support which can enhance coping strategies, resilience, and social connections.

Research priorities will be met by:

Funding research via our MSA Trust Grant Award programme

The MSA Trust has to date contributed £3,272,000 to research funding and continues to put out funding calls for further research. The SAP will continue to meet regularly to discuss the direction of funding priorities and specific calls for research topics. We continue to scrutinise the outcomes of our funded research and receive annual progress reports. We have already introduced clinically focused grants to ensure topics relevant to clinical care of people living with MSA are represented. The possibility of separate "small grants" for quality/care improvement projects should also be considered. We have also funded ongoing larger projects such as the PROSPECT-M-UK consortium as discussed below.

Clinical Research Training programme

We aim to develop clinicians of the future by funding MSA Research Fellowships, in partnership with the Association of British Neurologists. The first and second fellowships have been successfully completed, and a third fellowship has been recently appointed.

MSAT Research Symposium

Since 2023 we have organised an annual meeting to discuss developments in MSA research. This allows MSA-focused national and international researchers to network and discuss collaborations. It has also been a forum for recipients of research grants to present their findings, ensuring that we receive feedback on the progress of research and that researchers are able to disseminate their findings.

Follow-up Funding programme

The MSA Trust commits to funding appropriate follow-up research programmes to build on research findings and foster long-term research partnerships. It is recognised that a balanced approach is required between funding new research projects and supporting follow-up studies which ensure continuity and depth in research. The MSA Trust will therefore consider applications for follow-up funding as part of the wider grant application process. Follow-up projects will be subject to the same rigorous peer-review process as new research applications, ensuring compliance with AMRC guidelines.

PhD Funding

Nurturing academic talent and early years researchers is key to ensuring sustainability in MSA research. To this aim we will explore funding PhD programmes for applicants with suitable research ideas. Due to the recent financial pressures affecting the charity, including the increase in employer national insurance contributions, collaboration via matched funding from other organisations (e.g. charitable/academic/industry) will be essential.

Small Project Grants

Funding of up to £10,000 will be considered for clinical care projects which do not require the same large-scale grants as more academically based research projects. Small grant applications will still require a formal application and peer-review process

to ensure a high standard but will be considered separately to the usual grant application process. We will develop an application process and SAP procedure for this initiative.

Collaboration

The MSA Trust will continue to collaborate with other organisations such as the pharmaceutical industry, the academic community, other third-sector organisations, the NIHR and NHS. In addition, the MSA Trust will actively engage with the MSA community to ensure research aligns with patient and caregiver needs.

Digital Tools and Data Utilisation

There remains the potential for MSA Trust to leverage digital tools and enhance data sharing, particularly in collaboration with global initiatives such as Global Parkinson's Genetics Programme (GP2), to advance research and generate additional income. Further exploration and strategic planning are required to ensure that any data-sharing initiatives align with the organisation's mission, support MSA research and comply with UK ethics and data protection processes.

MSA Trust Research Considerations

Funding and Sustainability

Ongoing research initiatives (for example, brain banking) require sustainable funding models. The Trust recognises that some research programmes will require long-term funding strategies which are beyond the scope of the MSA Trust to fund. Sustainability in this area will need potential collaborations with pharmaceutical companies and charity partners, such as Ataxia UK and the PSP Association. We will progress these links during this research strategy period.

Outreach and Awareness

Improving signposting to research opportunities and findings through various channels, including social media, is crucial to enhance awareness and accessibility. By effectively communicating available research opportunities, academics, people living with MSA, their caregivers, and healthcare professionals can increase awareness of funding awards and opportunities participate in studies that may benefit them or contribute to the broader understanding of MSA.

Engaging with diverse audiences through social media and other platforms will help to raise awareness of MSA and its impact, fostering a supportive community. This can lead to increased participation in research, vital for generating robust data and advancing knowledge in the field.

Transparently communicating research findings can encourage further research collaboration by showcasing the relevance and importance of ongoing studies. Making research findings accessible to patients and their carers has the potential to empower patients and their families, enabling them to make informed decisions and strengthening the MSA community.

Global Diversity in Research

A diverse range of participants in research gives better results, allowing a more accurate understanding of MSA to be attained. MSA has different clinical presentations across populations because the disease can be sub-classified into two different variants, the parkinsonian variant (MSA-P) and the cerebellar variant (MSA-C). It is important that research encompasses the diversity of the MSA community, and the Trust is committed to both encouraging projects that seek diversity in recruitment and working with global partners to ensure representative samples in studies, for example by encouraging / facilitating recruitment to EXPRESS and PROSPECT-M-UK.

We are committed to encouraging high quality MSA research in institutions across the UK as well as open to funding research in other countries, ideally with a UK-based research partner.

Clinical and Practical Relevance

The Trust is committed to ensuring that the research programmes it funds remain relevant to clinical practice and that their findings can be translated into actionable outcomes for healthcare providers and patients.

MSA Trust Grant Award programme

Our current research grant awards from 2024 are addressing the key objectives set out in our research strategy as follows:

Dr Conceicao Bettencourt, UCL

Dr Bettencourt's previous research, funded by the MSA Trust, analysed brain tissue from donors with confirmed MSA and related diseases. This study found significant differences in DNA changes between MSA and healthy brain tissue, particularly affecting genes, and proteins important for oligodendrocytes, the brain cells that are primarily damaged in MSA. In this new project, the team will closely examine DNA modification (methylation) patterns in specific genes to better understand why oligodendrocytes are so vulnerable in MSA. Oligodendrocytes require a lot of energy to function properly, which depends on iron and certain fats (lipids). Iron is known to build up in the brains of people with MSA. Therefore, the researchers will also look at changes in iron and lipids in MSA brain tissue. Since some DNA changes may be reversible, identifying where these changes occur in the genome and in which cells are crucial for developing effective treatments.

Professor Jalesh Panicker, UCL

The research aims to identify signs that could indicate when someone is moving from a condition known as Pure Autonomic Failure (PAF) to MSA. Some people with PAF experience issues with their autonomic nervous system but may develop movement problems years later. About one-third of these individuals are diagnosed with MSA approximately six years after their initial diagnosis of PAF. By finding markers that can predict this transition, the researchers hope to identify individuals in the early "prodromal" phase of MSA. MSA affects various parts of the nervous system, but the lower spinal cord (specifically, the lumbosacral spinal cord) is particularly vulnerable and is linked to urinary problems in MSA. Professor Panicker's team has used pelvic neurophysiology tests to study the functions of this part of the spinal cord, revealing abnormalities in individuals with PAF. These findings suggest that damage may occur earlier than previously thought. Their collaborators have developed new biomarkers to help predict which individuals are at risk of moving from PAF to MSA. This could help with earlier diagnosis and treatment of MSA.

Professor Nigel Hoggard, **Royal Hallamshire Hospital, Sheffield**

Professor Hoggard's research is focused on energy production in the brains of MSA patients, which may provide new ways to detect the disease. Recent studies suggest that problems with the mitochondria, the energy-producing parts of cells, may occur before abnormal deposition of proteins like alpha-synuclein happen. This project aims to be the first non-invasive study that directly measures these energy issues in the brains of MSA patients using a special type of MR scan. Similar energy-production problems have been shown in patients with Parkinson's disease and motor neuron disease, indicating this as an important measure in neurodegenerative disorders and a potential marker to help with MSA diagnosis and tracking.

Dr Viorica Chelban, UCL

Our former ABN/MSAT research fellow, Dr Chelban aims to enhance understanding of the genetics and biomarkers of MSA to improve diagnosis and treatment. The project involves two workstreams; the first uses advanced techniques to detect misfolded proteins associated with MSA and to analyse other important proteins in the

body. Their goal is to create a comprehensive understanding of how MSA develops and its severity. By combining data from these tests with clinical information about patients, they hope to better track the progression of the disease. In the second part of the project, the team is conducting a large-scale genetic study involving 1,090 confirmed MSA cases and 5,000 healthy controls. They will use a method called Genome Wide Association Study (GWAS) to identify genetic factors that may increase the risk of developing MSA, influence its severity, and affect how long patients may live with the condition. The aim is to use these genetic insights to help develop new treatments. Research indicates that when drug mechanisms are supported by genetic evidence, their chances of success improve significantly.

Assistant Professor Maria Xilouri, University of Athens, Greece

Professor Xilouri follows up on earlier work funded by an earlier MSAT grant focusing on the role of a specific cellular process in MSA. MSA is marked by the buildup of a protein called alpha-synuclein in certain brain cells known as oligodendrocytes. These cells are crucial because they support and insulate nerve fibres by creating a protective layer called myelin. When alpha-synuclein and another protein called TPPP/p25α accumulate, it can lead to damage in these cells. One way the body normally clears out damaged proteins is through a process called the Autophagy-Lysosomal Pathway (ALP), which helps break down misfolded proteins and other cellular debris. In this project, the researchers will look at blood samples from MSA patients and healthy individuals to see if there are differences in the ALP process. They will analyse specific types of cells and small particles in the blood that are linked to brain activity. Preliminary findings suggest that changes related to the ALP might be detectable not only in the brain but also in the bloodstream of MSA patients. Better characterisation of such changes has the potential to identify potential targets for drug therapies in MSA.

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 believes that supporting the development of the next generation of clinician scientists in this area is critical to the success of research in MSA.

To this end 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 causes, prevention and treatment of MSA. Typically working alongside experienced clinical and research mentors with a 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, recruited in 2017, has worked alongside Professor Henry Houlden at University College London. 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 and an investigator on the MSA Exenatide study. In addition, Viorica works with the MSA Trust to host our Annual MSA Research Symposium, in collaboration with Queen Square Institute of Neurology, UCL, which brings MSA researchers from all over the world together to present their findings and facilitate networking and collaboration for future projects.

Our second Research Fellow Dr Yee Yen-Goh, recruited in 2021, earned her MRCP in Medicine from the Joint Royal Colleges of Physicians Training Board in 2014. She holds an MBBS with Distinction (2011) and a First-Class Honours BSc in Clinical Sciences (2009), both from University College London. Dr Goh has contributed to research in visuospatial attentional systems in hepatic encephalopathy and pre-surgical imaging in mesial temporal lobe epilepsy. Her work under the fellowship focuses on four key abnormal pathways to investigate biomarkers in MSA blood/cerebrospinal fluid, urine and skin. These markers are correlated with clinical features and investigations to identify biomarkers of MSA diagnosis, progression and prognosis.

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. We also understand the importance of new symptomatic treatments for disabling aspects of the condition. 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. Whilst MSA Trust will not generally solely fund pharmaceutical research, it may explore applying to pharmaceutical companies to support our own research funding.

In addition, we recognise there is a need to broaden our collaboration outside of academia and pharmaceutical companies to include NIHR, the NHS, Government, expert patient groups and associated charities (nationally and internationally). Building a broader research community, through symposiums and workshops is essential to foster partnerships and enhance the research landscape.

The MSA Trust is 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.

Update on clinical trials 2024-25

The **CYPRESS trial** (Theravance Biopharma) is a clinical trial 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 CYPRESS trial builds on results from the SEQUOIA study, which was carried out in patients with MSA, Parkinson's disease and other causes of postural hypotension and was also endorsed by the MSA Trust. While the SEQUOIA study overall did not show a benefit of the drug, when only people with MSA were analysed, it showed a benefit, justifying a further trial. The CYPRESS trial is a phase III trial involving an open-label phase, where all participants take ampreloxetine, followed by a double-blind placebo-controlled phase, 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 about symptoms of postural hypotension. Participants will have the opportunity to enter a longer term follow up study receiving the medication for 2 years once the initial phase ends. The MSA Trust have supported recruitment to this study by publishing information about the study on their website, sending email communications to its MSA community as well as helping to raise awareness of symptoms of postural hypotension amongst people living with MSA, their caregivers and health professionals.

The **HORIZON trial** is an early-stage Phase I trial being run by Ionis pharmaceuticals. The trial is testing the safety and effects on markers of MSA of genetic therapy to silence expression of alpha-synuclein, the gene for the protein that builds up in glial cytoplasmic inclusions causing neurodegeneration in MSA. The trial involves administration of the drug or placebo into the spinal fluid by lumbar puncture. The MSA Trust has supported the trial by publicizing it and directing potential participants towards information on where they can take part locally. Recruitment to the HORIZON trial is almost complete.

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 randomised 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 results of the study are currently being analysed.

The **ATH434 study** is a recently completed phase II trial run by Alterity Therapeutics examining the effect of a drug aiming to reduce iron deposition in the brain, a mechanism which is thought to underly some of the neurodegenerative changes seen in MSA. The study recruited globally and several centres in the UK were involved in recruitment. The results of the study have been recently announced and showed a potential effect on clinical and imaging measures of MSA.

The MSA Trust is pleased to support the **MASCOT study** by supporting colleagues involved in clinical elements of the phase III trial. MASCOT, run by Lundbeck examines the effect of a human monoclonal antibody, amlenetug which is designed to target and bind to extracellular α-synuclein, aiming to prevent its uptake and block aggregation seeding. The randomised, interventional, double-blind, placebo-controlled, parallel-group, optional open-label extension trial will be conducted in Europe, North America and Asia.

The MSA Trust continues its support of the **PROSPECT-M-UK study**, (funded until 2028 - £77k per annum). PROSPECT-M-UK 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 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 is being followed up in similar detail to the natural history cohort, but over the course of one year.

This study aims to better characterise 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-M-UK 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.

Building on the success of the PROSPECT-M-UK study, the MSA Trust is pleased to support the **ExPRESS study** which is commencing across multiple sites currently. ExPRESS aims to improve the early diagnosis of conditions like MSA, the accuracy of both diagnosis and prognosis and to increase the identification of rare Parkinsonian conditions.

With the help of the ExPRESS network, at least 500 patients with parkinsonism will be recruited between 2023 and 2028. Participants and their consultants will be asked to complete a short online questionnaire each about the nature of the patient's symptoms. The questionnaires will be repeated at regular intervals up to 36 months after referral from their GP. Participants will also be asked to donate a blood sample for DNA. Participants with a diagnosis of a rare Parkinson's Plus syndrome will have the option to take part in a face-to-face neurological assessment and have blood, cerebrospinal fluid (CSF) and skin biopsy samples collected. We will build a biobank of samples and data which will be used for improving diagnosis and increasing our understanding of disease biology.

Member Involvement

In 2022 the MSA Trust undertook its second needs survey of people with MSA and their carers, building on the results of the first needs survey in 2019. Findings from this survey were used to form the basis of our organisational strategy, to meet the needs of our members. Further needs surveys of our members will be considered and will continue to ask about research and research priorities, which will further be used to inform research priorities in future funding calls.

The importance of Patient and Public Involvement and Engagement (PPIE) in research design and execution is recognised by the Trust, and we shall seek to form a formal PPIE group to provide input on research proposals, improve MSA community engagement and ensuring diverse representation in studies is considered. In addition, we shall explore developing a service that provides PPIE services to external companies / pharmaceutical companies / research academics.

Research Related 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 2025.

As a member of the AMRC we fund high quality and ethical research involving animals only where no alternative is available, in alignment with the AMRC's guiding principles of animals in research. As a funder of research, the MSA Trust considers the 3Rs in our grant application form and guidance for applicants, the assessment process and guidance for reviewers as well as in our grant terms and conditions. More information on the guidance followed can be found here.

We expect researchers applying for research funding to follow the guidance set out by the AMRC with regards to the use of animals in research.

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