

INTERNATIONAL PROGRESSIVE MS ALLIANCE

More than hope. **Progress.**

REQUEST FOR APPLICATIONS: EXPERIMENTAL MEDICINE TRIALS

The International Progressive MS Alliance (Alliance) is pleased to announce a new funding program focused on innovative clinical trials in progressive MS – the Experimental Medicine Trials Initiative. The Alliance expects this new program will advance our knowledge of disease pathophysiology and expedite the development of therapies for people with progressive MS.

WHAT IS THE ALLIANCE?

The International Progressive MS Alliance is a global collaboration of MS organizations, researchers, healthcare professionals, the pharmaceutical industry, 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.

OVERALL GOALS FOR THIS REQUEST FOR APPLICATIONS (RFA)

In 2021, an Alliance publication (Facing the urgency of therapies for progressive MS – a Progressive MS Alliance proposal, [Nature Reviews Neurology 2021 Jun;17:185-192](#)) laid out the vision and rationale for this program.

Therapies for infiltrative inflammation in MS have advanced greatly, but neurodegeneration and compartmentalized inflammation remain virtually untargeted as in other diseases of the nervous system. Consequently, many therapies are available for the relapsing–remitting form of MS but progressive forms remain essentially untreated. The Alliance aims to expedite the development of effective therapies for progressive MS through new initiatives that foster innovative thinking and concrete advancements. Based on these principles, this new initiative focuses on Experimental Medicine Trials with the hope of providing advances in a relatively short period of time.

The Alliance defines Experimental Medicine Trials as early clinical trials that explore treatments and targets while also generating hypotheses about disease mechanisms through a coherent pool of biological, clinical, and performance-based measures. These trials should be informative even in the event of a negative outcome and may be a continuation of, or complement to, drug screening processes. There is a growing urgency in the drug discovery field to understand the causal biology behind MS progression, i.e., how various molecular, cellular, and physiological processes interact and contribute to the development and progression of MS pathology, and how interventions affect that biology. The Alliance believes that this urgency, paired with advancements in trial design and execution, provides a compelling opportunity for refocusing early-phase trials from tests of efficacy to innovative studies of disease mechanisms.

To this end, the goal of this funding initiative is to support innovative Experimental Medicine Trials that advance our knowledge of disease pathophysiology by defining the underlying mechanisms of an intervention, mechanisms of progressive MS pathogenesis, and/or harmonizing outcome measures that correlate with clinical efficacy for any given intervention. In the interest of balancing innovation and comparability, the Alliance is interested in supporting Trials that include one or more of the following aspects:

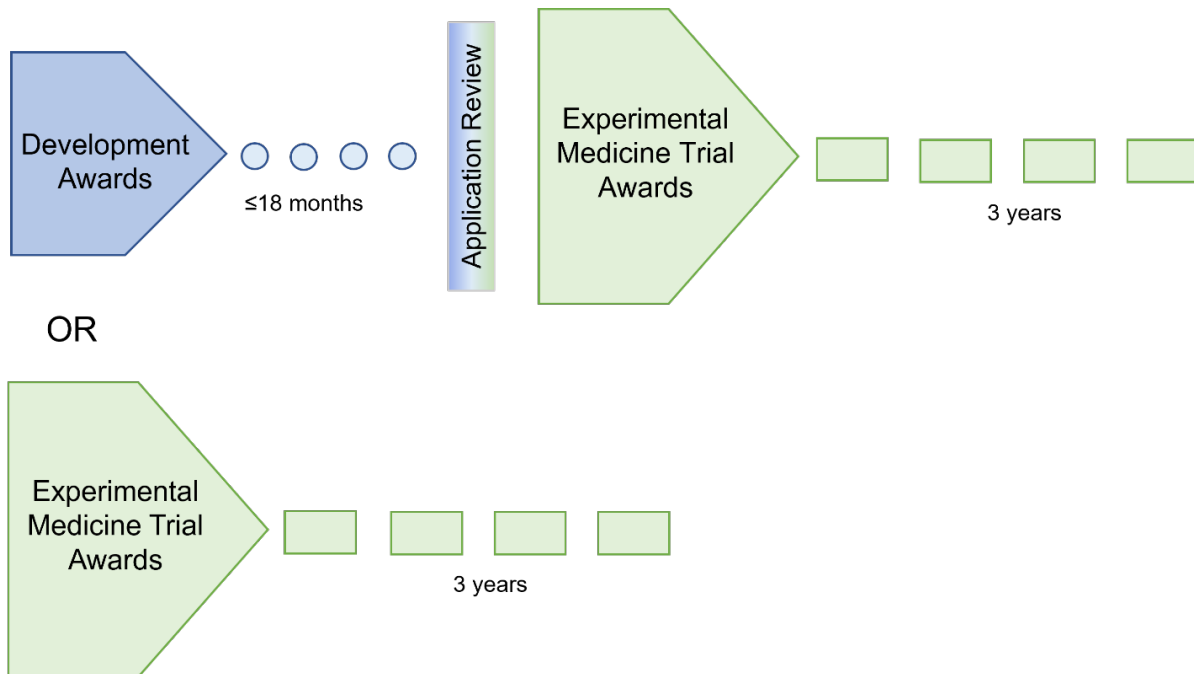
- Use of polytherapies (e.g., factorial trials, partial factorial clinical trials)

- Background of immunosuppression (evaluation of new drugs in combination with modern immunosuppressive therapy)
- Broad inclusion criteria and methodology (e.g., EDSS, comorbidities, age)
- Novel/alternative clinical trial designs (e.g., adaptive, enrichment, crossover designs, etc.)

All proposed Experimental Medicine Trials must be developed and informed by perspectives of people affected by MS, including trial design and key outcomes.

DETAILS:

In summary, the Alliance will offer an initial funding opportunity to support small Development Awards (e.g., validation studies, consensus efforts, etc.) that will result in a subsequent opportunity to apply for an Experimental Medicine Trial award. The Alliance will also accept applications for Trials that do not require Development Award support (that is, submit for full Experimental Medicine Trial support now).



Note: Funds are available to support both application pathways, and applicants should use the application pathway that best fits their project.

Once applications have been received, if the Alliance identifies potential synergies between proposals, if appropriate, we will consider working with groups to discuss potential collaborative opportunities.

Development Awards

Proposals for planning, developmental efforts and validation opportunities that support future Experimental Medicine Trials are requested. The Alliance welcomes innovative approaches to

answering this RFA that may leverage other studies or initiatives, including mining existing repositories, and will consider supporting the following:

1. Study design, conduct, and analysis (e.g., multi-site implementation studies, statistical methodology studies)
2. Studies related to therapeutic targets (e.g., futility trials, demonstrating target engagement, tethering target function to MS pathogenesis)
3. Studies at the intersection of pathophysiology and therapeutic mechanisms of action
4. Consensus development related to clinical trials in progressive MS

Maximum requests for Development Awards cannot exceed €100,000 total and efforts must be completed within 18 months. Following completion of a Development Award, the final deliverable will either be 1) a proposal for an Experimental Medicine Trial focused on progressive MS that builds on and applies the work outlined in the Development Award, or 2) documentation for why an Experimental Medicine Trial is not warranted (e.g., investigators learned that the mechanistic pathway is incorrect, findings are too weak and not clinically relevant, etc.).

Experimental Medicine Trials

The Alliance will also accept applications for Experimental Medicine Trials from teams that do not require Development Award support. Applicants should propose studies that aim to advance our knowledge of disease pathophysiology and expedite the development of therapies for progressive MS for more effective intervention(s).

A maximum budget of €1.5 million may be requested and the project should take no longer than 36 months to complete. Alternatives to early clinical trials that meet the goals of this RFA will also be considered, e.g., using components/cohorts in existing trials and studies or registries that can “simulate” trial conditions with outputs providing information on treatments and disease mechanisms. This consideration is based on the acknowledgment that infrastructure for trials is costly, and the Alliance seeks novel ways to speed up and improve clinical trials, driving therapies forward for progressive MS.

Proposals for Experimental Medicine Trials should provide mechanistic insights that advance our understanding of disease pathophysiology.

TIMELINE

Milestone	Date
RFA opens	15 January 2024
Informational calls	31 January 2024 at 11a EST or 5p EST
Pre-application deadline	15 March 2024
Full application deadline	29 March 2024
Notification of funding decisions	December 2024
Anticipated start date of funding*	February 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.*

ELIGIBILITY

A single 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. Unless otherwise discussed with the Alliance, the PI must be a scientist focused on basic, clinical, or epidemiological research who is considered eligible by his or her institution to apply for a research grant. Projects that include investigators from multiple institutions and organizations are strongly encouraged.

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. 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.

Commercial organizations are invited to participate in this RFA as collaborators when their particular skills and capabilities in drug discovery and development come to bear on the Alliance goals. 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). Applicants will be expected to describe any intellectual property arrangements between the commercial organization and the academic collaborators related to the application.

Please note: 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.

DIVERSITY, EQUITY, AND INCLUSION

The Alliance is committed to engaging underrepresented groups in clinical trials so that solutions are developed for everyone affected by multiple sclerosis. To that end, the Alliance expects investigators to employ and describe strategies to recruit, engage, and retain underrepresented groups, as well as report biological sex, gender, race and ethnicity, education, income, and place of residence for all trial participants.

PROPOSAL SUBMISSIONS

Development Awards

1. **Scientific Summary:** The scientific summary should capture the rationale, methods, and potential significance of the proposed research in one or two paragraphs.
2. **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.
3. **Research Narrative:** Provide a complete description of the research proposal (5 pages maximum).
 - a. **Overview of the Proposed Research –** Provide a summary of the background for this project, including the rationale for the intervention approach and the strength of evidence for the approach (theoretical, animal, cellular and/or human), as well

- as a concise statement of each objective of the proposed research project and a description of the experimental design and proposed methodology for successful execution of the proposed Development award.
- b. Statement of Expected Outcomes and Deliverables – Describe the results and deliverables you expect, the importance of your research proposal to progressive MS, the relevance to the goals outlined in this RFA and to the mission of the Alliance. Additionally, you must include a plan for sharing research data or explain why data sharing is not possible.
 - c. Work Plan and Timeline – Provide a concise timetable with steps, outcomes, deliverables, and milestones for the duration of the award.
 - d. References – Include full title and bibliographic reference for all work cited. There is no page limit, and this section is not included in the 5-page limit.
4. Budget and Budget Justification: Applicants must submit a detailed justified budget for each year of funding. Investigators may request funds in the following categories: salaries for personnel, patient costs, consumable supplies, travel, including inter-laboratory travel and scientific conferences, and other allowable expenses.
- a. Indirect costs may not exceed 10% of total direct costs when requested and required by Institutional policy. Indirect costs are not allowed for use in connection with funds requested or expended for purchase, modification, or installation of equipment. Indirect costs should not be requested, nor will they be provided, at institutions where indirect costs are prohibited by policies of the MS Society or government funding organizations of the applicant's country. Co-investigators and subcontractors may request indirect costs based on their institutions' policies. The Alliance will make final determination of allowance.
 - b. Commercial organizations may not request support for administrative costs.
5. Biographical Sketches: Brief 3-4 page biosketches of the PI and key co-investigators must be included ([NIH format is acceptable](#)). Biosketches should include a summary list of relevant publications.
- a. Provide a brief description of the roles of each team member in the proposed project.
6. Letters of Collaboration: Applicants may submit letters of collaboration that are directly relevant to the proposal.
7. 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.

Experimental Medicine Trial Awards

1. Scientific Summary: The scientific summary should capture the rationale, methods, and potential significance of the proposed research in one or two paragraphs.
2. 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.
3. Research Narrative: Provide a complete description of the research proposal (10 pages maximum).
 - a. Specific Aims – Provide a concise statement of each objective of the proposed

research project.

- b. Background and Preliminary Data – Provide a summary of the background for this project, including existing knowledge in the area and any preliminary data, if applicable.
 - c. Experimental Design and Methods – Describe the experimental and/or trial design as well as the proposed methodology for successful implementation of the proposed Trial.
 - d. Recruitment Plan – Describe the outreach plan for recruiting and retaining diverse study participants, as well as the planned composition of the study population, including biological sex, gender, race and ethnicity, education, income, and place of residence for the participants in the proposed trial.
 - e. Statement of Expected Outcomes and Deliverables – Describe the results and deliverables you expect, the importance of your research proposal to progressive MS, the relevance to the goals outlined in this RFA and to the mission of the Alliance. Additionally, you must include a plan for sharing research data or explain why data sharing is not possible.
 - f. Work Plan and Timeline – Provide a concise timetable with steps, outcomes, deliverables, and milestones for the duration of the award.
 - g. References – Include full title and bibliographic reference for all work cited. There is no page limit, and this section is not included in the 10-page limit.
4. Budget and Budget Justification: Applicants must submit a detailed justified budget for each year of funding. Investigators may request funds in the following categories: salaries for personnel, patient costs, consumable supplies, travel, including inter-laboratory travel and scientific conferences, and other allowable expenses.
- a. Indirect costs may not exceed 10% of total direct costs when requested and required by Institutional policy. Indirect costs are not allowed for use in connection with funds requested or expended for purchase, modification, or installation of equipment. Indirect costs should not be requested, nor will they be provided, at institutions where indirect costs are prohibited by policies of the MS Society or government funding organizations of the applicant's country. Co-investigators and subcontractors may request indirect costs based on their institutions' policies. The Alliance will make final determination of allowance.
 - b. Budgets supporting commercial organizations may not request support for administrative costs.
5. Biographical Sketches: Brief 3-4 page biosketches of the PI and key co-investigators must be included ([NIH format is acceptable](#)). Biosketches should include a summary list of relevant publications.
- a. Provide a brief description of the roles of each team member in the proposed project.
6. Letters of Collaboration: Applicants may submit letters of collaboration that are directly relevant to the proposal.
7. 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.

The Alliance will use the National MS Society's online application portal 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>).

REVIEW

Applications for Development and Experimental Medicine Trial Awards will be reviewed by Alliance scientific staff to determine a) whether the research proposal is appropriate and aligned with this RFA; and b) whether the PI meets the eligibility criteria.

Appropriate applications will then be reviewed by a panel of subject matter experts convened by the Alliance, which will include external peer reviewers, representatives from the Alliance Industry Forum and people affected by MS. The scientific review criteria for the application include the following:

- Adherence to the specific objective of the RFA and alignment and relevance to the mission and goals of the Alliance
- Enabling a better understanding of the pathophysiology and disease mechanisms in progressive MS through clinical trials
- Providing a comprehensive understanding of how a therapy affects human disease progression
- Involvement of people affected by MS in proposal development and execution
- The scientific potential for novelty and innovation
- Are the requested funds appropriate for the work, and do the importance and scientific potential justify the funding requested?
- Expertise of the investigators
- Appropriateness of the research environment

Scientific proposals will also be reviewed by Alliance Industry Forum partners. The Industry Forum is a key stakeholder group within the Alliance composed of scientific/clinical employees of for-profit organizations that operates in a pre-competitive setting to provide advice and recommendations to the Alliance Scientific Steering Committee. Industry Forum scientific review will include an evaluation of the strengths and weaknesses of the proposed research, opportunities for growth, and known threats or competition in the pharmaceutical space with consideration for therapeutic strategies and innovation. Please contact Alliance staff if you have any questions about this stage of review.

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 multiple sclerosis. This group will evaluate projects based on lived experience for their potential significance and relevance to progressive MS and overall impact on the progressive MS community and their feedback will be combined with the assessments of external scientific reviewers. Because of this review process, it is important that the plain language summary you prepare is relevant, accurate and intelligible to the MS community and consistent with 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. **You must involve people living with or affected by MS in the preparation of the proposal.** 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 Alliance Scientific Steering Committee (SSC) will consider the expert scientific and community reviews for each proposal and develop a recommended portfolio of projects for funding. The SSC will refer its recommendations to the Alliance Executive Committee for funding approval. The decision of the Executive Committee is final.

CONDITIONS

Awarded projects will be administered by the National MS Society, on behalf of the Alliance, and will be subject to the Society's policies and procedures for funding programs. Support for proposals submitted in response to this RFA will be determined based on budgets developed and fully justified by the PI.

The PI and/or team members will be required to present research progress at Alliance scientific meetings (dates and details TBD). 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.

The PI will be required to provide research and financial progress reports twice per year, as well as final narrative and financial reports within 90 days after the project ends.

Applicants must submit pertinent approval documents (e.g., ethics approvals) from the appropriate review bodies at the time of award.

CONTACT INFORMATION

Potential applicants are encouraged to contact program staff with inquiries about this funding opportunity and we welcome the opportunity to answer questions and provide appropriate guidance as needed.

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