INTERNATIONAL
PROGRESSIVE MS ALLIANCE

More than hope. Progress.

Achieving Improved Well-being in Progressive MS Through a Funding Pipeline

REQUEST FOR APPLICATIONS

The International Progressive MS Alliance is pleased to announce a new funding initiative designed to accelerate the development of behavioral therapeutic interventions for progressive multiple sclerosis (MS) through innovation and collaboration.

WHAT IS THE ALLIANCE?

The International Progressive MS Alliance (The Alliance) is an unprecedented global collaboration of MS organizations, researchers, healthcare professionals, the pharmaceutical industry, companies, trusts, foundations, donors, and people affected by progressive MS, working together to address the unmet needs of people with progressive MS. Our promise is more than hope, it is progress. Learn more about the Alliance at www.progressivemsalliance.org.

GAP

Progressive MS is a major cause of chronic neurological disability in adults, with a significant progressive long-term disability burden. The clinical consequences of progressive MS are varied and include weakness, cognitive impairment, fatigue, and pain. The impact of these symptoms is far-reaching and can include job loss, stress to family, and financial strain. Current disease-modifying therapies (DMTs) offer limited benefit in progressive MS. Rehabilitation is the primary treatment available to address symptoms, treat disability and improve well-being for people with progressive MS. However, there are few rehabilitation studies that focus on people with progressive MS.

The recent Alliance paper (Prioritizing progressive MS rehabilitation research: A call from the International Progressive MS Alliance, Multiple Sclerosis Journal 2021 Jun;27(7): 989-1001) identified and highlighted 4 symptom areas important to people with MS. The paper recommended the design and implementation of high-quality studies focused on symptom management and rehabilitation.

OVERALL GOALS FOR THIS REQUEST FOR APPLICATIONS (RFA)

The Alliance has identified a number of key areas of significant unmet need that should be addressed to improve the well-being of people living with progressive MS (Charting a global research strategy for progressive MS-An international progressive MS Alliance proposal, Multiple Sclerosis Journal 2022 Jan; 28(1):16-28).

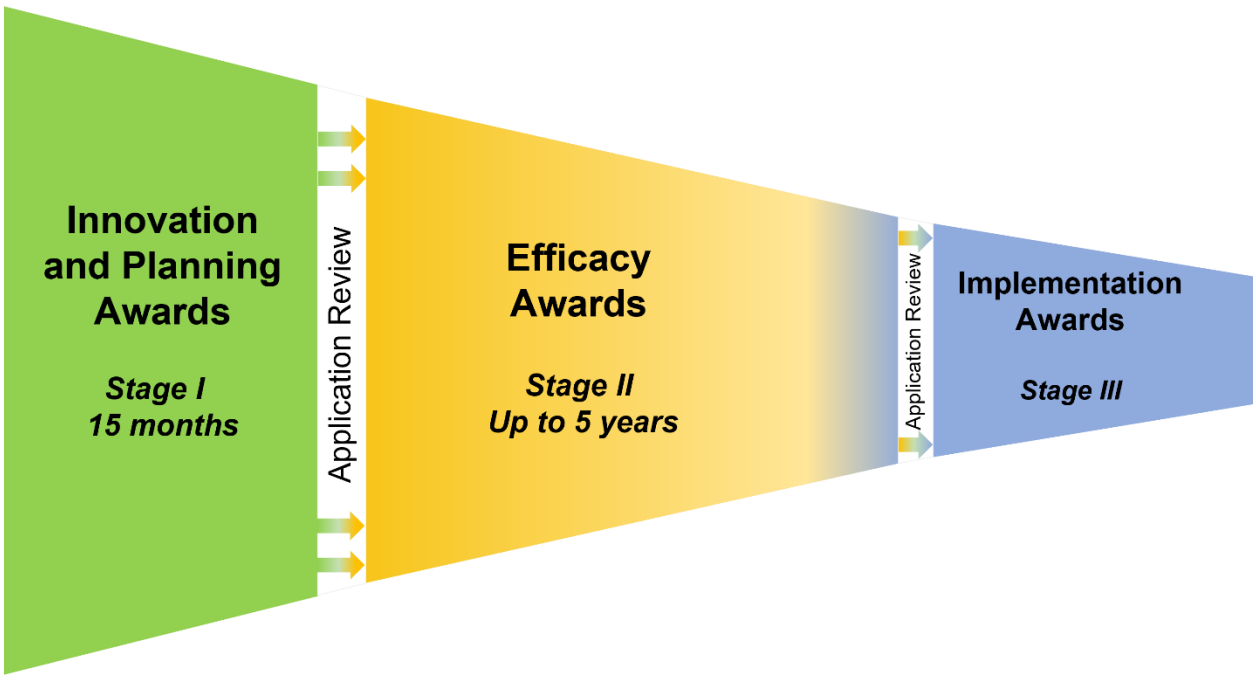
The intent of this RFA is to solicit innovative proposals to feed a pipeline of research for improving the evaluation and implementation of symptomatic treatment and rehabilitation using measurable outcomes so as to improve well-being for people with progressive MS.

Rehabilitation significantly improves people's health and well-being with MS. Rehabilitation aims to optimize physical, cognitive and emotional function, and quality of life, incorporating preventive, restorative, compensatory, and maintenance approaches.

Effective rehabilitation for people with progressive MS faces many challenges – specifically, (1) rehabilitation is complex and requires appropriate expertise for intervention delivery as well as persistent effort from the person receiving the intervention, (2) responsive and real-world outcome measures are needed to quantify change over short time spans, and (3) studies of rehabilitation must be carefully designed taking into account participant's age, ethnicity, ability level, symptoms and type of MS. Finally, advances in technology such as wearable technology and computer applications offer the opportunity to capture measurable changes in real-world function, and can be incorporated into project design; however, they require careful methodological study.

A continued challenge is the lack of understanding of how to optimize rehabilitation approaches. This stems from a lack of methodologically robust studies and limited high-quality evidence for rehabilitation approaches in people with progressive MS. The weight of evidence supporting symptom management comes from small pilot studies with insufficient power to measure changes in rehabilitative clinical care and limited effectiveness in improving a person's well-being. This in turn limits access to and implementation of such therapies. What is needed is a well-funded pipeline to create opportunities in the field to test strategies, the usefulness of outcome measures and support of clinical trials, and the implementation of that work for people with progressive MS (see Research Pipeline graphic). The **first stage** in the pipeline provides funding to create a team with sufficient expertise in clinical trial design, methodology, and implementation to develop necessary preliminary data, as well as to develop a strong conceptual and methodological framework including identification of valid, reliable, and responsive outcome measures. In this stage we invite exploration of innovative study designs (e.g., mixed hybrid design) in planning for the efficacy study. The **second stage** in the pipeline will focus on efficacy studies supporting the testing of specific intervention strategies and/or outcome measures, and projects that begin looking at implementation will also be considered. **The final stage** in the pipeline will be focused on implementing what was learned from the efficacy work into clinical practice. A plan for how and where people with progressive MS could expect to benefit from the efficacy work will be an essential element in this final stage.

Research Pipeline



GOAL

This RFA is the first stage of a research pipeline that will ultimately test innovative outcomes or treatments focused on the well-being of people living with progressive MS. This RFA is a planning grant that provides time and resources to develop ideas, construct your research team, and collect preliminary data (if needed) to ultimately develop and present an efficacy research proposal. At the end of this 15-month award, the deliverable will be a proposal for up to a 5 year efficacy trial (stage 2 of this research pipeline) focused on progressive MS. Proposals from this first stage RFA will deliver a team and project plan to test efficacy on one of two potential pathways – 1) to study innovative symptomatic treatments using valid, reliable, culturally sensitive and responsive behavioral outcome measures; OR 2) to develop innovative outcome measures to better quantify the impact of interventions to improve the well-being of people with progressive MS. The research team should include sufficient expertise in clinical trial design, methodology and implementation, and the plan should include a strong conceptual and methodological framework. Proposals should be focused on at least one of the four symptom areas of fatigue, mobility and/or upper extremity impairment, pain, or cognitive impairment.

Successful applications for stage 1 will demonstrate a strong expert team that offers the expertise for developing novel therapeutic interventions or outcomes for progressive MS that may synergize with other relevant initiatives. Further, these projects should have the potential to culminate with a large randomized controlled study ultimately suitable for implementation into local healthcare systems around the world. Preliminary data supporting the proposals are encouraged but not required.

Proposals should aim to achieve one of the following goals:

1. Discovery, advancement, and validation of new or existing behavioral outcome measures.
    a. Expected impact – development of a meaningful outcome measure that could be integrated into early clinical development within the Efficacy Award period.
    b. These include but are not limited to:
        i. Patient-reported outcomes
        ii. Clinician-assessed outcomes
        iii. Biomarkers (e.g., imaging markers)
        iv. Performance-based measures
        v. Use of novel technologies such as wearable technology, computer applications, etc.
2. Advancement of effective symptomatic treatments that offer real-world benefits to improve the well-being of people with progressive MS.
    a. Expected impact – Development of an intervention that results in a meaningful change in function.
    b. These include but are not limited to:
        i. Exercise

ii. Cognitive rehabilitation

iii. Mindfulness based therapies

iv. Use of novel technologies such as brain stimulation, instrumented treadmills, etc.

This RFA is not intended to solicit the typical investigator-initiated research grant; rather, it is designed to develop a pipeline of research that provides the necessary groundwork to prepare for clinical trials to achieve meaningful outcomes that include, but are not limited to, the reduction of fatigue, better management of pain, improved real-world walking or cognitive capacity in people with progressive MS.

Proposals focused on fundamental biomedical science without evaluating clinically meaningful improvements, or well-established interventions without innovation (e.g., general exercise without a novel goal) are out of scope for this RFA and will not be considered.

ELIGIBILITY

Proposed networks must have an organizational structure to foster and conduct integrated research activities and promote data sharing and knowledge exchange in the key areas outlined in this RFA. Eligible personnel and organizations include: (1) public research institutions, (2) non-profit research organizations, (3) commercial organizations with a medical research focus and mission.

Investigators leading the network must have demonstrated track records of directing outstanding research programs. At least 50% effort of the partnership is required to be performed in an academic or not-for-profit research organization.

Submitted proposals are required to fulfill the following criteria:

1. Network Structure:
    a. Each network must consist of researchers with expertise in clinical trial design, methodology, and implementation of behavioral interventions, with an awareness of global applicability. Forming a network should add demonstrable value to the project.
    b. A single public institution or non-profit research organization will be the official recipient of the grant. Sub-awardees may be public institutions, non-profit research organizations or commercial organizations. Organizations may be located in any eligible country.
        i. Please note that the Alliance is unable to provide funding to countries currently subject to United States Department of State sanctions, United Nations Security Council sanctions or any sanctions in place by Alliance member countries.
    c. Eligible organizations include public research institutions, non-profit research organizations, and commercial organizations (e.g., pharmaceutical or biotechnology companies, and contract research organizations) with a medical research focus and mission.
    d. Proposals that include commercial organizations must incorporate cross-sector collaboration (e.g., academic-industry collaboration) as part of the research plan.

At least 50% effort of the partnership must be performed in a public (e.g., academic) institution or non-profit research organization and all funds will flow through the academic/non-profit organizations (with sub-awards to other investigators in the network). Commercial organizations (e.g., pharmaceutical and biotechnology companies) with a medical research focus and mission are invited to participate in this RFA and bring their particular skills and capabilities in drug discovery and development to bear on the Alliance goals. The Alliance also appreciates willingness to co-fund important projects.

2. Research Team

    a. A single principal investigator (PI) located at a public institution or non-profit research organization must be identified as the overall leader for the entire project and the award must be administered at the organization where the PI is employed. It is expected that the person designated as the PI for this funding program is a scientist focused on clinical or rehabilitation research and is considered eligible by his or her institution to apply for a research grant.

    b. In addition to the PI, a research team consisting of no less than 2 collaborating investigators responsible for the direction of individual elements of the overall research program within the partnership should be identified. These investigators can be named from a commercial organization and/or public or non-profit organizations. The PI and collaborating investigators should be established scientists and/or clinicians with demonstrated leadership and research management experience.

        i. The Alliance encourages applicants to recruit sufficient collaborating investigators to ensure confidence that the multi-disciplinary research goals of the RFA will be achieved. The inclusion of young investigators is also encouraged.

    c. The research team should consist of research investigators with demonstrated track records in outcome development or intervention development, clinical trial design, trial methodology and implementation of behavioral interventions. There are no specific requirements regarding the number of investigators involved, but the partnership should have an adequate representation to ensure credibility for the development of outcomes or interventions, including clinical trial methodology and implementation elements of the proposal.

Important Note – The Alliance offers to act as a facilitator to enable multidisciplinary networks (public - private- non-profit) at an international level and to discuss issues (e.g., questions related to IP) that may arise during the preparation of innovation and planning award applications.

PROPOSAL SUBMISSION

The first stage consists of a proposal for a 15-month Innovation and Planning Award. Investigators receiving an Innovation and Planning Award will be expected to apply for and submit a full proposal for consideration for a multi-year Efficacy Award (i.e., the deliverable of the planning award is a full proposal for the Efficacy Award). Efficacy awards will only be available to teams that have received an Implementation and Planning Award.

First Stage – Innovation and Planning Awards:

1. The objectives of the **Innovation and Planning** Award are to:
    a. Support the formation and planning activities of the newly-configured investigative teams
    b. Provide start-up funds to collect necessary preliminary data and produce a research proposal for the full Efficacy Award competition
2. Planning activities include:
    a. Assembling the multidisciplinary investigative team, including in-person planning sessions
    b. Fully developing a research proposal focused on outcome measures or behavioral interventions in progressive MS
    c. Identifying novel approaches/disciplines to address knowledge gaps.
    d. Developing a clinical trial plan (e.g., resources and competencies; timeline and deliverables)

3. Proposals (5 pages maximum) for the Innovation and Planning Awards should include:
    a. Aims and deliverables (1 page)
    b. Overview of the Multidisciplinary Research Team and Proposal
        i. Description of and a brief rationale for the organizational structure and mechanisms in place to foster integrated research activities that address one of the key objectives outlined in this RFA (1 page)
        ii. Brief rationale and description of the future efficacy research proposal, including a brief outline of the research proposed, key aims, timeline and deliverables (1 page)
    c. Planning Activities and Timeline of the Innovation and Planning Award (1 page)
        i. The deadline for submission of the full Efficacy Award proposal will be fifteen months from the start of the Planning Award (see timeline below)
    d. Summary – Briefly describe how the proposed project meets the eligibility criteria, addresses at least one of the research priorities and aligns with the expected impact outlined in the RFA (1 page)
    e. Biosketches - Brief 3-4 page biosketches of the PI and key collaborating investigators must be included (NIH format is acceptable). The PI should also include a list of team members, research team structure, and anticipated roles of individual members
    f. Budget – full budget information for the planning activities will be required in the online application

The Alliance will use the National MS Society's online application interface for this RFA. All applications must be submitted in English. Only one investigator should apply per team and this person must first register with the online application site (https://nmss.fluxx.io).

PLANNING AWARD REVIEW

Full applications will be reviewed by a panel of subject matter experts convened by the Alliance, which will include people affected by progressive MS. Proposals will also be reviewed by the Alliance Scientific Steering Committee (SSC) and applicants may be invited to present their proposal to the SSC by conference call as part of the review process.

Note well – In addition to scientific review, the proposal will be evaluated by members of the MS community affected by progressive MS, selected for their personal experience or knowledge of MS. Their input will be combined with the assessments of professional scientific reviewers. Because of this review process, it is important that the plain language summary be relevant, accurate and intelligible to that audience and consistent with rest of the technical content of the proposal. It is recommended that applicants test their plain language summary with a knowledgeable member of the public, or more directly, with people who have progressive MS. As appropriate, we suggest involving members of the MS community in the preparation of the proposal and demonstrating how this input impacted the application. Finally, it is important that the plain language summary and the main proposal are consistent with regards to the objectives of the program and its benefit for the MS community. The community input will be part of the overall project score.

The following criteria will be used by external peer reviewers and the SSC to evaluate applications:

Significance and Relevance — The impact and importance of the long-term endeavor

- Originality, significance and expected contribution to gaps in knowledge and improving well-being in progressive MS
- The degree to which a barrier to treatment will be eliminated or outcome development will be enabled by this application
- Appropriateness of the theoretical approach or conceptual framework
- Appropriateness of the methods/approach (including the creation of knowledge)

Feasibility and Capability — The plan to achieve excellence

- Integration of People with progressive MS regarding the design and implementation of project
- Quality of the team structure and the organizational structure of the team, including involvement of collaborators and others in the design and conduct of the planning activities
- Clarity of the value (skills and resources) that each team member will bring to the aims of the research
- Quality, quantity and significance of past experience including published and/or creative outputs of the applicant and/or team members relative to their roles in the team and to their respective stages of career
- Strategies and timelines for the design and conduct of the activity/activities proposed
- Consideration for implementation into local healthcare systems around the world
- Experience in large scale clinical trial activities
- Probability of effective and timely attainment of research objectives for efficacy proposal

KEY DATES:

Milestone	Date
RFA release date	15 March 2023
Informational call for applicants	TBD
Pre-Application due	1 May 2023
Planning Award Application due	15 May 2023
Notification of funding decisions	November 2023
Public announcement of awards	November 2023
Anticipated start date of Planning funding*	January 2024
Efficacy proposal submission	March 2025

**This will be the earliest possible date for funding. Release of funds will be contingent on successful execution of research agreements between the institutions and the Alliance. Thus, funding dates may be later if considerable negotiation is required between the partners.*

Second Stage – Efficacy Awards: General guidance is provided below and final instructions will be provided 3-4 months before final efficacy proposals are due.

Recipients of Innovation and Planning Awards will be expected to submit their fully developed efficacy proposals approximately fifteen months from the start of their Planning Award. Efficacy proposal applications will include:

Plain Language Summary

Complete the fields in the online application asking for a plain language summary that describes the proposed research in language suitable for people without a scientific background who will be providing feedback on the proposal.

Scientific Summary

The scientific summary should capture the rationale, methods and potential significance of the proposed research in one or two paragraphs.

Research Plan (estimated 20 pages maximum)

Proposals will be expected to state the mission, vision, goals, and distinguishing features of the network that will ensure the likelihood of achievement of the RFA objectives. A clear and compelling research plan, for a funding period of up to five years, should be presented.

The research plan should adequately describe and be accompanied by specific milestones and a timetable for reaching them. Investigators responsible for execution of specific research components (i.e., division of labor) should also be clearly identified. Proposals should describe comprehensive communication and information-sharing plans within the team.

Clinical Translation – successful proposals will articulate how therapy development will be enabled by this application and provide a clear and viable path toward clinical applications (including a timeline and milestones) and will also consider additional funds that might be required, and the potential avenues for seeking additional funds, to fully develop proposed therapies.

Institutional Commitment – Applicant institutions/organizations should demonstrate strong departmental and institutional commitment which might include allocation of space, staff, cost-sharing, matching funds and other mechanisms of institutional support.

Budget

Applicants should be prepared to submit a detailed justified budget for each year. This information will be part of the online application and will not count against the 20-page narrative limit. Investigators may request funds in the following categories: salaries for personnel, patient costs, consumable supplies, inter-laboratory travel and other allowable expenses. For the Efficacy Awards, the Alliance will support research costs that have been fully justified in the application and not normally paid for by the host institution. The Alliance will not provide funds for indirect cost recovery. The Alliance recognizes that in some cases certain administrative costs associated with an Alliance-funded program will not be borne by the institution. In such cases applicants will be permitted to allocate Alliance funds to defray these expenses, provided that the applicant and host institution certify that these funds are required for execution of the project and that institutional or other funds are not available to cover these costs. These costs should be listed on the “Other Expenses” line item of the application.

Biographical Sketches

Brief 3-4 page biosketches of the PI and key collaborating investigators must be included (NIH format is acceptable). The PI should also include a list of team members, research team structure, and anticipated roles of individual members.

Letters of Collaboration

Applicants may submit letters of collaboration that are directly relevant to the proposal.

EFFICACY AWARD FULL PROPOSAL REVIEW

The review will be conducted by a scientific review committee convened by the Alliance. The review committee will be international, multidisciplinary and with expertise in the areas of research focus. Applicants will be required to present their proposal to the review committee and may be asked to engage in a dialog with the review committee regarding the specifics of their proposals.

The review criteria for the full application include:

1. Adherence to the specific scientific objectives of the RFA and alignment and relevance to the mission and goals of the Alliance. In particular, weight will be given to the teams which can demonstrate how their work will develop an outcome or an innovative intervention addressing at least one of the target symptoms in people with progressive MS.
2. Relevance of organizations’ and researchers’ contributions to address knowledge gaps in progressive MS.
3. Scientific critique of the proposed work plan and resources requested:
    a. Scientific merit, rigor, innovation and potential – these criteria will be the yardstick by which all proposals will be measured
    b. Are the funds requested essential for the work, and do the importance and scientific potential justify funding on the scale requested?
4. Proximity to clinical translation and treatment development

5. Potential for greatest long-term impact
6. Expertise and excellence of the investigators and organizations
7. Appropriateness of the resources and environment

Review panels will include members of the SSC and external expert reviewers. Recommendations from the panels will be considered by the SSC and final funding authorization will be provided by the Alliance Executive Committee. The Alliance will initiate negotiations on a sponsored research agreement with the teams that are selected.

CONDITIONS OF THE EFFICACY AWARDS

The Alliance will support projects with a maximum budget of €3 million with a maximum term of 5 years. Awards will be paid in regular installments and continued payments will be based upon achievement of specific milestones outlined in the proposal, detailed progress reports approved by oversight committees, and on the availability of funds. Teams will be required to provide research progress reports to the Alliance on a quarterly basis and financial reports every 6 months.

The PI and/or team members will be required to present research progress at Alliance scientific meetings. In addition, the leaders within the team will meet with the Alliance Scientific Steering Committee to review progress and receive feedback on an annual basis.

A final written report of the work accomplished and an accounting of expenditures will be required within 90 days after the project ends. The grantee organizations will also be required to comply with the Alliance's invention policy and other Alliance policies and procedures.

IMPLEMENTATION AWARDS

Information and details for stage 3 Implementation Awards will be developed as these awards progress.

CONTACT INFORMATION

ITALIAN MS SOCIETY	Gabriele Dati, Ph.D. Biomedical Research and Grant Office Coordinator Email: Gabriele.Dati@aism.it Tel: +39 010 271 3259
MULTIPLE SCLEROSIS INTERNATIONAL FEDERATION	Anne Helme, Ph.D. Head of Research and Access Email: anne@msif.org Tel: +44 (0) 20 7620 1911
MS SOCIETY OF CANADA	Pamela Kanellis, Ph.D. Assistant Vice-President, Research Managing Director, endMS Research and Training Network Email: Pamela.Kanellis@mscanada.ca Tel: +1 416-967-3024
MS SOCIETY, UNITED KINGDOM	Emma Gray, Ph.D. Executive Director of Research Email: Emma.Gray@mssociety.org.uk Tel: +44 (0) 20 8827 0220
NATIONAL MULTIPLE SCLEROSIS SOCIETY USA	Douglas Landsman, Ph.D. Vice President, Research Email: Douglas.Landsman@nmss.org Tel: +1 212.476.0536
MS RESEARCH AUSTRALIA	Julia Morahan, Ph.D. Head of Research Tel: +61 02 8413 7921 Email: jmorahan@msra.org.au