New and emerging treatments and developments in Multiple Sclerosis

Living well with multiple sclerosis conference

September 2015
In the past year, Alan Thompson has received honoraria and support for travel for consultancy from Biogen Idec and MedDay, honorarium for consultancy from Eisai, and honoraria and support for travel for lecturing from Serono Symposia International Foundation and Novartis.

He received support for travel from the MS International Federation as Chair of their Medical and Scientific Advisory Board, from the International Progressive MS Alliance, as chair of their Scientific Steering Committee and from the National MS Society (USA) as member of their Research Programs Advisory Committee. He receives an honorarium from SAGE Publishers as Editor-in-Chief for Multiple Sclerosis Journal.

September 2015
Outline

• Introduction - Context

• MS Management

• Current treatments

• The future – focus on Progressive MS
MS Is a Disabling Condition

QOL
EDSS and utility\textsuperscript{a} have shown a significant inverse relationship\textsuperscript{1}

Mortality
Mortality ratio of MS exceeds CV disease,\textsuperscript{2,\,b} stroke,\textsuperscript{3,\,c} and early breast cancer\textsuperscript{4}

Employment
50% of patients with MS are unemployed 10 years after diagnosis\textsuperscript{5}

Relationships
Compared with general population, patients with MS have a higher probability of separating/divorcing and doing so sooner\textsuperscript{5}

Healthcare costs
Bulk of cost attributed to services (29%) and long-term sick leave and early retirement (30%)\textsuperscript{6,\,d}

MS has a negative impact on...

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CV=cardiovascular; EQ-5D=EQ-5D=EuroQol 5-Dimension questionnaire.

a. Utility measures derived from EQ-5D
b. In patients with type 2 diabetes
c. In patients with valvular heart disease in Olmsted County, Minnesota
d. MS patients with EDSS ≥6.0
Natural History of MS

Preclinical

Relapsing

Secondary Progressive

relapses and impairment

MRI activity

brain volume

MRI burden of disease
Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis

W. Ian McDonald, FRCP, Alistair Compston, FRCP, Gilles Edan, MD, Donald Goodkin, Hans-Peter Hartung, MD, Fred D. Lublin, MD, Henry F. McFarland, MD, Donald W. Paty, MD, Chris H. Polman, MD, Stephen C. Reingold, PhD, Magnhild Sandberg-Wollheim, MD, William Sibley, MD, Alan Thompson, MD, Stanley van den Noort, MD, Brian Y. Weinshenker, MD, and Jerry S. Wolinsky, MD

Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the “McDonald Criteria”

Chris H. Polman, MD, PhD, Stephen C. Reingold, PhD, Gilles Edan, MD, Massimo Filippi, MD, Hans-Peter Hartung, MD, Ludwig Kappos, MD, Fred D. Lublin, MD, Luanne M. Metz, MD, Henry F. McFarland, MD, Paul W. O’Connor, MD, Magnhild Sandberg-Wollheim, MD, Alan J. Thompson, MD, Brian G. Weinshenker, MD, and Jerry S. Wolinsky, MD
Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,1 Stephen C. Reingold, PhD,2 Brenda Banwell, MD,3 Michel Clanet, MD,4 Jeffrey A. Cohen, MD,5 Massimo Filippi, MD,6 Kazuo Fujihara, MD,7 Eva Havrdova, MD, PhD,8 Michael Hutchinson, MD,9 Ludwig Kappos, MD,10 Fred D. Lublin, MD,11 Xavier Montalban, MD,12 Paul O’Connor, MD,13 Magnhild Sandberg-Wollheim, MD, PhD,14 Alan J. Thompson, MD,15 Emmanuelle Waubant, MD, PhD,16 Brian Weinshenker, MD,17 and Jerry S. Wolinsky, MD18

New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single scan. These revisions simplify the Criteria, preserve their diagnostic sensitivity and specificity, address their applicability across populations, and may allow earlier diagnosis and more uniform and widespread use.

ANN NEUROL 2011;69:292–302
MS Survey of 1,500 people with MS in 2015

‘MS patients 'face frequent misdiagnosis'

- 1 in 4 people with MS misdiagnosed with having a trapped nerve
- 1 in 10 people with MS told they’d had a stroke
- 39% of people with MS waited over a year for diagnosis
- 25% visit GP four or more times before referred
The unmet need is massive

<table>
<thead>
<tr>
<th>Disease modification</th>
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<tbody>
<tr>
<td>MRI, relapse reduction, delayed onset of CDMS, delayed disease progression, disease activity free, delayed onset of SPMS, prevention of SPMS</td>
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<table>
<thead>
<tr>
<th>Anti-inflammatory strategies</th>
<th>Neuroprotective strategies</th>
<th>Neurorestorative strategies</th>
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<tbody>
<tr>
<td>Symptomatic therapies</td>
<td></td>
<td></td>
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<tr>
<td>Cognition</td>
<td>Fatigue</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Bladder/Bowel</td>
<td>Mobility</td>
<td>Mood</td>
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<tr>
<th>MS prevention</th>
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<tbody>
<tr>
<td>Vitamin D</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>EBV</td>
</tr>
</tbody>
</table>
Oh My God!
The MS Nurse Was Right
About Everything!
Guidelines in MS

NICE guidelines
NHS England
Association of British Neurologists

2014-2015
Early accurate diagnosis crucial in multiple sclerosis

**What** are the different types of MS?

**How** should MS be diagnosed?

**What** are the management approaches?

**Figure 1** Axial FLAIR image that shows typical MS lesions: small and ovoid hyperintensities in T2-weighted sequences. Here they are located in the periventricular white matter and juxtaocular white matter.

**Multiple Sclerosis (MS)** is an inflammatory-demyelinating disease of the CNS. It often begins with relapsing attacks, but most patients develop secondary progressive MS (SPMS), characterised by a gradual and irreversible neurological decline. Although relapses which patients will follow a more rapid accrual of disability is still a challenge. Recently, the International Advisory Committee on Clinical Trials of MS has...
Management

Education

Treatment & monitoring
• Disease-modifying treatments (DMD)
  • Treatment of relapses
  • Symptomatic treatment

Multidisciplinary approach

Self-management
Management : Education

Education should aim at:

• Improving the understanding of the disease

• Increasing the knowledge about healthy lifestyles and their consequences

• Increasing awareness of noxious factors such as smoking

• Promoting patients’ empowerment
Management: Multidisciplinary approach

- Comprehensive annual assessments

- Focused on:
  - Mobility, balance, and falls
  - Mobility aids including wheelchair assessments
  - Use of arms and hands
  - Muscle spasms and stiffness

- Healthcare professionals involved
  - Consultant neurologists
  - MS nurses
  - Physiotherapists, occupational therapists, speech and language therapists, and continent nurses
  - Psychologists and social care specialists
  - Dieticians
Management: Self-management

- Patients are aware of their condition and their symptoms
- Patients can adopt self-management strategies to solve day-to-day issues and gain independence
- Patients are at the centre of all decision-making processes
- Important decisions include
  - Healthy lifestyle
  - Start of treatment and compliance
  - Stop of treatment
  - Pregnancy and other family-related decisions
National MS Society Wellness Initiative

Wellness

Life-long personalized process through which people make informed choices about their lifestyle behaviors and activities across multiple, inter-related dimensions with the aim of leading their best lives.
Wellness and Multiple Sclerosis

• Wellness is attainable for everyone. It is achieved by each person living with MS within the context of his or her priorities, abilities and limitations.

• The National MS Society is committed to connecting people to the information and resources they need to pursue their personal wellness goals.
The dimensions of wellness act and interact in ways that contribute to well-being. They are influenced by health and other factors and involve lifestyle behaviors and activities.
Top Traditional & Social Media Topics

- **Symptoms**: 230,511 mentions (35.5%)
- **Wellness**: 197,051 mentions (30.4%)
- **Diagnosis**: 95,905 mentions (14.8%)
- **Providers**: 57,680 mentions (8.9%)
- **Medication**: 44,881 mentions (6.9%)
- **Insurance**: 22,794 mentions (3.5%)
Social Media Wellness Themes

Alternative vs. Traditional Treatment
(July 2014 – June 2015)

- Diet
- Cannabis
- Exercise
- Vitamins / Supplements
- Stem Cells
- Copaxone
- Tysabri
- Tecfidera
- Avonex
- Gilenya
- Aubagio
- Mindfulness
- Rebif
- Lemtrada
- Betaseron

Mentions
Current Wellness Evidence
Diet, Exercise and Mood Interventions

• Insufficient evidence to establish efficacy or effectiveness in MS
  – Specific diets
  – Dietary supplements
    • Vitamin D
    • PUFA’s
  – Specific exercise program
  – Mindfulness or other practices to reduce stress or depressive symptoms.

• Poor identification of depressive symptoms and major depressive disorder
Objectives:

– Develop research priorities and a research plan that will accelerate research on diet, exercise, mood and other wellness focused interventions
– Suggest strategies to increase the MS wellness research workforce
– Consider the development of a MS Wellness Research Network
Information and Resources

• US Neurology paper:
  – Dunn M, Bhargava P, Kalb, R. Your patients with MS have set wellness as a high priority—and the National MS Society is responding. Multiple Sclerosis Special Report. US Neurology 2015.. This paper—targeted to practicing neurologists, documents the interest and need expressed by people with MS for support from their health care providers regarding lifestyle/wellness interventions. It reports what we currently know about such interventions as diet, exercise, mindfulness, identifies gaps and future research directions as well as programmatic recommendations.
HEALTHCARE WITHOUT WALLS

NeuroDirect
NeuroView
NeuroMail
Shorter communication

A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue
Rona Moss-Morris a,1, Paul McCrone b, Lucy Yardley e, Kirsten van Kessel c, Gary Wills d, Laura Dennison e

Boeschoten et al. BMC Psychiatry 2012, 12:137
http://www.biomedcentral.com/1471-244X/12/137

STUDY PROTOCOL

Randomized controlled trial of a teleconference fatigue management plus physical activity intervention in adults with multiple sclerosis: rationale and research protocol
Matthew Plow a, Marcia Finlayson b, Robert W Motl c and Francois Bouthier d

Original Research

Web-Based Self-Management for Patients with Multiple Sclerosis. A Practical, Randomized Trial

Deborah M. Miller, Ph.D., USW,1,2, Shirley M. Moore, Ph.D.,2, Robert J. Fox, M.D.,1, Ashish Atreja, M.D.,1, Alex Z. Fu, Ph.D.,1, Joo-Chi Lee, M.S.,1, Welf Sauge, B.S.,2, Maria Staedler,1, Swati Chakraborty, M.E.,1, C.M. Harris, M.D.,1, and Richard A. Rudick, M.D.3
Outcome measures

NICE Guidelines

MS Relapse ICP Page 2 of 5

Pain
- Identify whether pain is a significant contributing factor to current mobility.
- All pain, including hydroxychloroquine-induced pain, should be subed to full control and referred to an appropriate specialist.

Musculoskeletal pain:
- If pain is secondary to reduced or abnormal movement, arrange assessment by a specialist rheumatologist to investigate procedures which might be beneficial, such as exercise:
  - Passive movement
  - Improved seating
- Consider use of appropriate analgesic medicines if non-pharmacological measures prove unsuccessful in pain management.
- Consider transcutaneous nerve stimulation (TENS) and antidepressant medication in cases of continued unresolved secondary musculoskeletal pain.
- Routine use of ultrasound, low-grade laser treatment and antidepressant medication are not recommended.
- Consider cognitive-behavioral and imagery treatment methods only if patient has sufficiently well preserved cognition to participate actively.

Neuropathic pain:
- Characterized by sharp, often shooting, pains and painful hypersensitivity.
- Treat using anticonvulsants, such as:
  - Carbamazepine
  - Gabapentin
  - Antidepressants, such as amitriptyline
- Refer to specialist pain service if initial treatment fails to control symptoms.

Reference:
• Average **100** people per week contact the service

• Patient satisfaction up from **49% to 93%**

• **42% supported to self manage** avoiding attendance at GP surgeries or hospital

• Relapses clinically triaged - **90% accuracy rate**

• **76%** reported an increase on EQ-5D-5L (1-3)

• Currently analysing this data with NICE
The Future
Organisationally facing
Flip the power-base
3 Key Elements of Self Management

1. Electronic Health Records

2. Goal Orientated Care Plan

3. Motivational coaching
OptiMiSe
OptiMiSe Vision

• Own electronic records
• Goal orientated care plan
• Information & Evidence
• Ability to self-assess
• Ability to Benchmark to Peers
• Access to Motivational Coach
Current treatments
**Therapeutic era of Multiple Sclerosis**

- 1993 - First positive trial of therapeutic agent
- 1998 - Four agents available - reduce relapse rate
- 2004 - Second line agent licensed for more aggressive MS
- 2005 - Withdrawn because of serious side-effect
- 2006 - Reintroduced
- 2010 - First oral agent licensed
- 2015 – 12 treatments
Early treatment seems to be desirable

Figure: http://multiple-sclerosis-research.blogspot.co.uk/2012/06/research-dmt-slow-onset-of-progression.html
Early treatment seems to be desirable

Figure: [Link to Figure](http://multiple-sclerosis-research.blogspot.co.uk/2012/06/research-dmt-slow-onset-of-progression.html)
Brain health
Time matters in multiple sclerosis

Gavin Giovannoni
Helmut Butzkueven
Suhayl Dhib-Jalbut
Jeremy Hobart
Gisela Kobelt
George Pepper
Maria Pia Sormani
Christoph Thalheim
Anthony Traboulsee
Timothy Vollmer

Preparation of these recommendations was funded by an educational grant from F. Hoffmann-La Roche, who had no editorial influence on the content.
Effective drugs are available

Drugs licenced to treat relapsing MS

- Interferon beta 1a s.c.
- Interferon beta 1b s.c.
- Interferon beta 1a i.m.
- Glatiramer acetate
- Mitoxantrone
- Natalizumab
- Fingolimod
- Teriflunomide
- DMF
- Alemtuzumab
OTHER MOLECULES ARE COMING, SOME VERY SOON

✓ Interferon beta 1a s.c.
✓ Interferon beta 1a pegylated
✓ Interferon beta 1b s.c.
✓ Interferon beta 1a i.m.
✓ Glatiramer acetate 40 tiw
✓ Mitoxantrone
✓ Natalizumab
✓ Fingolimod
✓ Teriflunomide
✓ DMF
✓ Alemtuzumab
✓ Daclizumab
Timeline of MS Treatment Approvals

CIS
N=554, 3 trials

RRMS
N=32405, 65 trials

PPMS
N=2574, 5 trials

SPMS
N=2856, 7 trials

Mixed
N=17369, 62 trials

Overview
Alemtuzumab
Dalfampridine
Dimethyl Fumarate
Fingolimod
Glatiramer Acetate
IFNB-1b

IFNB-1a (Rebif)
IFNB-1a (Plegridy)
IFNB-1a (Avonex)
Mitoxantrone
Natalizumab
Teriflunomide

IFNB-1b (Betaseron)
GA (Copaxone)
Mitoxantrone (Novantrone)
Natalizumab (Tysabri)

Teriflunomide (Aubagio)
Alemuzumab (Lemtrada)
Dalfampridine (Ampyra)
Fingolimod (Gilenya)
Dimethyl Fumarate (Tecfidera)
IFNB-1a (Plegridy)

Compound timeline
FDA Approval
EMA Approval

# Treatment

## Treatment & monitoring – DMD: First-line treatments

<table>
<thead>
<tr>
<th>Drug, administration route</th>
<th>Reduction (%) in clinical activity (relapses) in clinical trials</th>
<th>Main side effects</th>
<th>Recommended safety monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vs. placebo</td>
<td>Vs. first-line DMD</td>
<td></td>
</tr>
<tr>
<td>Beta-interferon, SC or IM</td>
<td>30%</td>
<td>NA</td>
<td>- Flu-like symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Mild-moderate lymphopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Elevated liver enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hypersensitivity</td>
</tr>
<tr>
<td>Glatiramer acetate, SC</td>
<td>30%</td>
<td>NA</td>
<td>- Immediate post-injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Local injection-site skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hypersensitivity</td>
</tr>
<tr>
<td>Dimethyl fumarate, oral</td>
<td>45-50%</td>
<td>22%</td>
<td>- Flushing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Gastrointestinal events</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Lymphopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Elevated liver enzymes</td>
</tr>
<tr>
<td>Teriflunomide, oral</td>
<td>40-50%</td>
<td>No proved superiority of teriflunomide vs. SC beta-interferon</td>
<td>- Hair loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Elevated liver enzymes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Leukopenia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Elevated blood pressure</td>
</tr>
</tbody>
</table>
Treatment

Treatment & monitoring – DMD: First-line treatments

Indications
• RRMS: At least 2 relapses over the past 2 years (all first-line drugs)
• CIS: Within the first 2 years if high risk of 2nd relapse (beta-interferons)
Oral fingolimod modulates S1P receptors on lymphocytes and neural cells. It targets MS via actions in both the immune system and CNS.

Neural cells express S1P receptors known to modulate neuropathological processes relevant to MS.

Autoaggressive lymphocytes remain in the lymph nodes, away from the CNS → reversible REDISTRIBUTION, not depletion.

CNS, central nervous system; MS, multiple sclerosis; S1P, sphingosine 1-phosphate
Natalizumab: A Humanized, Monoclonal Antibody (mAb) Against $\alpha_4$ Integrins

Complementarity-Determining Regions (CDRs)

- CDR grafted from murine Ab
- Human IgG4 framework
- Retains full potency
NATALIZUMAB

A

Lymphocyte

α4 integrin

Lumen

VCAM1

Endothelial cell

Parenchyma

B

Natalizumab
Alemtuzumab
Target of activity

- Alemtuzumab is a CD52-directed immunomodulator
- CD52 is a surface protein expressed on adaptive and innate cells of the immune system to varying degrees

Innate immune system: Primary defense against pathogens including bacteria, viruses, and parasites
- Neutrophils
- Eosinophils
- NK cells
- Macrophage

Low CD52 expression

Adaptive immune system: Second line of defense against antigens
- T lymphocytes
- B lymphocytes

High CD52 expression

Alemtuzumab administration

Innate immune cells are largely spared and preserve functionality to fight infections

Alemtuzumab binding causes lysis and subsequent reduction of circulating T and B lymphocytes, resulting in decreased inflammation in the CNS
## Treatment & monitoring – DMD: Second-line treatments

<table>
<thead>
<tr>
<th>Drug, administration route</th>
<th>Reduction (%) in clinical activity (relapses) in clinical trials</th>
<th>Main side effects</th>
<th>Recommended safety monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vs. placebo</td>
<td>Vs. first-line DMD</td>
<td></td>
</tr>
<tr>
<td>Fingolimod, oral</td>
<td>55-60%</td>
<td>51-52%</td>
<td>Bradycardia and other heart conduction abnormalities - Lymphopenia - Macular oedema - Elevated liver enzymes - Elevated blood pressure</td>
</tr>
<tr>
<td>Natalizumab, IV</td>
<td>68%</td>
<td>NA</td>
<td>Perfusion reaction (nausea, vomiting, generally mild) - Hypersensitivity - Immunogenicity (antibodies against natalizumab) - Infections, including PML - Elevated lymphocyte count in peripheral blood</td>
</tr>
<tr>
<td>Alemtuzumab, IV</td>
<td>NA</td>
<td>55%</td>
<td>Perfusion reaction (marked) - Marked lymphopenia - Infections - Secondary autoimmunity</td>
</tr>
</tbody>
</table>
Treatment & monitoring – DMD: Second-line treatments

Indications

• At least 2 relapses over the previous year together with MRI evidence of inflammatory activity while on first-line DMD

Exceptionally, in highly active MS, all three can be used as first-line drugs
PML in association with Natalizumab

Cells with inclusions have positive nuclear signal for JC virus
Disease modifying drugs
a guide to treatments for relapsing MS
Visual Map of MS Clinical Trials

142 ongoing clinical trials in MS with a targeted total sample size of 55758 patients.
MS Trials by Patient Population

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS</td>
<td>554</td>
<td>3 trials</td>
</tr>
<tr>
<td>RRMS</td>
<td>32405</td>
<td>65 trials</td>
</tr>
<tr>
<td>PPMS</td>
<td>2574</td>
<td>5 trials</td>
</tr>
<tr>
<td>SPMS</td>
<td>2856</td>
<td>7 trials</td>
</tr>
<tr>
<td>Mixed</td>
<td>17369</td>
<td>62 trials</td>
</tr>
</tbody>
</table>

Despite the identified need for more clinical trials in PPMS and SPMS, RRMS remains the main focus for the Pharma industry.

- Marketed for MS
- Marketed but not for MS
- Not Marketed
- Other
Urgent need to find solutions for people with Progressive MS

- Large worldwide impact: at least half of all (2.3 million) MS patients
- Currently no effective treatment for progressive MS
- Onset of progression is the main determinant of disability
- Finding treatments for progressive MS is one of the top priorities for patients
- Every time another therapy is approved for RRMS, a large proportion of our constituents feel left out
Development of secondary progression is the dominant determinant of long-term prognosis, independent of disease duration and early relapse frequency.
Onset of progressive phase determines disability

Scalfari et al Neurology 2011
The JLA facilitates Priority Setting Partnerships. These bring patients, carers and clinicians together to identify and prioritise for research the treatment uncertainties which they agree are the most important. The JLA believes that:

- Addressing uncertainties about the effects of treatments should become accepted as a much more routine part of clinical practice

- Patients, carers and clinicians should work together to agree which, among those uncertainties, matter most and thus deserve priority attention

- Prioritise the top 10 uncertainties… that they agree are most important.
1. Which treatments are effective to slow, stop or reverse the accumulation of disability associated with MS? i.e. TREAT PROGRESSION
2. How can MS be prevented?
3. Which treatments are effective for fatigue in people with MS?
4. How can people with MS be best supported to self-manage their condition?
5. Does early treatment with aggressive disease modifying drugs improve prognosis?
6. Is Vitamin D supplementation an effective disease modifying treatment for MS?
7. Which treatments are effective to improve mobility for people with MS?
8. Which treatments are effective to improve cognition in people with MS?
9. Which treatments are effective for pain in people with MS?
10. Is physiotherapy effective in reducing disability in people with MS?
Challenges

• Defining phenotype

• Clarifying pathological mechanisms underpinning progression

• Identifying treatment targets

• Outcomes/Biomarkers

• Trial design
Defining Progressive MS

- Neurologist
  - accumulation of disability,
  - gradual change over time (Progressive myelopathy)
- Imager:
  - Progressive atrophy, expanding lesions
  - Reduced MTR, NAA, fractional anisotropy
- Pathologist:
  - Axonal pathology
  - Oligodendrocyte pathology
- Patient:
  - Loss of independence
  - Inability to work, worsening symptoms

Progressive MS is defined differently from different perspectives.
Defining the clinical course of multiple sclerosis
The 2013 revisions

Fred D. Lublin, MD
Stephen C. Reingold, PhD
Jeffrey A. Cohen, MD
Gary R. Cutter, PhD
Per Soelberg Sørensen, MD, DMSc
Alan J. Thompson, MD

Neurology® 2014;83:278-286
The 2013 Revisions (1)

Core Phenotypes and Modifiers

- The core MS phenotypes (relapsing and progressive disease) should be retained with some modification

- Assessment of disease activity, measured by clinical relapses or CNS lesion activity is an important modifier of the core phenotypes

- Assessment of ongoing progression of disability is an important modifier of the core phenotypes
Active Disease

Clinical: relapses, acute or sub-acute episodes of new or increasing neurological dysfunction followed by full or partial recovery \((in\ the\ absence\ of\ fever\ or\ infection)\)

Imaging (MRI): occurrence of contrast enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions
Definitions (2)

**Progressive Disease**

**Clinical**: steadily increasing objectively documented neurological dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur)

**Imaging (MRI)**: no standardized imaging measures of disease progression are established.

*Increasing number and volume of T1 hypo-intense lesions, brain volume loss and changes in MTI and DTI are being explored*
MS Clinical Forms: revised classification

Figure 2  The 1996 vs 2013 multiple sclerosis phenotype descriptions for progressive disease

1996
MS clinical description
Subtypes

- Progressive accumulation of disability from onset with or without temporary plateaus, minor remissions and improvements (PP)
- Progressive accumulation of disability after initial relapsing course, with or without occasional relapses and minor remissions (SP)
- Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery (PR)

2013
MS disease modifiers
Phenotypes

- Progressive accumulation of disability from onset
  - Active* and with progression** (PP)
  - Active but without progression
  - Not active but with progression (SP)

- Progressive accumulation of disability after initial relapsing course
  - Not active and without progression (stable disease)


*Activity determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions). **Progression measured by clinical evaluation, assessed at least annually. If assessments are not available, activity and progression are “indeterminate.” MS = multiple sclerosis; PP = primary progressive; PR = progressive relapsing; SP = secondary progressive.
Pathologic Mechanisms in Early vs. Late MS

- Inflammation
- Degeneration
Will the real multiple sclerosis please stand up?

Peter K. Stys, Gerald W. Zamponi, Jan van Minnen and Jeroen J. G. Geurts

Nat Rev Neurosci 2012

host’s immune reaction to it (orange). Thus, MS requires these two intertwined ingredients, one uniformly progressive, the other intermittent and highly variable, which establish the type of disease in any one patient. We propose that the ‘real’ MS is the underlying cytodegeneration, which is most faithfully reflected by primary progressive disease. SPMS, secondary progressive MS
Clinical Trials

Conventional trial design

Large numbers, lengthy, very expensive

Targeting inflammation (largely)

=> Need to consider new trial designs

=> Need to focus on neuroprotection/repair?
Moving to adaptive trials

<table>
<thead>
<tr>
<th>Treatment A</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment B</td>
<td>Placebo</td>
</tr>
<tr>
<td>Treatment C</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Stage 1**
- Control: \( n_1 \)
- A: \( n_1 \)
- B: \( n_1 \)
- C: \( n_1 \)
- D: \( n_1 \)

**Stage 2**
- Control: \( n_2 \)
- A: \( n_2 \)
- B: \( n_2 \)
- C: \( n_2 \)

**Interim Analysis**
- Based on early outcome(s); e.g., MRI and/or disability
- Purpose:
  - Treatment selection
  - Futility stopping
  - No early stopping for rejection of \( H_0 \)

**Final Analysis**
- Including data from stages 1 & 2
- Disability outcome; e.g., EDSS

Patients to extension study: Randomised to treatments A and C (To be decided)
The interim measure

Δ MRI

Δ EDSS
A novel adaptive design strategy increases the efficiency of clinical trials in secondary progressive multiple sclerosis

Jeremy Chataway\textsuperscript{1,2}, Richard Nicholas\textsuperscript{2}, Susan Todd\textsuperscript{3}, David H Miller\textsuperscript{1,4}, Nicholas Parsons\textsuperscript{5}, Elsa Valdés-Márquez\textsuperscript{3}, Nigel Stallard\textsuperscript{5} and Tim Friede\textsuperscript{5}
Trials in Progressive MS

- Phenytoin Optic Neuritis Study (Phase II)
- PROXIMUS Trial - oxcarbazepine in SPMS (Phase II)
- INFORMS – fingolimod in PPMS (Phase III)
- ASCEND – natalizumab in SPMS (Phase III)
- ORATORIO – ocrelizumab (rituximab cousin) in PPMS (Phase III)
- EXPAND – siponimod (fingolimod cousin) in SPMS (Phase III)

- MS Smart Trial – riluzole, amiloride, ibudilast in SPMS (Phase II)
- SPRINT-MS – ibudilast in PPMS/SPMS (Phase II)
- MS – STAT – high dose simvastatin
- CUPID – cannabinoids

- rituximab, mesenchymal stem cells, mastitinib, lipoic acid, erythropoietin, hydroxyurea, idebenone
Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial

• High-dose simvastatin (80mg) in SPMS
• Established secondary progression (narrative/EDSS) for ≥ 2 years

• EDSS 4.0 (500m) - 6.5 (20m/2 sticks)
  – Relapse free/no corticosteroids >3 months
  – DMT >6 months
  – Mitoxantrone >12 months
  – Never alemtuzumab/natalizumab
Outcomes

• Primary
  – Volumetric MRI BBSI

• Secondary
  – Disability (EDSS/MSIS-29v2/MSFC)
  – New and enlarging lesions T2 MRI
  – Relapses
  – Safety

• Other*
  – Neuropsychology
  – Immunology/Proteomics
Screening showing BBSI colour overlay
Primary outcome: BBSI change in whole brain volume (%/year)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) placebo</th>
<th>Mean (SD) simvastatin</th>
<th>Difference means (95% CI)*</th>
<th>in p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change WBV (%/year)</td>
<td>0.589 (0.528)</td>
<td>0.298 (0.562)</td>
<td>-0.254 (-0.423 to -0.085)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Number patients evaluated**

- Placebo: 64
- Simvastatin: 66

*Adjusting for minimisation variables and MRI site*
Change whole brain volume (%/yr)
Change in EDSS 0 to 24 months

Change in EDSS from Baseline to 24 months
Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial

John Zajicek, Susan Ball, David Wright, Jane Vickery, Andrew Nunn, David Miller, Mayam Gomez Cano, David McManus, Sharukh Mallik, Jeremy Hobart, on behalf of the CUPID investigator group

- assess the value of Δ⁹-THC in slowing progressive MS over 3 yrs

- assess the safety of Δ⁹-THC over the long-term.

- improve research methodology; using new, patient-orientated methods.
CUPID (THC): EDSS progression over 3 years

**Treatment group**

- **Placebo**
- **Active**

**P (EDSS progression)**

- 1.0
- 0.8
- 0.6
- 0.4
- 0.2
- 0.0

**Time to EDSS progression (days)**

- 0
- 200
- 400
- 600
- 800
- 1000
- 1200

- Treatment group
  - Active
  - Placebo
Key PPMS clinical trials

Completed, ongoing and planned trials in primary progressive MS (PPMS)

- **Glatiramer acetate**
  - Phase 3 PROMiSE Trial
  - April-2004¹

- **Rituximab**
  - Phase 2/3 OLYMPUS Trial
  - April-2009²

- **Fingolimod**
  - Phase 3 INFORMS Trial
  - Data release: Q2 2015

- **Masitinib**
  - Phase 2/3 PPMS and SPMS
  - Data expected 2015³

- **Ocrelizumab**
  - Phase 3 ORATORIO Trial
  - Data expected Q4 2015⁴

- **Laquinimod†**
  - ARPEGGIO PoC Trial
  - Data expected 2018⁵

- **Oral**
- **Injectable**

- PROMiSE (N=943) and OLYMPUS (N=439) are the two largest randomized trials in PPMS patients completed to date
Rituximab
Anti-CD20 Monoclonal Antibody

- Rituximab is a genetically engineered chimeric (mouse-human) monoclonal antibody that targets CD20-positive B lymphocytes

- CD20 is present on B and pre-B lymphocytes but not on stem cells or plasma cells

- Long duration of action

Time to Confirmed Disease Progression

All Intent-to-Treat Patients (N=439)

HR: 0.77
(95% CI: 0.55 - 1.09)
p-value=0.1442

Proportion of Patients

Time to Confirmed Disease Progression (weeks)
Time to Confirmed Disease Progression

**Subgroup Analysis**

- **Gd (-) at Baseline**
  - n=143
  - HR: 0.63
  - (95% CI: 0.34–1.18)
  - p=0.1427

- **Gd (+) at Baseline**
  - n=72
  - HR: 0.33
  - (95% CI: 0.14–0.79)
  - p=0.0088
INFORMS  
Study design

Randomised, multicentre, double-blind, placebo-controlled, parallel-group study in ~940 patients with PPMS

<table>
<thead>
<tr>
<th>Screening (Day -45 to Day -1)</th>
<th>Baseline (Day -14 to Day -1)</th>
<th>Double-blind treatment period*</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI Visit</td>
<td>Randomisation (1:1)</td>
<td>Placebo</td>
<td>n=487</td>
</tr>
<tr>
<td>MRI</td>
<td>Fingolimod 0.5 mg</td>
<td>Fingolimod 0.5 mg</td>
<td>n=336</td>
</tr>
<tr>
<td>MRI</td>
<td>Month 12</td>
<td>Month 24</td>
<td>End of treatment (Month 36)</td>
</tr>
</tbody>
</table>

*Double-blind treatment period will last until the last patient randomised in the study completes treatment (Month 36, if not discontinued earlier) or a patient completes the 5-year maximum duration of treatment. Following implementation of Amendment 5 in 2010, patients who were randomised to receive fingolimod 1.25 mg or matching placebo were switched in a blinded manner to fingolimod 0.5 mg or continued on placebo. Patients who were enrolled in the study following implementation of Amendment 5 were randomised to receive fingolimod 0.5 mg or matching placebo. Miller D et al. Poster P07.116 presented at AAN 2013.
Primary endpoint, a novel approach

- The primary endpoint is time to sustained disability progression (SDP)
- SDP is defined based on any of three types of event:
  - 3-month sustained increase of ≥20% from Baseline in the timed 25-foot walk test (25’TWT) \textbf{OR}
  - 3-month sustained increase from Baseline in the EDSS score defined as:
    - 1 point in patients with Baseline EDSS 3.5-5.0
    - 0.5 point in patients with Baseline EDSS 5.5-6.0
  \textbf{OR}
  - 3-month sustained increase of ≥20% from Baseline in the 9-hole peg test (9-HPT)

*Defined as an increase of ≥20% from baseline in 25’TWT or increase from Baseline in EDSS score (1 point in patients with Baseline of 3.5 to 5.0; 0.5 points in patients with Baseline of 5.5 to 6.0) or increase of ≥20% from Baseline in 9-HPT
Abstract AAN April 2015:

- The composite primary endpoint in INFORMS was not met: Fingolimod demonstrated **no difference** compared to placebo in the time to the composite 3M-CDP versus placebo.

- EDSS: Fingolimod did **not** delay the time to 3M-CDP as measured by the EDSS as single outcome compared to placebo.

- BVL: Percent brain volume change (PBVC) measured using SIENA (Structural Image Evaluation, using Normalization, of Atrophy) was **not** different in patients treated with fingolimod 0.5 mg when compared to patients treated with placebo.
Neuroprotection

Repair/Remyelination

Lifestyle

Rehabilitation

Enhancing plasticity
Partial sodium channel blockade has been shown to be neuroprotective in experimental models of inflammatory axonal injury.
Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial

Raju Kapoor, Julian Furby, Thomas Hayton, Kenneth J Smith, Daniel R Altmann, Robert Brenner, Jeremy Chataway, Richard A C Hughes, David H Miller

Summary

Background Partial blockade of voltage-gated sodium channels is neuroprotective in experimental models of inflammatory demyelinating disease. In this phase 2 trial, we aimed to assess whether the sodium-channel blocker lamotrigine is also neuroprotective in patients with secondary progressive multiple sclerosis.

Methods Patients with secondary progressive multiple sclerosis who attended the National Hospital for Neurology and Neurosurgery or the Royal Free Hospital, London, UK, were eligible for inclusion in this double-blind, parallel-group trial. Patients were randomly assigned via a website by minimisation to receive lamotrigine (target dose 400 mg/day) or placebo for 2 years. Treating physicians, evaluating physicians, and patients were masked to treatment allocation. The primary outcome was the rate of change of partial (central) cerebral volume over 24 months. All patients who were randomly assigned were included in the primary analysis. This trial is registered with ClinicalTrials.gov, NCT00257855.

Findings 120 patients were randomly assigned to treatment (87 women and 33 men): 61 to lamotrigine and 59 to placebo. 108 patients were analysed for the primary endpoint: 52 in the lamotrigine group and 56 in the placebo group. The mean change in partial (central) cerebral volume per year was −3.18 mL (SD −1.25) in the lamotrigine group and −2.48 mL (−0.97) in the placebo group (difference −0.71 mL, 95% CI −2.56 to 1.15; p=0.40). However, in an exploratory modelling analysis, lamotrigine treatment seemed to be associated with greater partial (central) cerebral volume loss than was placebo in the first year (p=0.04), and volume increased partially after treatment stopped (p=0.04). Lamotrigine treatment reduced the deterioration of the timed 25-foot walk (p=0.02) but did not affect other secondary clinical outcome measures. Rash and dose-related deterioration of gait and balance were experienced more by patients in the lamotrigine group than the placebo group.

Interpretation The effect of lamotrigine on cerebral volume of patients with secondary progressive multiple sclerosis did not differ from that of placebo over 24 months, but lamotrigine seemed to cause early volume loss that reversed partially on discontinuation of treatment. Future trials of neuroprotection in multiple sclerosis should include investigation of complex early volume changes in different compartments of the CNS, effects unrelated to neurodegeneration, and targeting of earlier and more inflammatory disease.

Funding Multiple Sclerosis Society of Great Britain and Northern Ireland.

Lancet Neurol 2010; 9: 681-88
Published Online
June 7, 2010
DOI:10.1016/S1474-4422(10)7031-9
See Reflection and Reaction
page 647
Department of Neuroinflammation, National Hospital for Neurology and Neurosurgery and the Institute of Neurology, Queen Square, London, UK (R Kapoor FRCP, J Furby MRCP, T Hayton MRCP, Prof K J Smith PhD, D R Altmann PhD, J Chataway FRCP, Prof R A C Hughes FRCP, Prof D H Miller FRCP); Medical Statistics Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK (D R Altmann); and Department of Neurology, Royal Free Hospital, Pond Street, London, UK (R Brenner FRCP)
Correspondence to: Raju Kapoor, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK
rajkapoor@uclh.nhs.uk
Figure 2: Primary outcome
Mean partial (central) cerebral volume by intention-to-treat comparison, including numbers of valid 6-monthly observations. Bars=SE.
Lamotrigine in SPMS

**Rate of change of speed (1/T25FW) (%/mo X10^3)**

<table>
<thead>
<tr>
<th></th>
<th>active</th>
<th>placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT comparison</td>
<td>-0.38</td>
<td>-0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>PP comparison</td>
<td>-0.20</td>
<td>-0.88</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Suggestion of slower volume loss in year 2**

**Positive NfH response in adherent group**

**Biomarker Report from the Phase II Lamotrigine Trial in Secondary Progressive MS – Neurofilament as a Surrogate of Disease Progression**

**Rate of change of speed (1/T25FW) (%/mo X10^3)**

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<tr>
<td>PP comparison</td>
<td>-0.20</td>
<td>-0.88</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Phenytoin is neuroprotective in acute optic neuritis: Results of a phase 2 randomized controlled trial

R Kapoor¹, ², R Raftopoulos¹, ², S Hickman⁴, A Toosy¹, ², B Sharrack⁴, S Mallik¹, ², D Altmann², P Malladi¹, M Koltzenburg¹, ², C Wheeler-Kingshott², K Schmierer³, G Giovannoni³, and DH Miller²

National Hospital for Neurology and Neurosurgery¹, UCL Institute of Neurology², and Queen Mary University of London³, London UK, and Royal Hallamshire Hospital, Sheffield UK⁴
Trial design

Primary outcome measure: RNFL thickness

Sample size vs treatment effect

<table>
<thead>
<tr>
<th>40%</th>
<th>50%</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>35</td>
<td>25</td>
</tr>
</tbody>
</table>

• Direct, noninvasive measurement of degeneration in retinal ‘white & gray matter’
• Correlates with visual loss and brain volume
• Sensitive, semiautomated measurement
• Longitudinal natural history data enables sample sizes to be calculated

• Numbers per arm ($\alpha=0.05$, $\beta=0.8$)
• Placebo-controlled, parallel group design, measurements at 0, 6 months
• Method: 6 month affected eye RNFL adjusted for fellow eye at baseline
• Allow 20% dropout/nonadherence
Primary outcome: RNFL

- Active-placebo adjusted difference 7.15 μm (95% CI 1.08, 13.22 p=0.02)
- 30% reduction of atrophy in active group

- PP comparison: Active-placebo adjusted difference 7.40 μm (95% CI 0.76, 14.04 p=0.03)

Bars are standard errors around the unadjusted group means
Effect of MD1003 (High Doses of Biotin) in Progressive Multiple Sclerosis: Results of a pivotal phase III Randomized Double Blind Placebo Controlled Study


CHU Reims, CHU Nice, CHU Rennes, CHU Toulouse, GH Pitié-Salpêtrière Paris, CHU Lyon, CHU Strasbourg, CHU Nancy, FOAR Paris, CHU Clermont-Ferrand, CHU Caen, CHU Nantes, CHU Dijon, CHU Montpellier, CHU Bordeaux, Medday Pharmaceuticals, CHU Marseille
Biotin targets two mechanisms that may underpin progressive MS

- **Oligodendrocyte**
- **Demyelinated axon**

**Fatty acid synthesis**

**BIOTIN**

**ATP Increase**

**ACC:** acetyl CoA carboxylase
### Primary Endpoint results

<table>
<thead>
<tr>
<th></th>
<th>MD1003 n(%)</th>
<th>Placebo n(%)</th>
<th>p-value (^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT population</strong></td>
<td>N=103</td>
<td>N=51</td>
<td>0.0051</td>
</tr>
<tr>
<td></td>
<td>13 (12.62%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Per protocol</strong></td>
<td>N=87</td>
<td>N=42</td>
<td>0.0093</td>
</tr>
<tr>
<td><strong>population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (14.9%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Fisher's Exact test

- Primary endpoint met with EDSS: 76.9%
- Primary endpoint met with TW25: 38.5%
Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial

MS-SMART Trialists

Dr Jeremy Chataway
MULTI-ARM trials: an effective way of speeding up the therapy evaluation process!
Interventions

- Amiloride 5 mg bd
- Riluzole 50mg bd
- Fluoxetine 20mg bd
Secondary and Primary Progressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis

- 96-week, randomized, placebo-controlled phase II trial of ibudilast in SPMS/PPMS (Concurrent treatment with IFN-β1 or GA is allowed)
- Primary Outcome: whole brain atrophy (BPF)
  - Secondary Outcomes:
    - DTI (descending pyramidal tracts)
    - MTR (whole brain), OCT (retinal nerve fiber layer)
    - Cortical atrophy (CLADA)
- Standardized 3T imaging at all sites
- EDSS, MSFC-4, PROs
- Utilize NeuroNEXT, NIH-funded, Phase II clinical trial network
  - Head-to-head comparison of imaging measures
    - Longitudinal validation to clinical outcomes
Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study

Peter Connick, Madhan Kolappan, Charles Crawley, Daniel J Webber, Rickie Patani, Andrew W Michell, Ming-Qing Du, Shi-Lu Luan, Daniel R Altmann, Alan J Thompson, Alastair Compston, Michael A Scott, David H Miller, Siddharthan Chandran

Lancet Neurology Feb 2012

10 patients with secondary progressive MS
Studied visual system
Autologous mesenchymal stem cells in secondary progressive MS

- 10 SPMS patients with previous optic neuritis
- Studied pre- and post stem cell Rx
- Significant improvement of visual acuity (unblinded)
- Laboratory evidence for remyelination (blinded)
  - ↓VEP latency (p=0.016) & ↑optic nerve area (p=0.006)

Connick et al Lancet Neurology 2012
• Constitution of IMSCT Study Group (Paris, March 2009) supported by CMSC, Canadian MS Society and ECTRIMS

• Consensus paper on the utilization of MSCs for the treatment of MS published in Mult. Scler. 2010

• Consensus paper set the guidelines for phase I/II clinical trials of MSCT in MS
Progressive MS Alliance

Mission

To expedite the development of effective disease modifying and symptom management therapies for progressive forms of multiple sclerosis
Setting a research agenda for progressive multiple sclerosis: The International Collaborative on Progressive MS

Robert J. Fox¹, Alan Thompson², David Baker³, Peer Baneke⁴, Doug Brown⁵, Paul Browne⁶, Dhia Chandraratna⁷, Olga Ciccarelli², Timothy Coetzee⁶, Giancarlo Comi⁷, Anthony Feinstein⁸, Raj Kapoor⁹, Karen Lee¹⁰, Marco Salvetti¹¹, Kersten Sharrock¹², Ahmed Toosy², Paola Zaratin¹³ and Kim Zuidwijk¹⁴
Countries actively involved in the Alliance
Scientific Steering Committee

Alan Thompson, UK, Chair
Timothy Coetzee, USA
Kathy Smith, USA
Paola Zaratin, Italy
Dhia Chandraratna, MSIF
Ceri Angood, MSIF
Susan Kolhaas, UK
Jeroen Geurts, Netherlands
Karen Lee, Canada
Giancarlo Comi, Italy, Vice-Chair
Bruce Bebo, USA
Robert Fox, USA
Marco Salvetti, Italy
Xavier Montalban, Spain
Nick de Rijke, UK
Raj Kapoor, UK
Per Soelberg Sorensen, Den
Anthony Feinstein, Canada
Reinhard Hohlfeld, Germany
Priority areas:

- Underlying Mechanism/Experimental Models
- Target pathways and drug repurposing
- Proof of concept trials (phase II)
- Phase III clinical trials & outcome measures
- Symptom management and rehabilitation
Global Research Funders

• Government
  – NIH, CDMRP, Medical Research Council (UK), CIHR (Canada)
• MS Societies
• Private foundations
  – Hilton Foundation, Wellcome Trust
• Pharmaceutical companies
Global Progressive MS Portfolio
Distribution of Projects by Alliance Priority

- Experimental Models: 245, 61%
- Targets/Repurposing: 99, 25%
- POC Strategies: 44, 11%
- Clinical Outcome Measures: 9, 2%
- Symptom Management/Rehabilitation: 5, 1%
Symptoms/Rehab Priority
Projects by Area of Focus

No of Projects
Bladder
Cognition/Memory
Exercise
Exercise/Cognition
General Rehab
Mindfulness
Mobility
Pain
QoL
Spasticity
Long term commitment towards PMSA goal

2013 – 2021 PLAN

2013 – 2017
HORIZON 1

2017 – 2021
HORIZON 2/3

CHALLENGES AWARDS 2013 - 2016

COLLABORATIVE TEAM AWARDS 2014 - 2017

INNOVATIVE OPERATIVE FUNDING MODELS TO ACELERATE RESEARCH
Benefits from the PMSA

• Providing multiple avenues for experts (MS organisations, academia, industry etc.) from around the world to meet and discuss the most urgent issues in Progressive MS research

• Growing global commitment to Progressive MS research to €22 million over the next 5 years

• For the first time ever, MS Societies are funding research together without considering geography – funding the best science anywhere in the world

• Raising profile and underlining need
Progressive multiple sclerosis 1
Pathological mechanisms in progressive multiple sclerosis

Progressive multiple sclerosis 2
Treatment of progressive multiple sclerosis: what works, what does not, and what is needed
Anthony Feinstein, Jenny Freeman, Albert C Lo

Progressive multiple sclerosis 3
Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives
Daniel Ortaneda, Robert J Fox, Jeremy Chataway
Take home messages

• Although we can diagnose better, there is an urgent need to raise awareness in community

• Great progress in treatments for relapsing/remitting MS. Now focus on risk-benefit analysis

• Needs to be replicated in progressive MS

• More work on models of care which provide greater continuity and encourage self-management.
# MSC Treatment of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Indication</th>
<th>Patients</th>
<th>MSC Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connick 2012</td>
<td>SPMS</td>
<td>10</td>
<td>Autologous culture-expanded BM MSCs administered IV</td>
</tr>
<tr>
<td>Karussis 2010</td>
<td>RR, SP, PP MS</td>
<td>15</td>
<td>Autologous culture-expanded BM MSCs administered IV and IT</td>
</tr>
<tr>
<td>Liang 2009</td>
<td>PP MS</td>
<td>1</td>
<td>Allogeneic umbilical cord MSCs administered IV and IT after CTX</td>
</tr>
<tr>
<td>Mohyeddin Bonad 2007</td>
<td>Treatment-refractory MS</td>
<td>10</td>
<td>Autologous culture-expanded BM MSCs administered IT</td>
</tr>
<tr>
<td>Rice 2010</td>
<td>Chronic MS</td>
<td>6</td>
<td>Fresh BM cells enriched for MSCs</td>
</tr>
<tr>
<td>Riordan 2009</td>
<td>Treatment-refractory MS</td>
<td>3</td>
<td>Autologous non-expanded adipose MSCs</td>
</tr>
<tr>
<td>Yamout 2010</td>
<td>SPMS</td>
<td>10</td>
<td>Autologous culture-expanded BM MSCs administered IT</td>
</tr>
</tbody>
</table>
Global Progressive MS Projects - Pushgraph™ Analytics

- 405 projects (out of 707) identified as relevant to progressive MS

- Total Multi-Year Commitment = $132,608,598
Progressive MS Map

Purple = Progressive
Orange = Non-Progressive
Challenges ahead

• Understand relevant aspects of human MS pathology
  – Validate a preclinical model that emulates human pathology
  – Develop high throughput screening tools
• Validate a Phase II outcome biomarker
  – Use trials to advance methodology
• Develop accepted clinical outcome measures
• Drive symptomatic treatments and rehabilitation

www.endprogressivems.org
Global Progressive MS Portfolio
Distribution of Projects by Priority/Stage

Understanding Progression
Clin. Trial Designs/Outcomes
Dev./Testing of New Agents
Sympt. Mgmt/Rehab

- Discovery: 213, 6, 18, 3
- Clinical Research: 23, 30, 6
- Clinical Trials: 6, 16

Number of Projects by Stage: 213 (Discovery), 30 (Clinical Research), 16 (Clinical Trials), 84 (Clinical Trials)
# 2010 Revised McDonald MS Diagnostic Criteria

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space (DIS) and time (DIT)*

<table>
<thead>
<tr>
<th>CLINICAL (ATTACKS)</th>
<th>LESIONS</th>
<th>ADDITIONAL CRITERIA TO MAKE DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack</td>
<td>None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS</td>
</tr>
<tr>
<td>2 or more</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>DIS; OR await further clinical attack implicating a different CNS site</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of ≥2 lesions</td>
<td>DIT; OR await a second clinical attack</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>DIS OR await further clinical attack implicating a different CNS site AND DIT; OR await a second clinical attack</td>
</tr>
<tr>
<td>0 (progression from onset)</td>
<td>One year of disease progression (retrospective or prospective) AND at least two of: DIS in the brain based on ≥1 T2 lesion in periventricular, juxtacortical or infratentorial regions; DIS in the spinal cord based on ≥2 T2 lesions; or positive CSF</td>
<td></td>
</tr>
</tbody>
</table>

# Paraclinical Evidence in MS Diagnosis

<table>
<thead>
<tr>
<th>Evidence for Dissemination of Lesions in Space (DIS)²</th>
<th>Evidence for Dissemination of Lesions in Time (DIT)³</th>
</tr>
</thead>
</table>
| ≥ 1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord  
  - Gadolinium enhancement of lesions is not required for DIS  
  - If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count |  
  - A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI or  
  - Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time |

<table>
<thead>
<tr>
<th>Evidence for Positive CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index</td>
</tr>
</tbody>
</table>

³ Swanton KL et al. J Neurol Neurosurg Psychiatry 2006;77:830-833  

These diagnostic criteria were developed through the consensus of the International Panel on the Diagnosis of MS. See cited articles for details. Funding through National Multiple Sclerosis Society (USA) and European Committee for Treatment and Research in MS; additional support from the Multiple Sclerosis International Federation and MS Ireland

National Multiple Sclerosis Society (USA) Professional Resource Center. 733 Third Avenue. New York, NY 10017-3288  
http://www.nationalMSsociety.org/PRC. MD_info@nmss.org  
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**Natalizumab** is a humanized ab against subunit alfa 4 of the integrins $\alpha_4\beta_1$ y $\alpha_4\beta_7$.
### Table 2 A: Trials in MS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Follow Up in Yrs</th>
<th>Entry EDSS</th>
<th>Active Treatment</th>
<th>Primary outcome measure</th>
<th>Primary Result</th>
<th>Comments</th>
<th>Publication Yr &amp; Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine-MSSG</td>
<td>547</td>
<td>1.5</td>
<td>3.0-7.0</td>
<td>Cyclosporine</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td>Two other co-primary endpoints were also used: time to wheelchair bound (+ve); daily living (-ve)</td>
<td>1990</td>
</tr>
<tr>
<td>CCMSSG</td>
<td>168</td>
<td>2 (mean)</td>
<td>4.0-6.5</td>
<td>Cyclophosphamide or plasma exchange</td>
<td>Comparison of rates of EDSS worsening</td>
<td>-ve</td>
<td>Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)</td>
<td>1991</td>
</tr>
<tr>
<td>EUSPMS</td>
<td>718</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Betaseron 8MU/alternate days vs placebo</td>
<td>Time to confirmed EDSS worsening</td>
<td>-/+ve</td>
<td></td>
<td>1998</td>
</tr>
<tr>
<td>SPECTRIMS</td>
<td>618</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Rebif (22 or 44mcg 3/week)</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></td>
<td>2001</td>
</tr>
<tr>
<td>IMPACT</td>
<td>436</td>
<td>2</td>
<td>3.5-6.5</td>
<td>Avonex (60mcg/week)</td>
<td>MSFC</td>
<td>-/+ve</td>
<td>Positive outcome on MSFC (upper limb but not walking component), but not EDSS</td>
<td>2002</td>
</tr>
<tr>
<td>MIMS</td>
<td>188</td>
<td>2</td>
<td>3.0-6.0</td>
<td>Mitoxantrone 5 or 12 mg/m2 every 3 months</td>
<td>Composite measure (EDSS/ambulation index/relapses)</td>
<td>-/+ve</td>
<td>50% of cohort RRMS; 5 domain outcome measure not validated; cardiotoxicity/leukaemia risk</td>
<td>2002</td>
</tr>
<tr>
<td>NASG</td>
<td>939</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Betaseron 8MU or 5MU/m2 alternate days</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></td>
<td>2004</td>
</tr>
<tr>
<td>ESIMS</td>
<td>318</td>
<td>2</td>
<td>3.0-6.5</td>
<td>Immunoglobulin 1g/kg/month (27 months)</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></td>
<td>2004</td>
</tr>
<tr>
<td>MAESTRO</td>
<td>612</td>
<td>2</td>
<td>3.0-6.5</td>
<td>MBP8298</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></td>
<td>2011</td>
</tr>
</tbody>
</table>

### Table 2 B: Current UK Trials in SPMS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Follow up Yrs</th>
<th>Entry EDSS</th>
<th>Active Treatment</th>
<th>Primary outcome measure</th>
<th>Reporting Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUPID (Phase III)</td>
<td>493</td>
<td>3</td>
<td>4.0-6.5</td>
<td>Tetrahydrocannabinol</td>
<td>Time to confirmed EDSS worsening; MSIS29 mean change</td>
<td>2012</td>
</tr>
<tr>
<td>MS-STAT (Phase IIb)</td>
<td>140</td>
<td>2</td>
<td>4.0-6.5</td>
<td>Simvastatin</td>
<td>MRI brain atrophy</td>
<td>2012</td>
</tr>
</tbody>
</table>
CUPID (THC): EDSS progression in patients with baseline EDSS <6 (post-hoc analysis)

Log rank test $P = 0.01$

$n = 110$

Time to EDSS progression (days)

Treatment group
- Active
- Placebo
Acute neuroprotection

An exploratory phase IIa study to evaluate phenytoin as neuroprotective strategy in acute optic neuritis

1. ≤14 days since symptom onset
2. Visual acuity worse than or equal to 6/9 in affected eye
3. No history of optic neuritis or disease in either eye; corrected VA in unaffected eye better than or equal to 6/6
4. If patients has MS EDSS 5.5 or less

Informed consent

Patients can be offered at the discretion of the treating physician treatment with a short course of steroids

PHENYTOIN
Randomised acutely (+14 days) to phenytoin* or placebo
* acute oral loading dose (15mg/kg rounded up to nearest 100mg) followed by maintenance dose 4mg/kg (rounded up to the nearest 50mg) or maximum 300mg/day for 14 weeks
Randomisation based on minimisation via web

Further investigations and baseline MRI brain within 28 days of symptom ONSET

Alternative diagnosis

Not part of ITT cohort

Primary outcome at 26 weeks
Retinal nerve fibre thickness in affected eye

Secondary outcomes at 48 weeks
Low contrast visual acuity
Visual evoked potential latency and amplitude
MRI outcomes
Blood and urine Biomarkers
Safety profile

Estimated power calculations*

<table>
<thead>
<tr>
<th>Clinical Classification</th>
<th>Placebo 1</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative diagnosis</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>ITT population</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>90</td>
</tr>
</tbody>
</table>

* Data from a longitudinal study of OCT findings obtained in 11 patients with acute demyelinating optic neuritis who were followed serially from initial presentation for 12-18 months at Moorfields Eye Hospital and the Institute of Neurology (A. Kirkness, D. Attman, D. Chang-Woo and Dr. Miller; unpublished) was used to calculate the size, based on the most efficient analysis of data on the primary outcome and power of 80% to detect a treatment effect of 50% at 5% significance level, allowing for a combined loss to follow-up and non-adherence of 10%.
# Baseline Characteristics (154 patients)

<table>
<thead>
<tr>
<th></th>
<th>MD1003 (n=103)</th>
<th>Placebo (n=51)</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>51.5</td>
<td>58.8</td>
<td>NS</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>51.8 (9.1)</td>
<td>50.7 (8.4)</td>
<td>NS</td>
</tr>
<tr>
<td>PPMS (%)</td>
<td>40.8</td>
<td>25.5</td>
<td>NS</td>
</tr>
<tr>
<td>SPMS (%)</td>
<td>59.2</td>
<td>74.5</td>
<td>NS</td>
</tr>
<tr>
<td>MS duration, years, mean (SD)</td>
<td>14.8 (8.9)</td>
<td>17.4 (10.3)</td>
<td>NS</td>
</tr>
<tr>
<td>EDSS, mean (SD)</td>
<td>5.98 (0.8)</td>
<td>6.2 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant DMT (%)</td>
<td>40.8</td>
<td>41.2</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment with fampridine (%)</td>
<td>41</td>
<td>54.9</td>
<td>NS</td>
</tr>
</tbody>
</table>
Primary endpoint: Proportion of patients with improvement at M9 confirmed at M12

- Definition of improvement:
  EDSS decrease by at least 1 point if baseline EDSS 4.5-5.5 and 0.5 point if baseline EDSS 6-7 or Timed 25-Foot Walk (TW25) \(\geq 20\%\) compared to baseline

- Baseline values: best EDSS and TW25 between M-1 and M0
"This report is independent research funded by the Medical Research Council (MRC) and Multiple Sclerosis Society (MS Society) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership."
Scientific Strategy Timeline

- **Sept 2013**: Science Strategy Meeting
- **Sept 2014**: RFA 1 – Challenge & Infrastructure
  - Rehab Meeting
- **Sept 2015**: RFA 2 – Collaborative Networks
  - Industry stakeholders meeting
  - Industry stakeholders engagement
- **Sept 2016**: Alliance Scientific Meeting
Meeting Review

Progressive MS: from pathophysiology to drug discovery

Marco Salvetti, Douglas Landsman, Peter Schwarz-Lam, Giancarlo Comi, Alan J Thompson and Robert J Fox
Current Progressive MS Research Initiatives

1. Over 100 investigator initiated research projects
2. MS Outcomes Assessment Consortium
3. Clinical Trials- MS SMART, SPRINT MS
4. SUMMIT natural history and risk factors study
5. Revision of Lublin-Reingold Clinical Course Descriptor
6. International Progressive MS Alliance