Special article

Collaborative research in myositis-related disorders: MIHRA, a global shared community model

L.A. Saketkoo[1], J.J. Paik[2], H. Alexanderson[3], M.M. Dimachkie[4], F.C. Ernste[5], E. Naddaf[5], B. Shafranski[6], L. Gupta[7,8], C.A. Mecoli[2], D. Saygin[9], J. Albayda[2], P. Basharat[10], J.A. Day[11], A. Valenzuela[12], R. Bromley[13], I. de Groot[13,14], S.E. Edison[15], A. Lanis[16], C. Lood[17], M. Regardt[3], B.Y. Yi[2], A.C. Benitez[18], H. Chinoy[8,19], L. Christopher-Stine[2], D.A. Isenberg[20], B. Lang[21], C.V. Oddis[9], A. van Royen[22], J. Vencovsky[23], V.P. Werth[24], P.M. Machado[25,26]

Affiliations: see page 6.

Lesley Ann Saketkoo, MD, MPH
Julie J. Paik, MD, MHS
Helene Alexanderson, PhD
Mazen M. Dimachkie, MD
Floranne C. Ernste, MD
Elie Naddaf, MD
Barbara Shafranski
Latika Gupta, MD
Christopher A. Mecoli, MD, MHS
Didem Saygin, MD
Jemima Albayda, MD
Pari Basharat, MD
Jessica A. Day, MBBS, FRACP, PhD
Antonia Valenzuela, MD, MS
Rachel Bromley
Ingrid de Groot
Suzanne E. Edison, MA, MFA
Aviya Lanis, MD
Christian Lood, PhD
Malin Regardt, PhD
Belina Y. Yi, DO
Alejandro C. Benitez, MD
Hector Chinoy, FRCP, PhD
Lisa Christopher-Stine, MD, MPH
David A. Isenberg, MD
Bianca Lang, MD
Chester V. Oddis, MD
Annet van Royen, MD, PhD
Jiri Vencovsky, MD, PhD
Victoria P. Werth, MD
Pedro M. Machado, MD, PhD

Please address correspondence to:
Lesley Ann Saketkoo
New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, University Medical Center, Comprehensive Pulmonary Hypertension Center and Interstitial Lung Disease Clinic Program, Louisiana State University and Tulane University Schools of Medicine, Tulane Avenue 1430, New Orleans, LA 70118, USA.
E-mail: lsaketk@tulane.edu

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ABSTRACT

Myositis International Health and Research Collaborative Alliance (MIHRA) is a newly formed purpose-built non-profit charitable research organization dedicated to accelerating international clinical trial readiness, global professional and lay education, career development and rare disease advocacy in IIM-related disorders. In its long form, the name expresses the community's scope of engagement and intent. In its abbreviation, MIHRA, conveys linguistic roots across many languages, that reflects the IIM community's spirit with meanings such as kindness, community, goodness, and peace.

MIHRA unites the global multi-disciplinary community of adult and pediatric healthcare professionals, researchers, patient advisors and networks focused on conducting research in and providing care for pediatric and adult IIM-related disorders to ultimately find a cure. MIHRA serves as a resourced platform for collaborative efforts in investigator-initiated projects, consensus guidelines for IIM assessment and treatment, and IIM-specific career development through connecting research networks.

MIHRA's infrastructure, mission, programming and operations are designed to address challenges unique to rare disease communities and aspires to contribute toward transformative models of rare disease research such as global expansion and inclusivity, utilization of community resources, streamlining ethics and data-sharing policies to facilitate collaborative research. Herein, summarises MIHRA operational cores, missions, vision, programming and provision of community resources to sustain, accelerate and grow global collaborative research in myositis-related disorders.

Introduction

Idiopathic inflammatory myopathies (IIMs), are a group of rare diseases that are heterogenous in symptoms and prognosis. These disorders include juvenile myositis (JM), dermatomyositis, anti-synthetase syndrome, immune-mediated necrotising myopathies, inclusion body myositis, and subsets with controversial nomenclature such as polymyositis and overlap myositis. These disorders are characterised by potential multi-organ involvement including neuromuscular, musculoskeletal, cardiovascular, respiratory, cutaneous, gastrointestinal, and immune system involvement. Due to the rarity and complexity of IIMs, international research collaborations are critical.

Who is, who are MIHRA?

The Myositis International Health and Research Collaborative Alliance (MIHRA) is a newly formed purpose-built non-profit charitable research organization dedicated to serving researchers, patients and networks focused on conducting research in pediatric and adult IIM-related disorders to ultimately find a cure. MIHRA unites a multidisciplinary membership of healthcare professionals, researchers and patient advisors including dietitians, nurses, occupational therapists,

physiotherapists, psychologists, social workers, speech and language therapists, biostatisticians, epidemiologists, basic, clinician and translational scientists, and physicians (*e.g.*, paediatric and adult dermatologists, gastroenterologists, geneticists, immunologists, neurologists, pathologists, psychiatrists, pulmonologists, radiologists, and rheumatologists), among others. MIHRA serves as a hub for collaborative efforts in investigator-initiated projects, consensus guidelines for IIM assessment and treatment, and IIM-specific career development through connecting research networks such as the JM Working Groups of Childhood Arthritis and Rheumatology Research Alliance (CARRA), Pediatric Rheumatology European Society (PReS), MYONET registry, International Myositis Society (iMyoS), Rheumatologic Dermatology Society (RDS), as well as patient and professional non-profit organizations and societies, and medical institutions. We are committed to accelerating international clinical trial readiness, global professional and lay education, and rare disease advocacy in IIMs.

MIHRA's infrastructure, mission and operations were designed to address the challenges unique to rare disease communities. Guided by input from a patient-centered advisory committee, partner organizations and scientific members, MIHRA aspires to contribute toward transformative models of rare disease research through strategic expansion and inclusivity on a global scale. Our approach prioritizes efficient utilization of governmental, private and industry funding, and seeks to streamline processes to facilitate collaborative research, including a single site Institutional Review Board (IRB) and data-sharing policies. MIHRA also advocates for national and international policies on expeditious handling of studies, appropriate compassionate use and repurposed therapeutics in IIM and rare diseases in general, ensuring a collective voice in these matters.

In its long form, the name Myositis International Health and Research Collaborative Alliance encapsulates the community's scope of engagement and intent. In its abbreviation, MIHRA, conveys linguistic roots across many languages, that reflect the IIM community's spirit with meanings such as kindness, community, goodness, and peace.

The inception of MIHRA

MIHRA was born out of the recommendation of the International Myositis Assessment and Clinical Studies Group (IMACS), who set up an Advisory Committee to focus on the future of IMACS. In the past 25 years, IMACS has achieved tremendous strides in IIM care and research despite limited resources and funding. The strength of the IIM community lies in its unity, fostering a deeply collaborative environment. Throughout this period, IMACS community members dedicated countless hours to coordinating activities, receiving administrative, organizational and website support from the Environmental Autoimmunity Group at the National Institute of Environmental Health Sciences/National Institutes of Health. However, close affiliation with a United States (U.S.) governmental agency, imposed constraints on advocacy and funding. As collaborative projects within the community expanded in complexity, there emerged a need for funding to expedite progress using newer technologies and capabilities. Additionally, formal representation for advocacy within the expert community has been desired but remains lacking.

To address these gaps and support these processes, a dedicated group of IMACS members took on the task of investigating optimal strategies to meet the expanding needs of the research community. They conducted iterative examinations of organizational components, models, and the holistic needs of the community. The objective was to develop a framework that would support a feasible, sustainable and economically viable rate of growth, accommodating the increasing complexity of projects while enhancing value for the IIM research community. Furthermore, the initiative aimed to expedite a focus on global clinical trial readiness and strengthen partnerships with other professional societies, patient organizations and industry. A methodological, phased approach was adopted, soliciting insights from various organizations in rare diseases, partners and stakeholders, and examining their operational models. Through iterative, consensus-building exercises, the IIM community's core values were identified.

This concerted effort culminated in the decision to establish a non-profit, charitable, global research organization based in the U.S., dedicated to enhancing support for the IIM community. This new entity aims to empower IIM research efforts and foster a collaborative environment with like-minded partner organizations and across IIM networks.

MIHRA's vision, mission and values

Employing multi-tiered consensus methodology, the MIHRA leadership team formulated a Vision (Fig. 1):

- *To create a world where we can cure myositis together.*

This vision is complemented by a multi-faceted Mission (Fig. 1):

- To optimize the health and well-being of people living with myositis worldwide.
- To cultivate global expertise and promote synergy across myositis endeavors.
- To secure future research and clinical care through mentorship programs and education.
- To drive international collaborative research and clinical trial readiness in myositis.

Aligned with the culture of IMACS, and fundamental to MIHRA's operation, mission-driven activities, and community member conduct, MIHRA embraces the following Values:

- Global inclusivity and purposeful expansion across geographical, socio-economic profile, gender, race, ethnicity, professional discipline, and partner/stakeholder representation.
- Equity in division of resources, funding, work and representation with attention to avoiding unconscious bias toward inequitable expectations of 'emotional labor' and relegation to 'active participation but remote representation'.

Fig. 1. The vision and mission of MIHRA. Courtesy of MIHRA Foundation, rights reserved.

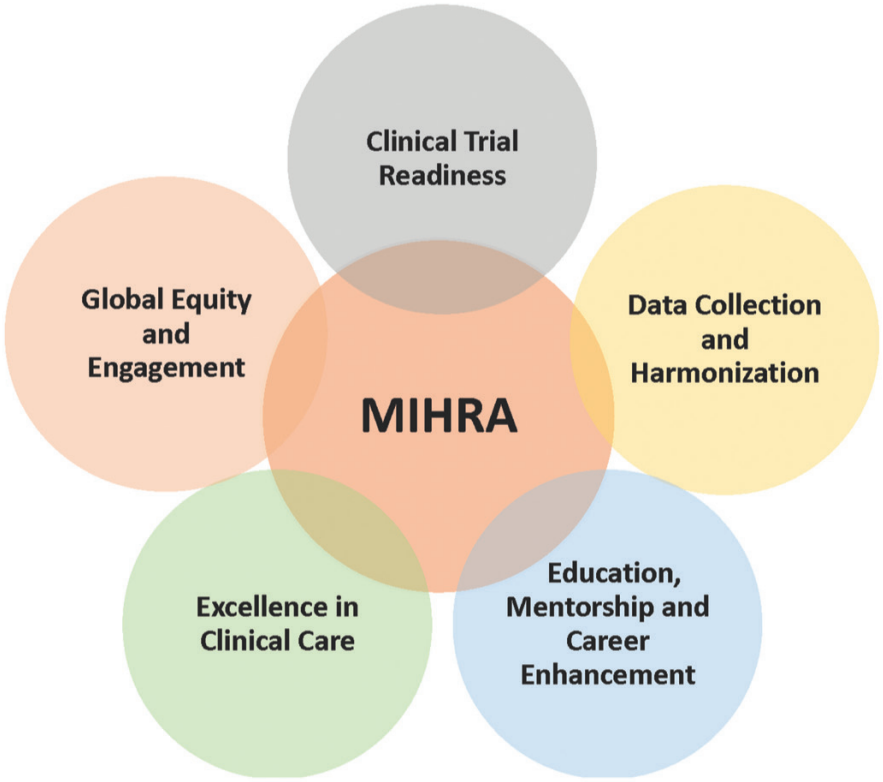

Fig. 2. Five MIHRA organizational cores. Courtesy of MIHRA Foundation, rights reserved.

- Community-driven leadership.
- Proactive mentorship that lends priority to cultivating trainees and junior faculty in positions of co-leading project management and authorship.
- Prioritization of collegial compassion that prioritizes well-being of self and that of others over urgency of production and reflects a true thinking environment for which responsible, safe expression and perceptive listening is the organization's cultural expectation.

MIHRA's organizational cores

Five organizational cores (Fig. 2) were identified that operate as critical drivers of global collaborative research:

1. *Clinical Trial Readiness:* addresses reliability and feasibility of design, outcome measures, and recruitment potential to accelerate the conduct of global patient-centric trials.
2. *Data Collection and Harmonisation:* highlights blending of existing multi-registry data, encourages an immediate global culture of database entry, with the conception of a single global database with high level user experience (UX)/user interface (UI) design that will generate global real-world data.
3. *Education, Mentorship and Career Enhancement:* is a proactive focus on cultivating the future of IIM research, increasing clinical confidence and research interest across disciplines and specialties through fellowship grants and an accredited professional education.
4. *Excellence in Clinical Care*: global standardisation of care with attention to consensus guidelines for diagnosis, assessment, treatment and longitudinal care; as well as strategies to support access to IIM care and therapeutics.
5. *Global Equity and Engagement:* a principle that embodies the commitment to collegial inclusion across geographical, socio-economic strata, gender, race, ethnicity, professional discipline, and partner/stakeholder representation, and also rectifies the substantive lack of patient global representation, which is crucial to understanding the diverse patterns of presentation and natural history of these diseases.

MIHRA's operational framework

MIHRA is fundamentally a dynamic networking platform that facilitates global engagement to solve critical research and clinical care challenges in IIM-related disorders. MIHRA operates as a fostered integration of individuals and partnerships with professional societies, patient advocacy organizations, industry, private foundations and donors.

MIHRA programming (Fig. 3) engages members through a series of mission-driven activities orchestrated by MIHRA committees and scientific working groups (SWGs). Alongside MIHRA Core Committees, SWGs are a dynamic collection of scientific task forces that address specific unmet needs in IIM-related disorders (these include standardization and validation of bio-specimen collection, processing, storage and shipping procedures; calcinosis assessment for clinical practice

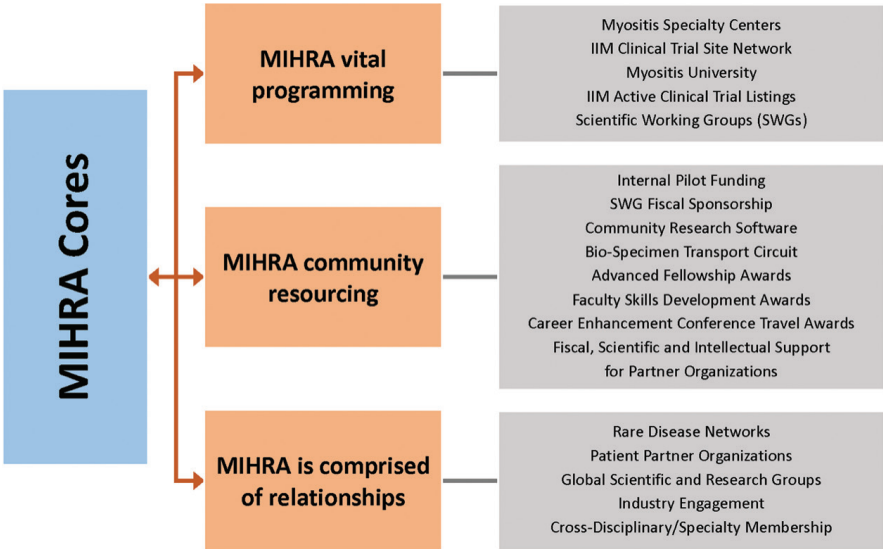

Fig. 3. MIHRA operational framework. Courtesy of MIHRA Foundation, rights reserved.

and trials; exercise and rehabilitation; psychological impact and well-being; the roles of HLA and mitochondria in IIM; cardiovascular and cardiac function; interstitial lung disease, pulmonary hypertension and diaphragmatic involvement; outcome assessment for clinical practice and research studies; new treatment pathways). The SWGs also provide vital research and input to support the work of MIHRA Core Committees. Every activity conducted under MIHRA strengthens one or several of the organization's Cores, and virtually all MIHRA activities are in conjunction with our partners and includes the perspective of people living with IIMs.

A key impediment to rare diseases research is timely access to adequate funding to initiate or continue investigations into critical disease aspects that yield vital information that safeguards the reliability and generalisability of trial design. This includes the development of reliable, validated and responsive outcome measures and endpoints that are considered relevant to people living with IIMs, as well as qualitative insights on patient experience, preferences and priorities, and consensus research in diagnosis and/or treatment. Thus, MIHRA is positioned for the attainment, oversight and distribution of funding and community resources for MIHRA-affiliated collaborative projects and activities. MIHRA serves to receive and disburse funding for collaborative community research efficiently and with assurance that funds are invested in science over indirect institutional costs. Similarly, MIHRA acts as a fiscal sponsor providing a cost-effective and time-efficient fiscal home base for collaborative community projects raising their own funds. As a grant awarder and fiscal sponsor for internal projects, MIHRA circumvents financial and administrative impediments (costs and project delay) commonly encountered in the governance of project funding by academic entities. Additionally, MIHRA provides community resources which are critical to secure and accelerate common research endeavors, such as organizational licensing for research software and platforms, as well as transport of biospecimens between MIHRA project sites.

Another major role of MIHRA is to maintain essential and centrally defining activity streams that uphold and fortify the Five MIHRA Cores across the IIM research community and for all IIM stakeholders globally which include:

1. *Myositis University*. This is a response to the expressed needs of the IIM patient community and developed in collaboration with partner patient organisations. The primary objective is to cultivate global clinical confidence in the diagnosis and care of people with IIMs through clinician access to cost-free CME/MOC/CE/CEU accredited professional education modules across specialties and disciplines. Myositis University provides readily available education on critical areas of IIM care, co-hosted by partners from professional societies. This collaborative effort empowers patients to guide their clinicians towards reliable, non-branded IIM education delivered by experts in the field.
1. *MIHRA mentorship and career enhancement programming*. This global program augments learning and career development in IIMs through travel bursaries for IIM-related conference attendance and for short-term visiting mentee learning experiences. It also offers advanced fellowship grants for clinical or basic science graduates to intensify their training in an IIM-rich learning environment, along with visiting peer grants for peer-to-peer mentorship in skills or experience development in a particular area of IIM (e.g., for minimally invasive (suture-less) muscle biopsy training). Mentorship programming includes mentee-mentor dyads, topical seminars on career and IIM-specific concepts, as well as skills workshops.
2. *MIHRA Active Clinical Trial Listings*. This initiative provides a public-facing readily available compilation and categorisation of currently active IIM studies for patients seeking to participate in clinical trials, thus importantly increasing the likelihood of subject recruitment and global IIM clinical trial success. This resource additionally enables clinical researchers to easily purvey and gain useful insight on the current landscape of clinical studies, enabling further collaborations.
3. *MIHRA IIM Specialty Centres*. MIHRA, addressing an ongoing patient need, and with insight from patient organisation partners, has launched a publicly accessible resource for patients to be able to locate IIM-dedicated clinics. MIHRA IIM Specialty Centers Network comprises a platform of members

committed to standards of IIM care thus fostering global clinical excellence and inclusivity. The platform, aligned with the MIHRA Database Harmonisation Core, cultivates a non-pressured data-sharing culture urging minimal and incremental subject data entry based on work capacity. Member centers are encouraged to contribute toward any single existing registry, such as MYONET or their local registry, with priority emphasis on follow-up visits to address current challenges of longitudinal data collection in rare diseases. Worldwide contribution to a longitudinal blended data collection promotes diversity and global generalizability of natural history investigations.

4. *MIHRA Clinical Trial Site Network*. This network functions as a clearinghouse for data on capacity, feasibility, and cohort characteristics of MIHRA IIM Specialty Centers Network members that have established or are establishing participation in IIM clinical trials. The repository serves clinical trial readiness through: identifying sites that are able to support trial design features for specific studies; protecting trial resources from costly design miscalculations; mapping collective resources and capacities to guide realistic clinical trial designs; recognizing and working towards improving site infrastructure or capabilities common in the community; and creating member forums to share insights to help resolve site-specific challenges.

The MIHRA way forward

For years, rare disease research has been subjected to the unequal footing of logistical and fiscal procedures of the mainstream research stage. MIHRA's infrastructure and operations were strategically designed to address these challenges, and augment chances for success in the rare disease research space. Given that low prevalence is the defining characteristic of rare diseases, treatment and care advancements are vitally reliant upon collaborative research efforts. MIHRA's organizational strategies are engineered to counter the burdens and barriers common to rare diseases research, offering alternative mechanisms to fuel and inspire productivity and morale while allowing researchers to channel their energy and focus on pivotal issues that directly impact viability of clinical trial readiness and consensus-building in standard of care.

MIHRA envisions a future with national policies and regulatory perspectives that favor rare disease research, incorporating both enhanced funding and expedited site initiation processes. The scarcity of funds available for rare disease research is fraught with additional synergistic handicaps that further erode fiscal feasibility and seriously compound impediments against clinical research efficiency and success. Beyond large indirect costs levied by academic institutions, low patient prevalence inherently creates costly prolonged recruitment phases, exacerbated by disease duration windows and complex phenotypic criteria. This financial strain is reflected in the toll on resource allocations but also in the patient life-years lost waiting for trial completions and regulatory approvals, along with the cost-related dismissals of potentially beneficial open-label extensions of placebo-controlled trials.

The efficacy, timeliness, and cost efficiency of clinical trials in rare diseases are further strained by the necessity for phenotypically inclusive trial designs, such that a positive trial can potentially result in multiple regulatory approved indications. In IIMs, this means communication with and education of regulatory bodies, such as U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), on the impact of these diseases and, very importantly, trial design endpoints that include skin and muscle predominant disease, as well as capturing tandem therapeutic responsiveness in other extra-muscular organs such as lungs. These efforts will hopefully lead to patient-focused drug development.

MIHRA furthermore aims to encourage research and care models around mental health issues for patients with IIMs, collaborating to raise awareness, identify funding and investigate interventions that can better support the mental health of patients and their families. Rehabilitation care and research is another key area for MIHRA support that is vital for patient health outcomes in rare diseases, but also hampered by negligible support from government, industry and health systems.

In addition to time-efficient and fund-preserving fiscal mechanisms, MIHRA is committed to investing in strategies that facilitate ease and immediacy of collaboration. An effective approach to expediting multi-center collaboration involves implementing single-site, central IRB, a model already operationalized in the U.S. for multi-center collaborative projects receiving federal funds. MIHRA intends to work steadily on a country-by-country basis to forge collaborative polices for data transfer and adherence to various IRB/Research Ethics Committees (REC) requirements across consortium nations.

Exploring avenues for sustained development involves proactively engaging in global perspectives and initiatives, fostering collegial inclusion, and addressing the notable absence of comprehensive patient representation. Understanding how these deficiencies have influenced current conceptions of disease presentation and natural history patterns is crucial for advancing research in rheumatic and neuromuscular diseases, and rare diseases generally.

As MIHRA operations expand over the coming years, the input from a patient-centered advisory committee and scientific members of MIHRA will play a vital role in championing fairness in research and care for rare diseases. Advocating for research funding in rare diseases requires public and policy-maker education on how pathogenetic and clinical models of rare diseases historically have conferred greater understanding of more common diseases, and thus has served the collective good. Additionally, guidance in compassionate use statements and drug repurposing initiatives will enhance MIHRA's impact in advancing humane and effective healthcare strategies.

MIHRA aims to lead transformative change in rare disease research by modelling policies and mechanistic op-

erations, and by serving as a dedicated voice representing, advocating and proposing transformative strategies that promote fairness in rare disease research.

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Affiliations
[1]New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, Louisiana State University and Tulane University Schools of Medicine, New Orleans, LA, USA; [2]Johns Hopkins Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Karolinska Medical Unit Occupational Therapy and Physical Therapy, Karolinska University Hospital, and Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [4]Department of Neurology University of Kansas, Kansas City, KS, USA; [5]Mayo Clinic, Rochester, Minnesota, USA; [6]Patient Research Partner, New Jersey, USA; [7]Department of Rheumatology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK; [8]Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, UK; [9]Division of Rheumatology, University of Pittsburgh, Pittsburgh, PA, USA; [10]Western University, Ontario, Canada; [11]Walter and Eliza Hall Institute for Medical Research, Melbourne, Australia; [12]Department of Rheumatology and Clinical Immunology, Pontificia Universidad Catolica de Chile, Santiago, Chile; [13]The Myositis Association, Columbia, MD, USA; [14]Spierziekten Nederland (Dutch patient association for NeuroMuscular Diseases), Dutch Myositis Network, TMA Medical Advisory Board, Netherlands; [15]CureJM Foundation, Maryland, USA, [16]Seattle Children's Hospital, Seattle, WA, USA; [17]Division of Rheumatology, University of Washington, Seattle, WA, USA; [18]Rheumatology Department at the National Hospital Alejandro Posadas, University of Buenos Aires, Argentina; [19]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK; [20]Centre for Rheumatology, Division of Medicine, University College London, UK, [21]Department of Paediatrics and Medicine, Dalhousie University and IWK Health, Halifax, NS, Canada; [22]Universiteit Utrecht, Netherlands; [23]Institute of Rheumatology, Prague, Czech Republic; [24]Department of Dermatology, University of Pennsylvania and Corporal Michael J. Crescenz VAMC, Philadelphia, PA, USA; [25]Department of Neuromuscular Diseases and Centre for Rheumatology, University College London, UK; [26]Department of Rheumatology and Queen Square Centre for Neuromuscular Diseases, University College London Hospitals NHS Foundation Trust, London, UK.

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