Exploring opportunities and challenges for improving Multiple Sclerosis management – Calls to Action

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Chair of the scientific committee of the Multi-Stakeholder Colloquia on MS
Conflicts of interests/financial support

- Consulting fees and honoraria from Bayer Schering, Biogen Idec, Merck-Serono, Novartis, Teva, Genzyme-Sanofi and Almirall

- Research support from Bayer Schering, Biogen Idec, Merck-Serono, and Teva
Prevalence of Multiple Sclerosis (MS)

MS patients per 100,000 individuals

- >100
- 60-100
- 20-60
- 5-20
- 0-5
- Unknown

- Leading cause of non-traumatic disability in young adults
  - Europe: 600,000 MS patients and 1,000,000 caregivers
- Diagnosed in the peak of their productive life, with >50% becoming unemployed within 3 years

Multiple Sclerosis International Federation (MSIF) Atlas of MS 2013
Different stakeholders...different platforms

**Regulators**
- EU: EMA with CHMP
- National

**Payers**
- Responsible for funding of approved medicines (National)
- Advised by national HTA

**Healthcare professionals**
- Neurologists: ECTRIMS, ECP...
- Radiologists: MAGNIMS
- Rehabilitation therapists: RIMS
- MS nurses, psychotherapists,...

**Patients**
- EMSP

**Pharmaceutical industry**

EMSP= European Multiple Sclerosis Platform; ECTRIMS= European Committee for Treatment and Research in MS; ECF= European Charcot Foundation; MAGNIMS= Magnetic Resonance Imaging in MS; RIMS= Rehabilitation in MS; EMA= European Medicines Agency; CHMP= Committee for Medicinal Products for Human Use; HTA= Health technology assessments
Different stakeholders...different language?

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\sum_{k=0}^{n} \binom{n}{k} x^k a^{n-k}
\]

Multiple voices towards Commission
Goal of the Multi-Stakeholder Colloquia

Improve cross-talk

Explore and provide **integrated solutions for better care** of MS, by bridging the viewpoints of different stakeholders

EMA= European Medicines Agency; HTA= health technology assessment
Key faculty of the Multi-Stakeholder Colloquia (1)

Participation from:

- Patient associations
- Health economists
- Healthcare professionals
- Regulatory experts
**Key faculty of the Multi-Stakeholder Colloquia (2)**

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<tr>
<th>Leo Ayerakwa</th>
<th>George C. Ebers</th>
<th>Carsten Lukas</th>
<th>Conor Devine</th>
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<td>Yoram Baram</td>
<td>Piet Eelen</td>
<td>Stine Lykke Andersen</td>
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<td>Thomas Berger</td>
<td>Andre Elferink</td>
<td>Jana Lizrova Preiningerova</td>
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<td>Karl Broich</td>
<td>Andreas Faller</td>
<td>Jacqueline Palace</td>
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<td>Diego Centonze</td>
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<td>Declan Chard</td>
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<td>Manuel Comabella</td>
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<td>Daan JA Crommelin</td>
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<td>Josep Darbà</td>
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<td>Luiza Wieckzynska</td>
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Outcomes of the Multi-Stakeholder Colloquia

10 Calls to Action
for improving MS management in Europe
Calls addressing the need for increased funding of both research and education to estimate and communicate the total burden of MS
Call 1: Increase awareness/understanding about the burden of MS, from the patient & caregiver perspective

Wheelchair-bound at older age

- Young people
- Afraid of their future
- Loss of mobility
- Loss of energy
- Decrease in cognitive function
- Dependency on caregivers
- Unemployment
- Social isolation
- Reduced quality of life

Most European citizens

Patients with MS and caregivers
Call 2: Improve communication towards the European community on the cost burden of MS

In Europe, total direct and indirect costs are estimated at €31,000 per MS patient per year

Direct AND indirect costs increase significantly with higher disability levels. It is important to take this information into account when evaluating drug costs.

The EDSS is the most frequently used tool to monitor disability progression in MS but has several limitations such as:

• Poor inter- and intra-rater reliability
• Too much focus on capturing physical disability/mobility

More effort/research should be undertaken to develop a tool which captures less visible but bothersome symptoms

Calls addressing the need for increased funding to define patient-centred endpoints and explore and validate biomarkers
**Call 3: Perform patient research to (re)define treatment goals and clinical study endpoints**

Patient perspectives differ from physician perspectives, with patients giving high value to not only physical but also mental/emotional health.

**Call 3: Perform patient research to (re)define treatment goals and clinical study endpoints**

<table>
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<th>Classical clinical efficacy outcomes</th>
<th>Newer clinical efficacy outcomes</th>
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<tr>
<td>- Relapse</td>
<td>- Direct Access File System</td>
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<td>- EDSS</td>
<td>- Gait: T25FWT</td>
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<td>- MRI lesions</td>
<td>- Upper extremity motor skills:</td>
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<td>9-hole peg test</td>
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<td>- MRI whole brain atrophy</td>
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**Measuring individual treatment success**

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<tr>
<th>Risk of adverse events/Convenience of use</th>
<th>Outcomes considered important by patients</th>
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<tbody>
<tr>
<td>- Mode of administration</td>
<td>- Cognition</td>
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<tr>
<td>- Need for regular monitoring</td>
<td>- Fatigue</td>
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<td></td>
<td>- Mobility/activities of daily living</td>
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<td>- HRQoL</td>
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Patient’s perspectives/expectations should be taken into account when evaluating “value for money” during drug approval & HTA decision making

EDSS= Kurtzke Expanded Disability Status Scale; MRI= magnetic resonance imaging; T25FWT= time 25-foot walk test; HRQoL= health-related quality of life; HTA= health technology assessment
Call 5: Develop a protocol for standardisation of MRI in MS to optimise its use as a marker of disability progression

Clinical indicators of a higher risk of disability progression are
- Later age at onset
- Male gender
- High number of relapses in the first 2 years from onset
- Incomplete recovery from the first relapse
- High number of abnormal lesions at the MRI scan

The rate of disability progression in MS is variable
- It is currently not possible to predict the disease course in an individual person with MS at onset
- It is difficult to capture clinically relevant disability progression in clinical trials with disease-modifying drugs of 2 years duration

Research should focus on finding markers, preferably surrogate endpoints, for long-term disability progression

* ≥2 gadolinium-enhancing and ≥9 T2 lesions; MRI= magnetic resonance imaging
Whole brain atrophy is higher in MS patients than healthy controls.

Whole brain atrophy is higher in patients progressing to an EDSS ≥ 6 after 8 years of follow-up.

In order to make MRI markers applicable as markers of disability progression in daily clinical practice, it is essential to develop/use a **standardised MRI protocol**. Certification of centres/neuro-radiologists implementing this standardised protocol may help acceleration.

Call 6: Support research to find molecular biomarkers which can predict disability progression & treatment response

There is a need for non-imaging biomarkers to:

- Predict & monitor disease progression:
  - CIS → RRMS → SPMS
  - Disability
- Stratification for treatment
- Monitoring of treatment efficacy & risks

Validation processes can best be performed by European consortia engaged in biomarker research

- Best candidates in the cerebrospinal fluid: Immunoglobulin G index/oligoclonal bands, Chitinase-3-like-1 protein
- Best candidates in blood: vitamin D

Patient’s perspectives/expectations should be taken into account when evaluating “value for money” during drug approval & HTA decision making

Calls addressing the need to align the market authorisation decision-making process with the health technology assessment process
Call 7: Align CHMP & health technology assessment decision making processes

There are widespread **inequalities** in access to MS therapy across Europe.

Integration of the CHMP/EMA and HTA decision processes may decrease inequality. In addition, patient perspective should also be taken into account.

European Multiple sclerosis Platform (EMSP). MS Barometer 2013; CHMP= Committee for Medicinal Products for Human Use
Call 8: Develop separate EMA guidelines for evaluating follow-on products of non-biological complex drugs

Simple drugs

Small molecules

- e.g. paracetamol
- Characterised at fine level of detail

Generics guidelines

Complex drugs

Biologicals/Proteins

- e.g. interferon
- Characterised at reasonable level of detail

Biosimilars guidelines

Non-biologicals

- e.g. glatiramer acetate
- Cannot be fully characterised

It is essential that EMA develops clearly defined guidelines for demonstrating similarity of follow-on NCBDs in order to guard the safety of MS patients.
Calls addressing the need to keep MS patients active and working, as long as possible
Call 9: Stimulate the implementation of specialised care centres and support MS patients in being active & working

Activity stimulates muscle function

- Keeps them mobile & out of a wheelchair
- They can continue to work & socialise
  - Positive impact on their mental quality of life
  - Their family members can continue to live their own life & perform their own job

Reduces indirect costs and improves the quality of life (intangible costs)

Exercise-related activities for MS patients should be supported and incentive for employers to retain/employ MS patients should be provided.
Call 10: Support the continuation of the multi-stakeholder colloquia to stimulate innovation

EMA=European Medicines Agency; HTA=health technology assessment