Multi-stakeholder Colloquium – Opportunities and Challenges in Multiple Sclerosis Management

Expert Review by: Patrick Vermersch1, Ralf Gold2, Chris Holloway3, Alex Rovira4, Gavin Giovannoni5 and Mondher Toumi6

1. Professor of Neurology, University of Lille, France; 2. Professor of Neurology, St. Josef-Hospital, Ruhr University, Bochum, Germany; 3. Group Director of Regulatory Affairs & Chief Scientific Officer, ERA Consulting Group, Walsrode, Germany; 4. Department of Radiology, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 5. Queen Mary University, London, Blizard institute, Barts and the London School of Medicine and Dentistry, London, UK; 6. Professor of Public Health, Aix-Marseille University, Marseille, France

Abstract
In Europe, despite recent therapeutic advances, there are many deficiencies in the management of multiple sclerosis (MS). Diagnostic and monitoring measures, guidelines, development of new treatments and best practice care are often suboptimal. These shortcomings were discussed at two MS multi-stakeholder colloquia that were convened in Brussels, Belgium in May 2014 and May 2015, and gathered experts from a range of different specialties to identify the key issues and propose means of tackling them. After considering all the testimony and discussion, the organising committee drew up a list of 10 calls to action, which included: increase awareness and understanding in the EU about the burden of MS; obtain better insights into the direct and indirect cost burden of MS; (re)define treatment goals and clinical study endpoints; develop new tools to better capture the total clinical burden of MS; develop a protocol to standardise magnetic resonance imaging (MRI); develop biomarkers of treatment response prediction and disability progression; integrate drug licensing and cost-effectiveness decision-making processes; develop separate European Medicines Agency guidelines for evaluating follow-on products of non-biological complex drugs and biologicals; implement a set of evidence-based standards of care and incentives to support people with MS to remain physically and mentally active. Addressing these ambitious calls to action requires cooperation from various health bodies and governments and some will require additional funding, but they are achievable and worthwhile. They would help minimise disease impact and would reduce disease progression and the consequent burden on people with MS, their caregivers, and on health budgets. These calls to action set out a strategy for future MS management and should be acted upon with urgency.

Keywords
Multiple sclerosis, diagnosis, improving management, stakeholders, treatment development, regulatory issues, funding, treatment access, guidelines

Disclosure: Patrick Vermersch has received consulting fees and honoraria from Bayer Schering, Biogen Idec, Merck-Serono, Novartis, Teva, Genzyme-Sanoft, Amtrill and Roche. He has also received research support from Bayer Schering, Biogen Idec, Merck-Serono, and Teva. Ralf Gold has received research support and speaker’s honoraria from Bayer Schering, Biogen, Chugai, ELAN, Merck Serono, Novartis, Roche, Sanofi-Genzyme and Teva and consulting honoraria from ZLB Behring, Baxter and Talecris. Chris Holloway has received honoraria or consultation fees from Teva. Alex Rovira serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, and on the editorial board of the American Journal of Neuroradiology and Neuroradiology. He has received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, OLEA Medical, Stendhal, Novartis and Biogen Idec, and has research agreements with Siemens AG. Gavin Giovannoni has received personal compensation for participating on advisory boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from: Abbvie, Bayer Schering Healthcare, Biogen Idec, Canbiex, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, Gw Pharma, Ironwood, Merck Serono, Novartis, Pﬁzer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals. Mondher Toumi has provided consulting through Aix Marseille University and through Creativo- Ceutical to most companies engaged in commercialising MS products: scientiﬁc board contribution, presentation in scientiﬁc meeting, strategic consulting.

Acknowledgements: Medical writing assistance was provided by James Gilbart at Touch Medical Media, London and funded by Teva Pharmaceuticals Europe B.V. This article reports the proceedings of a sponsored satellite symposium and as such has not been subject to the journal’s usual peer-review process.

Support: This article was supported by an unrestricted grant from Teva Pharmaceuticals Europe B.V.

DOI: http://doi.org/10.17925/ENR.2016.11.01.41

Over the past two decades, advances in the availability of new treatments and understanding of the disease have significantly improved the prognosis for many people with multiple sclerosis (PwMS). Despite this, in Europe, various aspects of management, diagnosis and monitoring of MS, the availability of guidelines, the development of new treatments and the provision of best-practice care are frequently suboptimal. Full awareness of the disease and its total burden is often lacking and patients’ access to the most appropriate treatments is highly variable between different territories. Reasons for low adoption of innovations are complex and affected by cultural factors. In addition, the methods used to assess the disease and its progression have notable limitations, and the protocols for use of diagnostic techniques, such as magnetic resonance imaging (MRI) are inconsistent between different treatment centres. To address these shortcomings, multi-stakeholder...
Table 1: Key initiatives of the European Multiple Sclerosis platform

<table>
<thead>
<tr>
<th>EMSP Initiative Title</th>
<th>Description</th>
<th>Parameters/Dimensions Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Register for Multiple Sclerosis (EUReMS)¹²</td>
<td>European MS data collection for research and better outcomes – a common dataset extractable from the existing registers in Europe</td>
<td>Data intended to address research questions with a ‘European dimension’ in 4 areas: 1. Epidemiology; 2. Pharmacoeconomics of DMTs; 3. Patient reported outcomes; 4. Socio-economic studies</td>
</tr>
<tr>
<td>MS Barometer²</td>
<td>Aims to provide an accurate picture of the situation for PwMS across Europe (via responses from clinicians and patient organisations to key questions about obstacles and barriers faced by PwMS in Europe)</td>
<td>7 areas: 1. Access to treatment and care; 2. Research; 3. Education/employment/job retention; 4. Involvement/empowerment of PwMS; 5. Reimbursement of MS costs; 6. National data collection; 7. New medicines</td>
</tr>
<tr>
<td>MS Nurse Professional¹¹</td>
<td>Online education supporting the crucial role of European MS nurses – address the need for unification of European MS nurses</td>
<td>A foundation course, in 5 languages, providing modular training to support the role of European MS nurses; focused on core competency of MS nurses: 1. Advocacy; 2. Health education; 3. Symptom and treatment management; 4. Provide a benchmark for MS nursing practice and nursing care across Europe</td>
</tr>
<tr>
<td>Defeating MS Together¹</td>
<td>The European Code of Good Practice in MS aims to highlight the issues faced by PwMS across the EU and the measures needed to drive improvements</td>
<td>Has 12 calls for action over 10 years in 5 key areas: 1. Ensuring access to MS treatment, therapies, rehabilitation and services; 2. Better understanding and treatment of paediatric MS; 3. Focusing MS research; 4. Enabling employment, job retention and education; 5. Supporting and empowering MS caregivers</td>
</tr>
<tr>
<td>Under Pressure⁷</td>
<td>A photojournalistic translation of the MS Barometer findings on inequalities in healthcare and social support in Europe</td>
<td>A means of allowing people with MS to tell their own stories about the impact of the condition on their lives through pictures from their daily lives</td>
</tr>
<tr>
<td>Believe and Achieve¹⁰</td>
<td>Aims to create work opportunities for young PwMS through partnerships with businesses across Europe</td>
<td>A pilot programme of 10 employers who will employ one young PwMS on a paid internship placement for 12 months; programme will raise awareness of employment issues for PwMS in Europe and provide employers with guidance on staff retention</td>
</tr>
</tbody>
</table>

DMT = disease-modifying treatment; EMSP = European Multiple Sclerosis platform; MS = multiple sclerosis; PwMS = people with multiple sclerosis

Satellite Symposium Proceedings Multiple Sclerosis

1. Increase awareness and understanding in the European community of the burden of multiple sclerosis on patients and caregivers

In the general population, among legislators and some healthcare providers, the extent of MS and its impact on younger populations is not widely recognised or understood. These gatherings of diverse disciplines enable valuable exchanges of views between sectors that infrequently interact. The colloquia were designed to initially identify and discuss the issues facing MS understanding and management in Europe and then to propose actions to address the issues identified. Based on this evidence, the scientific committee of the MS multi-stakeholder colloquia identified 10 key calls to action. Addressing all these calls will require cooperation and funding from governments, healthcare organisations and payers, and active support from HCPs and patient groups. Such worthwhile actions may ultimately eliminate disparities in MS care levels in different countries in Europe, they could reduce the burden on patients and caregivers burden and improve long-term outcomes.

2. Obtain better insights into the direct and indirect (patient and caregiver) cost burden of multiple sclerosis

The economic impact of MS is high but the exact costs (both direct and indirect) are insufficiently studied; recent figures may be underestimates of the true impact of the disease. MS generally strikes in mid-life; data from studies conducted during the last decade indicate that it has a very high cost burden compared with other brain conditions such as stroke, dementia, Parkinson’s disease and epilepsy (Figure 2) despite having a lower prevalence than some other brain disorders (e.g. anxiety, migraine, addiction etc.). An MS International Federation (MSIF) review estimated that in 15 countries worldwide, in 2010 the entire cost of the disease was $41,335 (£33,136)/patient/year ($69,118 [#55,410] in the US, equivalent to a total of $28 billion [£22.5 billion]). An earlier international study in 2005 estimated the total cost in Europe to be €12.5 billion (£16 billion). Of this, direct costs represented slightly more than half of the total cost ($6.0 billion [£7.5 billion]), informal care was estimated at €3.2 billion ($4 billion), and indirect costs due to morbidity was €3.2 billion ($4 billion).

A systematic review of 17 studies conducted in Europe and the US published between 2006 and 2012, found that the annual average cost of MS per patient was $41,133 (£33,971) (in terms of US Dollar Purchasing Power Parity) for 2009.
Multi-stakeholder Calls for Improving MS Management

Power Parity). Meanwhile, the total direct and indirect costs of MS in Europe have been estimated to be €31,000/patient/year (Figure 3). Such estimates are not always comparable or reliable; methods to measure cost of disease are well established but are not applied in all territories and regions. Definitive data on MS economic impact and burden in different territories across Europe are much needed to justify the allocation of greater resources for managing the disease.

3. Perform patient research to (re)define treatment goals and clinical study endpoints from a humanistic/patient perspective

Patient and physician perspectives in MS frequently do not coincide. For disease effects that decrease QoL, physicians tend to prioritise physical aspects, whereas patients prioritise mental and emotional aspects, general health, relapses, disease progression and adverse events. This difference in attitude was emphasised by a web survey of 651 MS patients that revealed that treatment safety concerns (progressive multifocal leukoencephalopathy [PML], liver failure and leukaemia) were more important to them than reducing relapse rate.

Figure 1: “Under Pressure” – A photojournalistic project capturing pictures from the lives of people with multiple sclerosis showing that disability strikes relatively young people

Figure 2: Cost of multiple sclerosis compared with other diseases in Europe

Figure 3: Economic burden of multiple sclerosis in the United States and Europe

Satellite Symposium Proceedings  Multiple Sclerosis

Table 2: Biomarkers that show promise in multiple sclerosis diagnosis or monitoring

<table>
<thead>
<tr>
<th>Diagnostic/Monitoring Biomarkers in Multiple Sclerosis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofilament heavy chain</td>
<td>in CSF – predictive of progression</td>
<td></td>
</tr>
<tr>
<td>Neurofilament light chain</td>
<td>in CSF or blood – marker of axonal degeneration and disability progression</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin G OCB</td>
<td>in CSF – predicts earlier conversion to CDMS and brain atrophy</td>
<td></td>
</tr>
<tr>
<td>IgG index</td>
<td>in CSF – predicts disability progression</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin M OCB</td>
<td>in CSF – predicts earlier conversion to CDMS and disease severity</td>
<td></td>
</tr>
<tr>
<td>HLA-DRB1*1501 polymorphism</td>
<td>in blood – associated with early disease onset, progression from RRMS to SPMS and worse brain atrophy</td>
<td></td>
</tr>
<tr>
<td>Chitinase-3-like-1</td>
<td>in CSF – predicts earlier conversion to CDMS and disability progression</td>
<td></td>
</tr>
<tr>
<td>Low vitamin D levels</td>
<td>in blood – predicts earlier conversion to CDMS and disability progression</td>
<td></td>
</tr>
</tbody>
</table>

Biomarkers important in Treatment Selection

| Neutralising antibodies | Secreted in response to IFNβ treatment in some patients | |
| Anti-John Cunningham virus antibodies (JCV) | PML risk with natalizumab treatment | |
| L-selectin (CD62L) CD4+ T cells | PML risk with natalizumab treatment | |
| Serum interleukin-21 (IL-21) | Indicative of secondary autoimmunity in patients treated with alemtuzumab | |

CDMS = clinical definite multiple sclerosis; CSF = cerebrospinal fluid; IFNβ = interferon beta; MS = multiple sclerosis; OCB = oligoclonal bands; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

In MS, therefore, further research is needed to identify what determines treatment success for the patient. It should also be recognised that the patient determines treatment success and satisfaction, rather than the physician. It would be advantageous to adopt this principle in the design of clinical trials in which endpoints should include more patient-reported outcomes such as fatigue levels, cognition, activities of daily living and QoL measures. These factors should be as important as relapse rate and disability progression in drug approval/licensing and in value-for-money decision making by health authorities. QoL determination is a critical criterion in patient-reported MS treatment efficacy, but it is important to recognise that condition-specific measures do not capture comorbidities. To address this, a broad definition of QoL in MS as well as a generic EuroQol 5D test (EQ-5D) are needed.

4. Develop new tools to better capture the total clinical burden of multiple sclerosis

The measures used to determine the clinical burden of MS are not standardised, not uniformly applied and many provide incomplete or unsatisfactory assessments. The EDSS has been used for many years to assess disability progression, but it has limitations including poor inter- and intra-rater reliability and low sensitivity to small changes in disability. EDSS is less useful for patients with severe disability at baseline and captures only physical ability/mobility/motor skills. Various other assessment scales are available in MS, including the Multiple Sclerosis Functional Composite (MSFC), the Multiple Sclerosis Impairment Scale (MSIS), the Family Assessment of Multiple Sclerosis Trial Outcome Index (FAMS-TOI) and various others but these also have limitations.

Some neurologists argue that scales that better capture the less visible symptoms such as cognition, fatigue and bladder, bowel and sexual function should be routinely used in MS. For example, the Brief International Cognitive Assessment for MS® could improve assessment of fatigue and cognition. The development of such improved tools and their universal adoption could provide more comprehensive disability assessment, clarify MS diagnosis and enable better determination of treatment efficacy.

5. Develop a protocol for standardisation of magnetic resonance imaging in multiple sclerosis to optimise its use as a marker of disability progression in clinical research and daily clinical practice

Currently, markers of disease progression in PwMS are limited in number and few provide any reliable prediction of likely disease course. MRI is the most widely used and reliable marker used in MS and provides valuable information on pathology, diagnosis, prognosis and monitoring. Some MRI techniques can help predict future progression and treatment response. For example, future relapse risk increases with the initial number of T2 and contrast-enhanced lesions, and number and topography of lesions predicts long-term disability. Clinical observation of MS signs often fails to capture the extent of disease activity. Indeed, sub-clinical disease activity as detected by MRI, can be substantially greater than that indicated by clinical assessment of relapse. In addition, MRI can capture some aspects of the neurodegenerative component of the disease, such as T1 hypointense lesions (a marker of focal irreversible tissue damage) and brain volume loss (a marker of brain atrophy). Significant associations have been reported between baseline T1 lesion count, 10-year T1 hypointense lesion volume and EDSS progression, and measures of overall brain atrophy predict disability and disability progression.

Whilst MRI assesses many valuable markers of MS status, pathophysiology and likely progression, the protocols used vary substantially between different treatment centres and territories. In addition, access to MRI equipment, particularly the latest instruments, is inconsistent across Europe. Consequently, many patients receive delayed or incorrect diagnosis, insufficient disease monitoring and suboptimal treatment. The lack of consistent protocols is emphasised by the variability in the methods used for measuring whole brain atrophy, the most robust MRI method to quantify the extent of brain tissue loss or damage, and in the varied capabilities of different centres to provide this measure.

There is, therefore, a pressing need for robust and standardised acquisition/interpretation MRI methodology in MS that could include decision tree algorithms. Furthermore, there is a need for accreditation of centres and radiologists to help ensure best MRI practice is provided across all European territories.

6. Support research to find other biomarkers to predict and monitor individual treatment response with regard to long-term disability progression

Other than MRI, there are few proven biomarkers for use in MS diagnosis, monitoring or treatment response. There is a substantial unmet medical need for reliable biomarkers in MS that could be used in clinics and physicians’ offices. Such biomarkers would be a valuable addition to clinical examination/symptoms and could increase confidence and speed in MS diagnosis and hasten the initiation of appropriate treatments.
Multi-stakeholder Calls for Improving MS Management

Several biomarkers show promise in MS diagnosis/monitoring (Table 2), these include several in CSF: neurofilament heavy and light chains, immunoglobulin G (IgG) oligoclonal bands (OCBs), IgG index, and immunoglobulin M (IgM) OCBs. Biomarkers in blood include an HLA-DRB1*1501 polymorphism and low vitamin D levels. Other biomarkers that inform treatment selection in MS include: neutralising antibodies stimulated in response to interferon beta (IFN-β), anti-John Cunningham virus (JC) antibodies, L-selectin (CD62L) CD4+ T cells (natalizumab) and possibly serum interleukin-21 (in response to alemtuzumab). Further research is needed in the quest for new and better MS biomarkers and in the validation of existing candidate biomarkers.

7. Integrate committee for medicinal products for human use and health technology assessment decision-making processes

The process of making new treatments available for regular clinical use first involves licensing by the Committee for Medicinal Products for Human Use (CHMP) within the European Medicines Agency (EMA) and, second, involves agreement to use or fund them in particular markets by health technology assessments (HTAs), but these are disparate processes. The CHMP/EMA concentrate on efficacy and safety (and, more recently, on novelty). The HTAs are performed by national bodies such as the UK National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS) in France and the German Institute for Quality and Efficiency in Health Care (IQWiG) or payers such as insurance companies and pharmacies, and they emphasise value for money/cost effectiveness/affordability. The HTAs have different remits and priorities for reimbursement and the lack of coordination between CHMP and HTAs results in widespread inequalities in access to MS treatment in different European territories (as shown by the MS Barometer). Figure 4. For example, fampridine received only conditional approval for improving mobility in MS because the CHMP was not convinced by patient-reported outcome data and demanded more studies. CHMP and HTAs have different objectives, so merging the two assessments would be difficult but adaptation or alignment of the functions may be possible. The function of HTAs is unclear/unknown to most patients; these bodies mostly comprise HCPs and payers. More patient involvement is needed in these authorities/committees to better reflect their perspectives and priorities.

8. Develop separate European Medicines Agency guidelines for evaluating follow-on products of non-biological complex drugs

As the patents of several older disease-modifying therapies (DMTs) are expiring, this opens the door to generic biosimilars and follow-on products. These have the potential to reduce the costs of MS treatment. Biosimilars such as interferons or monoclonals can be produced as biosimilars; these are similar to the original and can be characterised. However, the non-biological complex drugs (NBCDs) such as glatiramer acetate (GA) cannot be precisely characterised or reproduce the composition of the original product.

An example of a biosimilar IFN-β1a intramuscular product is Biferonex® (BioPartners GmbH, Reutlingen, Germany). Whilst similar to the original product (Avonex®, Biogen, Cambridge, Massachusetts, United States), this biosimilar showed lower clinical efficacy due to differences in production methods. A clinical study showed that the number of relapses over 24 months (primary endpoint) with Biferonex was not significantly different to that of placebo. The follow-on NBCD products, Probioglat® (Probiomed, Ciudad de México, Mexico), Escadra® (Raffo, Munro, Buenos Aires), and gлатiramеr (Natco) have differing molecular characteristics and polypeptide compositions to the original GA product (Copaxone®, Teva Neurosciences, Petah Tikva, Israel). These follow-on compounds upregulate different genes (e.g. CD14 expression) and have different in vitro inflammatory properties to Copaxone and their clinical and biological properties may also be different.

The development of complex drugs is further complicated by the differences in approval policies for these products in Europe versus the US. In the US, several complex drugs including GA have been approved based on data for the original product. In Europe, biosimilar products have been licensed, but clinical experience is required to support their use. There is a generally favourable approach from regulatory bodies towards generic follow-on drugs, but there are concerns as to whether they have the same properties as the original drug. The EMA has a process for biosimilar approval and this is adapted for NBCDs. Regulatory guidance for approval of these products, however, is evolving and may need further development as increasing numbers of generic drugs are emerging.

9. Stimulate implementation of evidence-based standards of care, with audit tools and incentives to support people with multiple sclerosis to remain physically and mentally active and at work

For the patient, MS is a journey during which their abilities, QoL and capacity to work are likely to decline. Studies of European populations have found that that 50% of patients with EDSS 3 and 80% of patients with EDSS 6 are unemployed or on long-term sick leave. To minimise disease impact, it is vital to establish and maintain centres of excellence, with a multidisciplinary care team to provide an integrated care pathway that contains evidence-based standards of care and well-defined healthcare objectives. These will help address all aspects of the disease and the challenges patients face.

Good patient management should involve patient activation (involvement in healthcare) and rehabilitation strategies to maintain health and QoL. These measures can help PwMS stay in work and reduce the disease and economic burden. Such services, however, are not available to all and...
few know about them: a UK National Audit of PwMS (2011) found that only 43% of patients knew they had access to rehabilitation services. It is therefore necessary to rethink the relationship between PwMS and HCPs and the architecture of the health service. Ideally, PwMS and HCPs would be considered as partners in MS management. Since PwMS and their physicians have limited regular contact, new technology should be adopted to remotely monitor signs and enable a rapid response to any change. Treating MS requires the cooperation of several different medical and support functions; coordinated multidisciplinary management of PwMS should be normal practice and should follow established evidence-based guidelines.

10. Support continuation of multi-stakeholder colloquia

Interaction between stakeholders, including diverse professionals, patients and caregivers involved in MS management and its provision is valuable but rare. Most meetings in MS are confined to specific skill sets, notably neurologists, and involve few other specialties involved in the delivery of therapy to PwMS, nor do they include patients and their caregivers. Multi-stakeholder colloquia enable all involved in MS to gain insights and pass knowledge and experiences beyond the confines of their usual speciality or location. These meetings are uniquely placed to capture this by means of different attributes in clinical practice, treatment goals for multiple sclerosis patients and how PwMS and their physicians have limited regular contact, new technology should be adopted to remotely monitor management. Since PwMS and their physicians have limited regular contact, new technology should be adopted to remotely monitor management.

11. Conclusions

The calls to action discussed above are ambitious; addressing them will require active involvement and support from key stakeholders including governments and healthcare organisations. Some calls will require allocation of significant additional funding for provision of treatments or research programmes. Some of the calls urge prompt adoption of best practice but agreement on standard protocols will require cooperation of medical organisations across regions. This may be challenging but appears achievable. Improving awareness of MS and its burden also seems achievable given cooperation between different stakeholders. Addressing the calls will likely improve the situation of many PwMS and help retard disease progression, reduce their burden on caregivers and maintain them in employment for longer. This could provide greater economic benefits than taking no action and incurring ever-greater care costs as patients become increasingly disabled. These calls are critical to the future strategy of reducing the general burden of MS across Europe and should be acted upon with urgency.

4. European Multiple Sclerosis Platform, Satellite Symposium Proceedings to determine current opinions in MS management and aim to stimulate action to put pressure on governments and healthcare authorities to amend practices and policies that currently hinder better practice.

The multi-stakeholder colloquia should therefore continue as long as PwMS across Europe do not have equal access to optimal treatments or receive adequate support measures to help manage their disease.

11. McCarroll J, Tyas D, et al., The effect of disease, treatment goals for multiple sclerosis patients and how PwMS and their physicians have limited regular contact, new technology should be adopted to remotely monitor management. Since PwMS and their physicians have limited regular contact, new technology should be adopted to remotely monitor management.
Multi-stakeholder Calls for Improving MS Management