International Pediatric MS Study Group Strategic Plan 2014-2018

I. Executive Summary

The International Pediatric MS Study Group (IPMSSG) is entering its second decade of activity. Its mission is to improve the care of children with multiple sclerosis and acquired demyelinating diseases worldwide, promoting clinical initiatives, education and research. Today, it is a network of over 130 active voluntary members from 36 countries who are involved in clinical care or research in pediatric demyelinating diseases. The governance of the Study Group is led by a Steering Committee of nine members, elected by the global membership.

The IPMSSG is unique in that it represents clinicians based in countries without a national MS organization, and provides a common platform for addressing global issues pertinent to MS and pediatric demyelinating diseases. This is particularly important for a rare disease such as pediatric MS, in which international cooperation is required for research studies and clinical trials.

The Steering Committee has prepared this strategic plan to communicate its long-term strategic objectives, priority activities and overall case for support to ensure its sustainability and growth in the future.

The strategic plan envisions that the IPMSSG will continue to be led by its volunteer members supported by a paid coordinator based within a host organization that can provide an administrative home for the group. This baseline support will allow the IPMSSG to pursue additional resources to undertake priority initiatives in its four core focus areas: clinical care, education, research and clinical trials advocacy.

Included in this plan are details with regard to each priority activity's outcomes, impact, deadlines and key performance indicators. Risk and challenges are identified along with the need to develop a risk mitigation strategy which the Steering Committee will monitor on an ongoing basis.

Required baseline financial and administrative resources are presented at the end of the strategic plan.

II. Introduction to the International Pediatric MS Study Group

Vision

The unifying vision of the Study Group is "*to optimize worldwide care, education and research in pediatric multiple sclerosis (MS) and other acquired inflammatory demyelinating disorders of the central nervous system*." (IPMSSG Charter, 2013)

Mission

To improve the care of children with multiple sclerosis and acquired demyelinating diseases worldwide, promoting clinical initiatives, education and research.

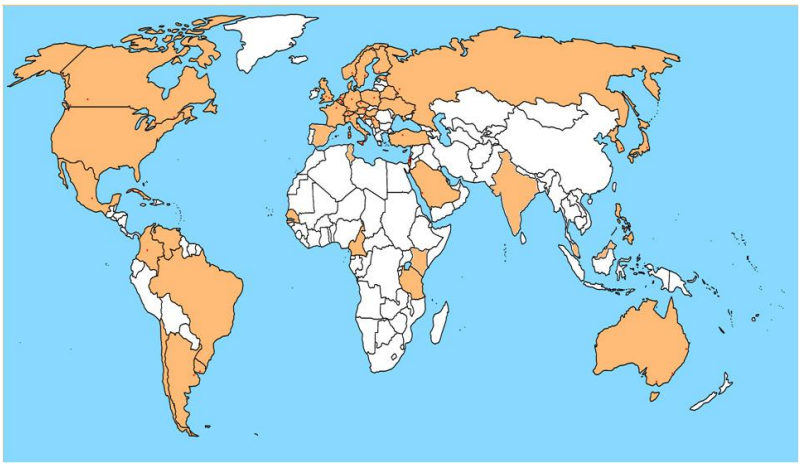
Guiding principles

The guiding principles of the Study Group are to:

- foster opportunities for collaboration amongst clinicians, researchers and allied health professionals who work in the field of pediatric demyelinating disease
- enhance the understanding of the medical and psychosocial needs of children and adolescents with pediatric MS and related disorders and improve their care
- maximize international participation in activities of the Study Group
- serve as a expert resource for clinicians and researchers in countries that don't have a sufficient awareness of pediatric MS within their health system or national MS society
- ensure above all else that the safety of children is the paramount factor in pediatric MS clinical care, clinical trials and research

The *fundamental belief* of group members is that enhanced worldwide collaboration in educational, research, clinical trials and outreach activities will improve the quality of care, increase the quality and pace of research, and increase awareness and understanding of pediatric MS and related disorders. We also believe that investigation into pediatric MS and related disorders will improve our understanding of MS in general.

Countries represented in the IPMSSG (shaded in beige)



III. Where We Have Come From and Where We Are Now

The IPMSSG arose from an invitational meeting supported by the National MS Society in 2004. Subsequent meetings revealed a strong desire to build an international collaborative association of interested clinicians and researchers. In 2007, a charter was developed, which was revised in 2013 to meet the needs of the evolving and expanding membership.

The Study Group is currently comprised of over 130 active voluntary members from 36 countries who are involved in clinical care, educational efforts, or research in pediatric demyelinating diseases. The governance of the Study Group is led by a Steering Committee of nine members, elected by the global membership. Each of the Steering Committee members serves a four-year term.

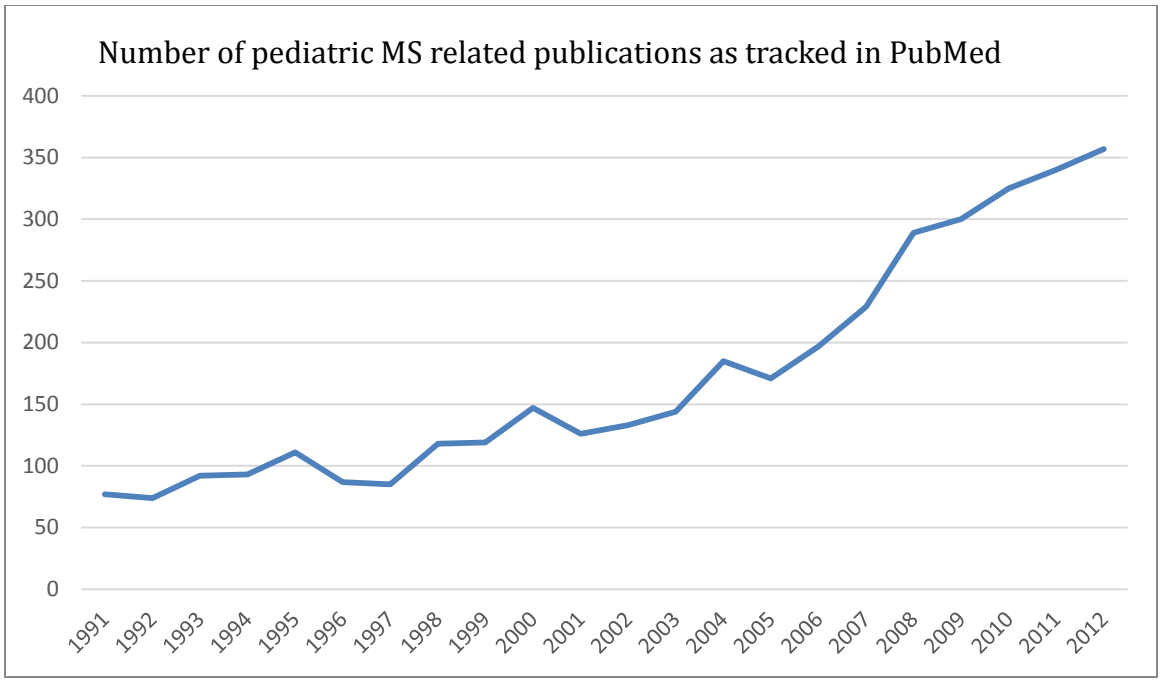
The Steering Committee supports three standing subcommittees: Clinical Care, Education and Outreach, and Research. Task forces are created as required. Currently one task force exists, the four-member Clinical Trials Task Force (CTTF) that was created to be a point of contact and ongoing discussion with regulatory agencies and industry. The operational committees and CTTF will guide the proposed project activities which are presented in this strategic plan.

Since its inception, the group has made the following significant contributions to the field:

- Development of standardized consensus definitions for pediatric MS and demyelinating diseases, published in 2007 and revised in 2013
- Publication of a compendium of review articles on the state of knowledge of key areas in pediatric demyelinating diseases including clinical presentation, treatment, neuroimaging, cognitive and psychosocial issues (*Neurology* 2007)
- Exploration of methodology for an international study on environmental risk factors for pediatric MS (funded, Pilot Grant –MS International Federation and Italian MS Society 2010-3)
- Consensus statement and international workshop with regulatory agencies to develop consensus guidelines on clinical trials in pediatric MS (Neurology 2013; MSJ 2012)
- Network opportunities made possible by the IPMSSG inspired several research collaborations and many local smaller meetings on pediatric demyelination.

IV. Unique Capacities and Strengths of the IPMSSG:

The field of pediatric multiple sclerosis rapidly expanded after 2005, likely due to increased recognition of the disorder, consensus definitions and focused discussions and meetings. Take note of the growth in pediatric-MS related publications since 2007, when the Charter of the IPMSSG was first created.



In the past decade or so, several national pediatric MS networks were developed, each of which have strengths in clinical care and research in those regions. However the IPMSSG is unique in that it can serve as a representative for clinicians based in countries without a national organization, as well as providing a common platform for addressing issues that may be global in scope.

This is particularly important for a rare disease such as pediatric MS, in which international cooperation is required for research studies and clinical trials. In addition, development of reference documents including consensus diagnostic definitions and clinical trial guidelines with international cooperation ensures that unified, state-of-the-art information is gathered, thereby allowing the field to move forward more rapidly.

V. Long-term Strategic Objectives

In order to create this strategic plan, comprehensive interviews were conducted in late 2013 with all members of the Steering Committee. These interviews confirmed that the current structure of the group with four areas of focus (see below) is the right framework to enable the group to fulfill its vision. Below are the long-term strategic objectives that respond to current needs and opportunities in pediatric MS in the four focus areas.

Clinical care: Given that pediatric MS is a rare disease, without any approved treatments for children, the Study Group strives to improve the care of children with MS by harnessing the Group's experience and expertise, and continuing to develop and promulgate clinical care guidelines and best practices.

Education and Outreach: Much of the world still lacks awareness of the reality of pediatric MS and the enormous challenges such a diagnosis brings to children and their families. Many neurologists may only have one or two patients in their care at any given time. Creating awareness-raising outreach activities for physicians, patients and national MS societies and offering educational opportunities for clinicians and allied health professionals are essential. The Study Group must optimize communication tools such as a its website to be a balanced, up-to-date source of information, updates, and a source of communication about new trends, events and research projects.

Research: Three priorities are fundamental to the core research mission of the IPMSSG: (i) facilitate research initiatives that require international collaboration, and that could not be addressed at a local or single nation level; (ii) enable international collaboration, with a focus on increasing feasibility of participation in world regions where research in pediatric demyelination has been limited; and (iii) ensure relevance of IPMSSG research to pediatric patients, families, and to the research community. In the long-term, the Study Group will seek to create research opportunities that implement these objectives.

Clinical Trials: The Study Group is committed to seeking safe and effective treatments for children with MS by studying agents in well-structured, robust clinical trials, as mandated by regulatory authorities. It will continue to engage with regulatory agencies and industry, and inform the global membership, to achieve safe and successful clinical trials.

VI. Priority Activities

In 2014, the Study Group must seek and secure long-term funding and confirm a locus for its administrative support. Funding commitments of 3-5 years, from multiple sectors and sources, will be needed to ensure the sustainability of the Study Group. These funds are considered baseline support which will allow the Study Group to function with stabile administration and governance.

The Study Group also requires an administrative home and platform. We recommend that this be housed within the offices of the MS International Federation which aligns best with the global vision of the Study Group and the mission of MSIF.

In addition to the two priority activities described above, the Study Group will also give priority to seeking the requisite funding and support resources to conduct the following activities in its four focus areas. Each of the projects and initiatives described below will require funding in addition to the baseline funding that supports the group's administration. The scope and timeline for each project will be agreed upon by the Steering Committee before funding is sought and resources committed to it.

Clinical Care:

i) Development of a patient and family advisory group: The group agrees that an international patient and family pediatric MS advisory group should be developed in order to further advise the IPMSSG on clinical, educational and research needs and to provide an important complement to the clinician viewpoints. The group should be comprised of children and adolescents with MS, their parents and young adults with pediatric-onset MS, with representatives from a variety of different regions and countries. Terms of reference for the group will be developed to integrate its input into IPMSSG initiatives, and ensure its participants reflect a global context.

ii) Clinical registry: The accurate reporting of estimated prevalence of pediatric MS is becoming increasingly important given the need to identify potential subjects for research studies and clinical trials, and for funding agencies to correctly allocate resources. Databases exist in some regions, and therefore the development of an international pediatric MS registry can build upon these resources. This initiative has been in discussion for many years within the IPMSSF Steering Committee. A launch of the registry can only take place after policies are established around participation, management and access which ensure sustainability and fair utilization.

iii) Updated review articles: There have been many advances in the field since the publication of the original IPMSSG review articles in 2007. A new set of review articles is being planned for 2015. Ongoing consensus publications by the IPMSSG, now regarded as reflecting expert opinion in the field, are essential.

iv) IPMSSG Promotion of Training Opportunities: We would like to ensure that the Study Group is a conduit for the promotion of relevant training opportunities that occur in other organizations (e.g., MSIF McDonald Fellowships, national MS societies' PhD and post-doctoral grants, ECTRIMS). The Study Group can communicate these to and through its members to potential candidates, with a particular emphasis targeting countries in which no pediatric MS care or trained faculty exist.

Education:

i) IPMSSG Global members meetings: A meeting of global members is being planned for September 2014, to coincide with the joint ECTRIMS-ACTRIMS meeting in Boston. An agenda with focused workshops discussing key areas of controversy in acquired pediatric demyelinating diseases, along with updates in recent activities is being developed. The intent of this meeting is to gain new insights into controversial areas and to foster international cooperation amongst IPMSSG members. The meeting is intended to yield discussion papers which will be posted on the IPMSSG website. This type of meeting should be held at least every other year. Ideally, sufficient funding for each meeting will be secured to allow for travel subsidies for interested participants who require financial support for

travel in order to attend. If and when funding permits criteria for the subsidies will be developed by the Steering Committee.

ii) Communications Strategy and Website update: The IPMSSG website could quickly become a key portal for the communication of new information, IPMSSG activities and collaborative efforts for clinicians, researchers and patients with their families. However, it is in dire need of updating. As an initial step, and in advance of committing time, human and financial resources to the redevelopment of the IPMSSSG website the Steering Committee will create a communications plan which will identify the broader communications objectives and requirements. Once redeveloped and properly promoted, the website will be a highly valued source of information exchange and communication for clinicians, researchers and patients. It will have background information, and updates of new information, events, and feedback on IPMSSG activities (e.g. results of membership surveys, updates on ongoing research projects, updates from the minutes of the steering group, operational committees, Clinical Trial Task Force, and summaries of educational events and recent papers. The website will also support outreach and new membership recruitment and application.

Research:

i) Conduct an international collaborative research project defining risk determinants for pediatric MS: Genetic factors and environmental exposures have and continue to be studied in pediatric MS cohorts in several countries independently. Consideration of methods to compile data from existing national datasets to answer key questions, and developing means to create formal new multinational procurement of biological materials, clinical and environmental data are planned.

ii) Conduct an international collaborative research project exploring cognitive decline in pediatric MS: This was identified as a key area to study on a global basis. It is unclear if cognitive decline varies between regions or populations, and whether most children with MS have access to neuropsychological testing and educational accommodations.

Clinical Trials:

i) Continue discussion with regulatory agencies: The 2012 IPMSSG Clinical Trials Summit (Washington, DC) demonstrated that it was crucial to inform regulatory agencies including the FDA and EMA about the demographics and clinical features of pediatric MS to inform clinical trial design and implementation. However, post-meeting, discussions with pharmaceutical companies have demonstrated that advice regarding clinical trial design differs in some aspects between the two agencies. Given the small population of pediatric MS patients, it is crucial that one unified global trial per drug be performed.

ii) Engage with other rare disease entities: We can learn much from the approaches of other rare disease groups such as Children's Oncology Group (COG) and Pediatric Rheumatology,

particularly with respect to approaches to clinical trials, and global regulatory agency issues. The goal of this sub-aim is to develop a forum to discuss common themes with other rare disease entities.

VII. Outcomes and Impact

Successful securing of long-term funding commitments will enable us to create and confirm a more permanent administrative home and staff support for the Study Group. The outcomes and impact will be:

- Continued growth in membership
- Solid governance reflecting international participation and regular rotation of members
- Evidence of increased collaboration in research, education and clinical care
- Increased recognition of the Study Group as the entity that speaks for clinical care and research issues in pediatric MS
- Greater capacity for the IPMSSG to undertake initiatives in all four focus areas

<u>Clinical care:</u>
The development of a patient and family advisory group will

- Bring added knowledge and hope to patients and their families
- Ensure that IPMSSG activities focus on the goal of optimized patient care
- Help identify gaps in guidelines for care or simply gaps in knowledge on clinical care
- Provide insight into issues in the often challenging time when a patient transitions from pediatric to adult care
- Offer opportunities for mutual learning and support amongst patients and families
- Increase access to better knowledge and care in those areas of the world where knowledge and resources are lacking

The creation of a clinical registry will:

- Expedite research and ensure that enrollment in clinical trials is successful
- Supply added data for advocacy efforts with regulatory agencies to accept trial designs and outcome measurements better suited to the rare disease nature of pediatric MS
- Enhance methods for long-term post-trial observation of children exposed to therapeutic agents in order to determine long term benefits, late toxicities, and impact on fertility and other life outcomes
- Monitor the disease course and examine the clinical, social, and health care consequences as children with MS transition into adulthood

Regularly updated review articles will:

- Ensure that the experience and expertise of the IPMSSG are broadly disseminated
- Improve treatment and symptom management of children and teens with MS
- Ameliorate the burden of MS

The promotion of relevant training opportunities will:

- Increase pediatric MS awareness and clinical care in those countries in which knowledge and care are sub-optimal

- Allow an expanding base of trainees in both clinical care and basic research and their expert mentors to create a network of knowledge and collaboration focused upon patient care and management

Education:

A bi-annual IPMSSG Global members meeting will:

- Become the premier conference for pediatric MS clinicians and researchers
- Be the forum in which to present the state-of-the art knowledge and practice in pediatric MS
- Increase worldwide pediatric MS clinical and research knowledge
- Expand the network of expertise and experts within the IPMSSG

Development and implementation of a comprehensive communications strategy and website update will:

- House the most comprehensive and accessible repository of information about pediatric MS for clinicians and researchers, and patients and their families
- Ensure that the IPMSSG is supported in its work by having a highly visible and marketed presence for clinicians, patients and MS societies

Research:

Defining risk determinants for pediatric MS will:

- Confirm putative risk determinants and yield potential prevention and therapeutic targets
- Potentially impact preventative approaches in the adult MS population as well

Research into cognitive decline in pediatric MS will:

- Provide a long-recognized but under-resourced multinational research initiative targeting the symptom that is often the most debilitating in a pediatric MS patient
- Provide understanding into cognitive decline across a large, cross-cultural cohort with the potential to identify treatment and rehabilitation strategies

Clinical Trials:

Continued engagement with regulatory agencies and industry will:

- Ensure safety and feasibility are the key considerations in their oversight of clinical trials
- Increase the likelihood that clinical trials in children will achieve sufficient patient numbers
- Ensure that clinical trials enroll and complete meaningful analyses
- Diminish the risk that children will either be unable to access potentially transformative therapies, or be exposed to toxicities not deemed significant in adult MS trials

Initiating dialogue and joint workshops with other rare disease entities will:

- Translate the learnings from other rare disease organizations into the context of pediatric MS and expedite the IPMSSG's advocacy efforts
- Increase the opportunity to engage with regulatory agencies in a collaborative alliance with other rare diseases which will also benefit their stakeholders
- Increase the scope and efficacy of IPMSSG advocacy activities

VIII. Timelines

Initial priorities for 2014 are to secure long-term funding commitments and an administrative platform as early as possible in 2014.

The timelines for the focus area project activities are below.

Clinical Care:

i) The development of a patient and family advisory group (2015)
ii) Clinical registry (2016)
iii) Updated supplement (2015)
iv) IPMSSG Promotion of Training Opportunities (ongoing)

Education:

i) Bi-annual IPMSSG Global members meeting (2014, 2016, 2018)
ii) Communications strategy and website update (late 2014)

Research:

i) Defining risk determinants for pediatric MS (2015-2018)
ii) Cognitive decline in pediatric MS (2017 -2020)

Clinical Trials:

1) Continue discussion with regulatory agencies (ongoing)
ii) Engage with other rare disease entities (2015-2018)

IX. Deadlines and Key Performance Indicators for Priority Activities

Secure long-term funding

- Funding proposals sent to at least 5 prospects (mid 2014)
- Three-year funding commitments secured (late 2014)

Secure an administrative platform

- Request made to MSIF and, if accepted, an agreement in place (mid 2014)

Clinical Care:

i) Development of a patient and family advisory group

- Discussions held with existing groups (2014)
- Terms of reference established and group recruited (2015)

ii) Development of a clinical registry

- Confirm a common data set (2015)
- Develop policy around registry participation, utilization and sustainability (2015)
- Survey all members to build an inventory of existing datasets (2015)

- Design and launch clinical registry (2016)

iii) Publication of updated supplement

- Secure funds (2014)
- Drafting of manuscripts (2014)
- Publication (2015)

iv) IPMSSG Promotion of Training Opportunities

- Develop an inventory of relevant training programs and competitions for physicians as well as allied health care personel e.g. nurses, social workers (2014)
- Develop a quarterly bulletin promoting these opportunities and disseminate to IPMSSSG members and update the IPMSSG website accordingly (2014)
- Monitor for year-over-year increase in training grantees (2015 - ongoing)

Education:

i) Bi-annual IPMSSG Global members meeting

- Attendance of 50% of membership at each meeting (2014, 2016, 2018)
- Conduct post-meeting evaluation and recommend future themes and format (2015,2017)
- Create and promote post-meeting deliverables such as discussion papers, guidelines (2015, 2017)

ii) Comprehensive communications strategy and website update

- Develop a communications strategy and secure resources for implementation (2014)
- Redesign website (late 2014)
- Monitor key indicators for website utilization (2015-ongoing)
- Update website content at least once/quarter (2015-ongoing)

Research:

i) Defining risk determinants for pediatric MS

- Secure funding (2015)
- Conduct research project (2015-2018)

ii) Cognitive decline in pediatric MS

- Create a research writing group and write proposal (2015)
- Secure funding (2016)
- Conduct research project (2017-2020)

Clinical Trials:

i) Continue discussion with regulatory agencies:

- Annual teleconference with FDA and EMA
- Face-to-face meeting with FDA and EMA every other year (2015, 2017)

ii) Engage with other rare disease entities

- Conduct network teleconferences with at least 3 entities (2015)

- Host an in-person meeting of representatives (2016)

X. Risks and Challenges

In its first ten years of existence, the IPMSSG has faced and largely overcome many challenges that present themselves when an emerging, voluntary association of very busy clinicians and researchers seeks to achieve an ambitious mission. In the coming five years we are aware of these risks and challenges:

- Insufficient funding overall
- Goals and activities that are too ambitious
- Erosion of national societies "non-financial" support as the Study Group achieves greater independence
- Insufficient global representation and inclusion

It will be the responsibility of the Steering Committee to ensure a risk management plan is in place and that its review is a standing item at regularly scheduled teleconferences.

XI. Resources required (Financial, Personnel, Infrastructure)

Infrastructure and Personnel

- Ongoing administrative support via one coordinator
- Annual elections and rotation of committees

Administrative hub

- MSIF office support
- Website support

Financial (Non-project specific)

- Coordinator - £ 20,0000/annum
- Administrative "host" organization allied staff and infrastructure support - £ 25,000/annum
- Website maintenance - £7,500/annum
- Meeting expenses (teleconference and in-person SC meeting with limited travel support) - £15,000/annum

Approved by the IPMSSG Steering Committee
March 2014