

MS Treatments

Current and Emerging

Focus on Progressive MS

Neurological Information Day

September 2015

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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. .

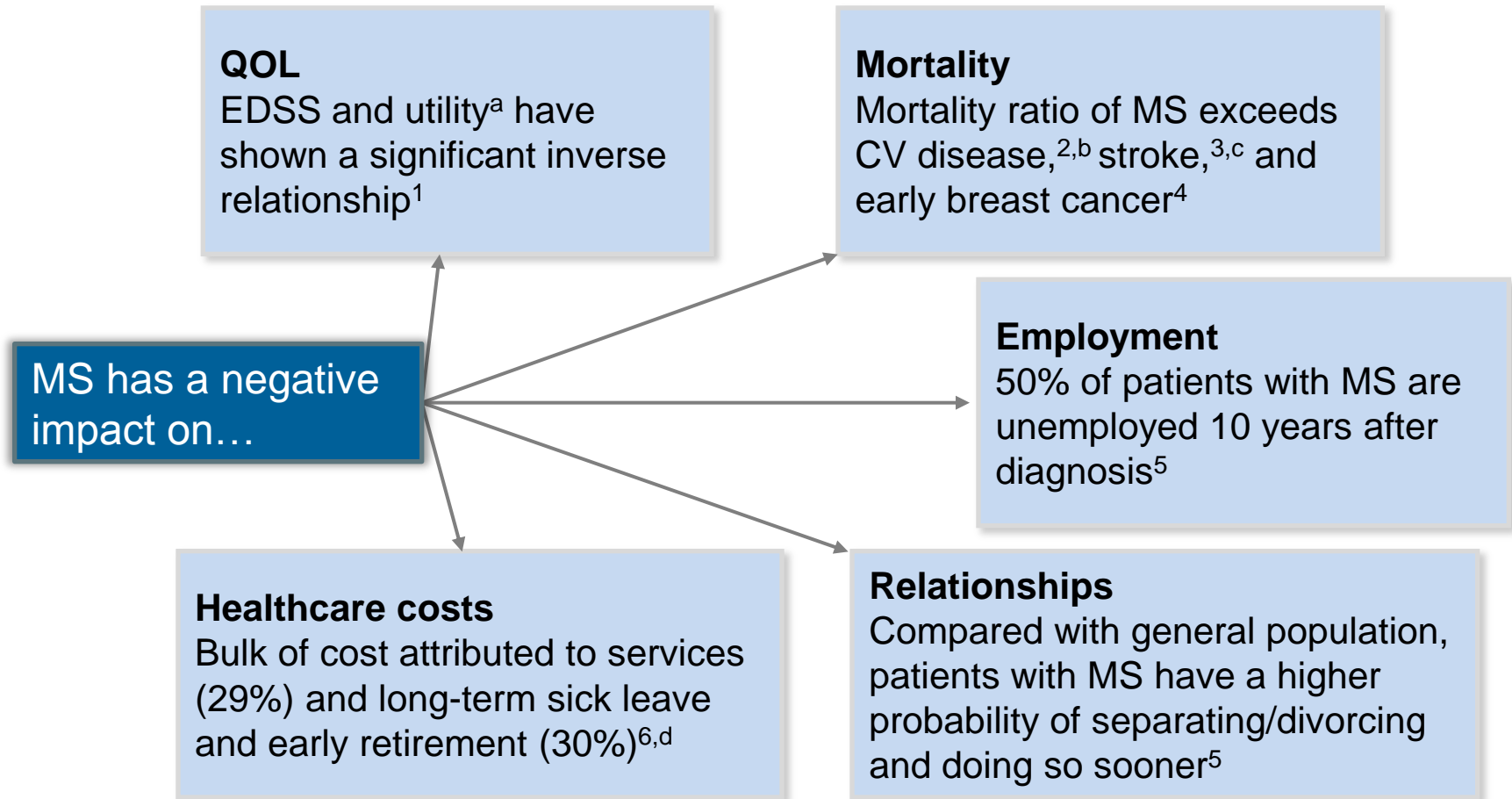
He received support for travel from the MS International Federation as Chair of their Medical and Scientific Advisory Board, from the International Progressive MS Alliance, as chair of their Scientific Steering Committee and from the National MS Society (USA) as member of their Research Programs Advisory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

September 2015

Outline

- Introduction/Context
- MS Management
- The challenge of Progressive MS

MS Is a Disabling Condition



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

1. Orme M et al. *Value Health*. 2007;10:54-60.

2. De Marco R et al. *Diabetes Care*. 1999;22:756-761.

3. Petty DW et al. *Mayo Clin Proc*. 2005;80:1001-1008.

4. Hooning MJ et al. *Int J Radiat Oncol Biol Phys*. 2006;64:1081-1091.

5. Pfleger CC et al. *Mult Scler*. 2010;16:121-126.

6. Berg J et al. *Eur J Health Econ*. 2006;7 (suppl 2):S75-S85.

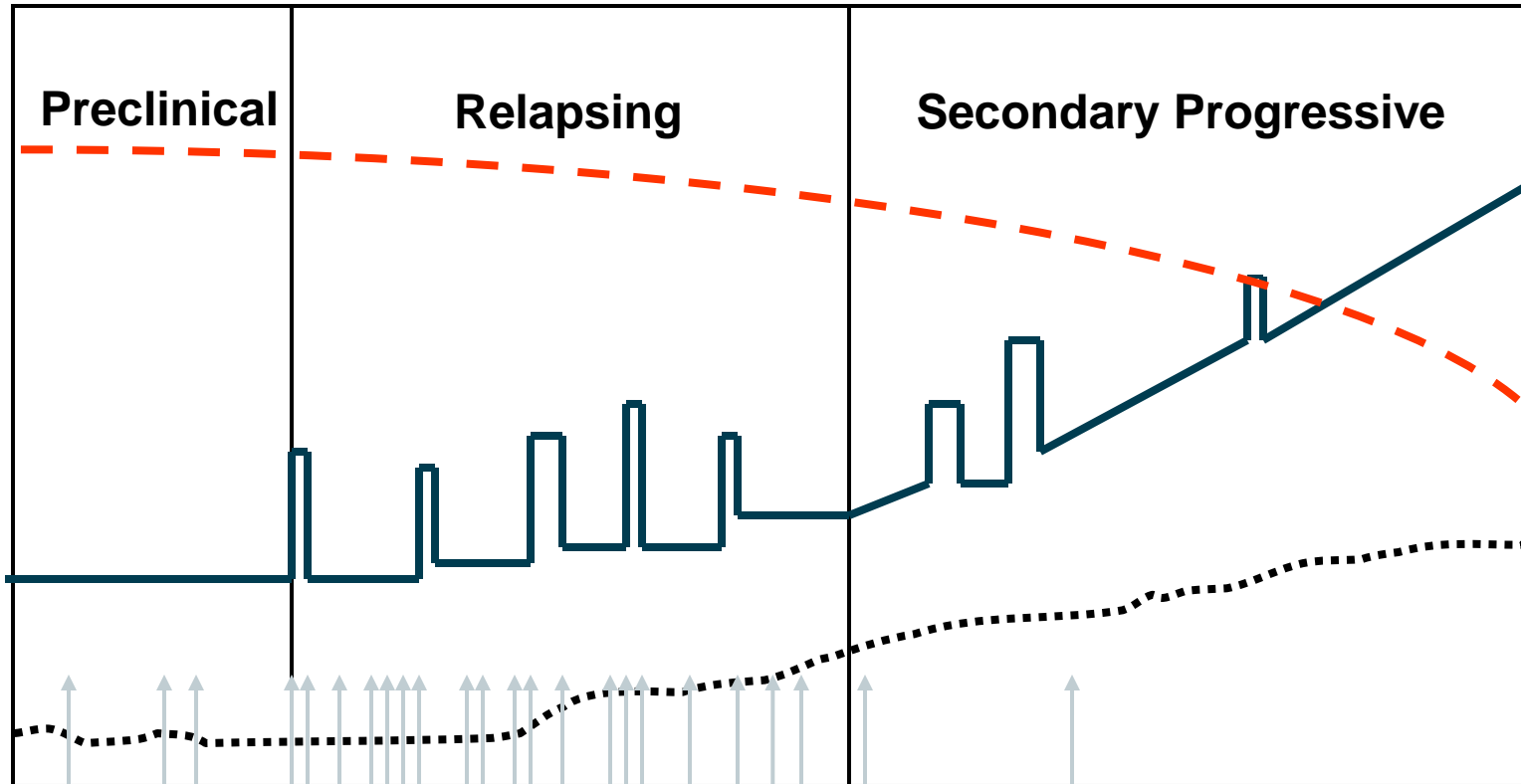
a. Utility measures derived from EQ-5D

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



-  relapses and impairment
-  MRI activity
-  brain volume
-  MRI burden of disease



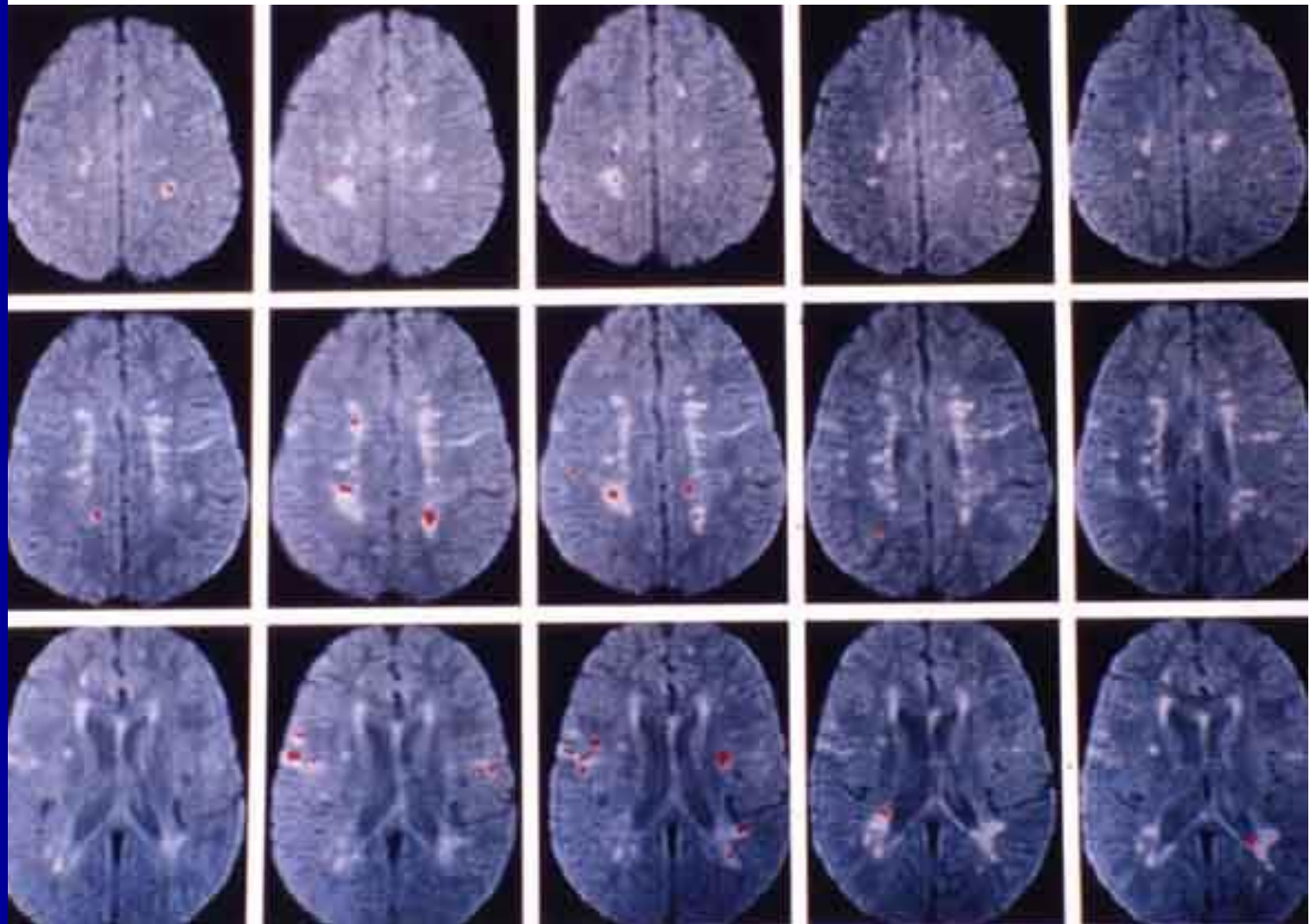
Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis

W. Ian McDonald, FRCP,¹ Alistair Compston, FRCP,² Gilles Edan, MD,³ Donald Goodkin,⁴
Hans-Peter Hartung, MD,⁵ Fred D. Lublin, MD,⁶ Henry F. McFarland, MD,⁷ Donald W. Paty, MD,⁸
Chris H. Polman, MD,⁹ Stephen C. Reingold, PhD,¹⁰ Magnhild Sandberg-Wollheim, MD,¹¹
William Sibley, MD,¹² Alan Thompson, MD,¹³ Stanley van den Noort, MD,¹⁴ Brian Y. Weinshenker, MD,¹⁵
and Jerry S. Wolinsky, MD¹⁶



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

Chris H. Polman, MD, PhD,¹ Stephen C. Reingold, PhD,² Gilles Edan, MD,³ Massimo Filippi, MD,⁴
Hans-Peter Hartung, MD,⁵ Ludwig Kappos, MD,⁶ Fred D. Lublin, MD,⁷ Luanne M. Metz, MD,⁸
Henry F. McFarland, MD,⁹ Paul W. O'Connor, MD,¹⁰ Magnhild Sandberg-Wollheim, MD,¹¹
Alan J. Thompson, MD,¹² Brian G. Weinshenker, MD,¹³ and Jerry S. Wolinsky, MD¹⁴



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.



National
Multiple Sclerosis
Society

2010 Revised McDonald MS Diagnostic Criteria¹

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT
AND RESEARCH IN MULTIPLE SCLEROSIS

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

CLINICAL (ATTACKS)	LESIONS	ADDITIONAL CRITERIA TO MAKE DX
2 or more	Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	DIS; OR await further clinical attack implicating a different CNS site
1	Objective clinical evidence of ≥ 2 lesions	DIT; OR await a second clinical attack
1	Objective clinical evidence of 1 lesion	DIS OR await further clinical attack implicating a different CNS site AND DIT; OR await a second clinical attack
0 (progression from onset)		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

1. Polman et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald Criteria. Ann Neurol 2011;69:292-302.* See reverse for DIS and DIT



National
Multiple Sclerosis
Society

Paraclinical Evidence in MS Diagnosis

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT
AND RESEARCH IN MULTIPLE SCLEROSIS

Evidence for Dissemination of Lesions in Space (DIS)²

- ≥ 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

Evidence for Dissemination of Lesions in Time (DIT)³

- 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

Evidence for Positive CSF

Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index

² Swanton KL et al. Lancet Neurology 2007;6:677-686 / Swanton KL et al. J Neurol Neurosurg Psychiatry 2006;77:830-833

³ Montalban X, et al. Neurology 2010;74:427-434

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

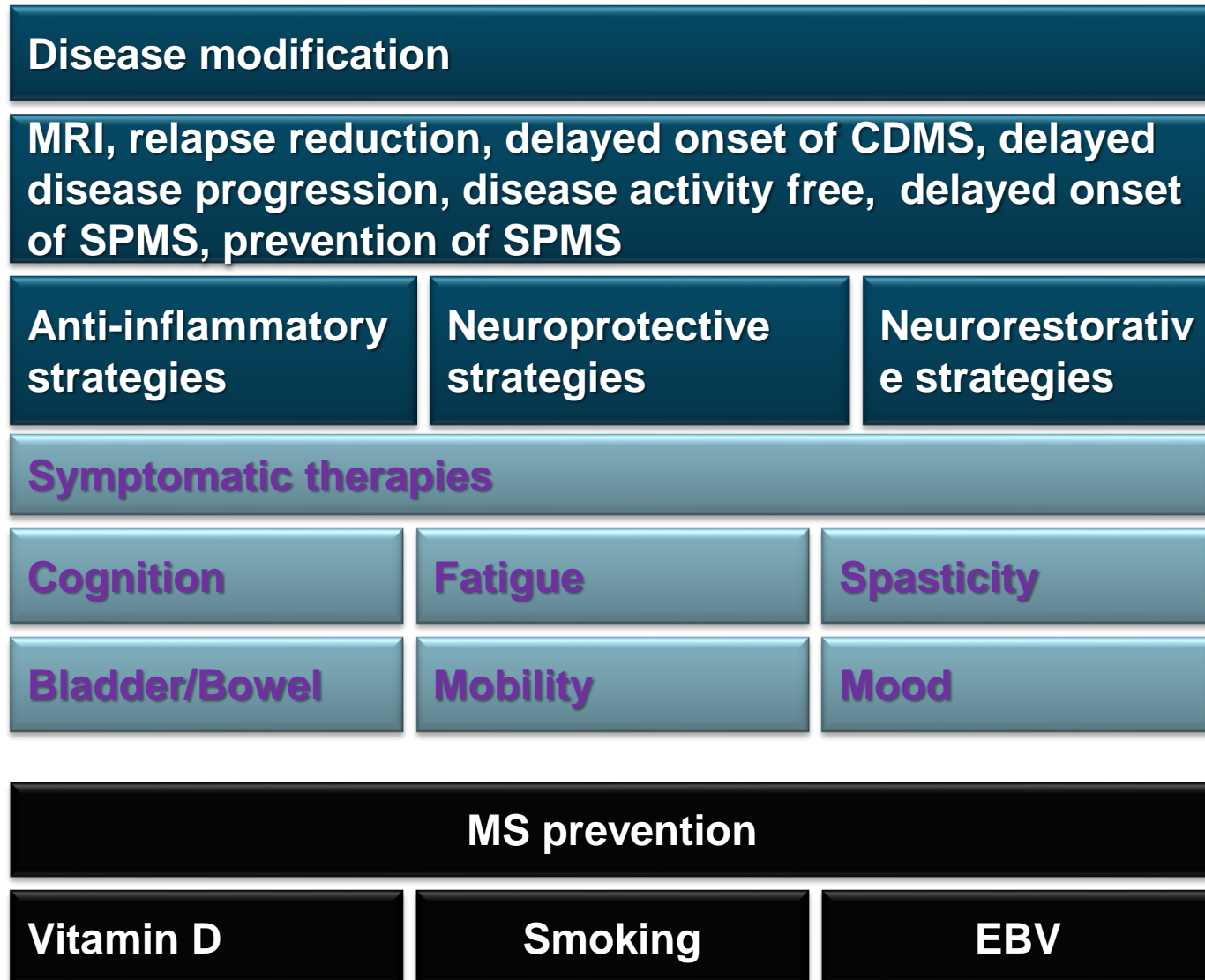
National Multiple Sclerosis Society (USA) Professional Resource Center. 733 Third Avenue. New York, NY 10017-3288
<http://www.nationalMSSociety.org/PRC>. MD_info@nmss.org
 © 2011 National Multiple Sclerosis Society

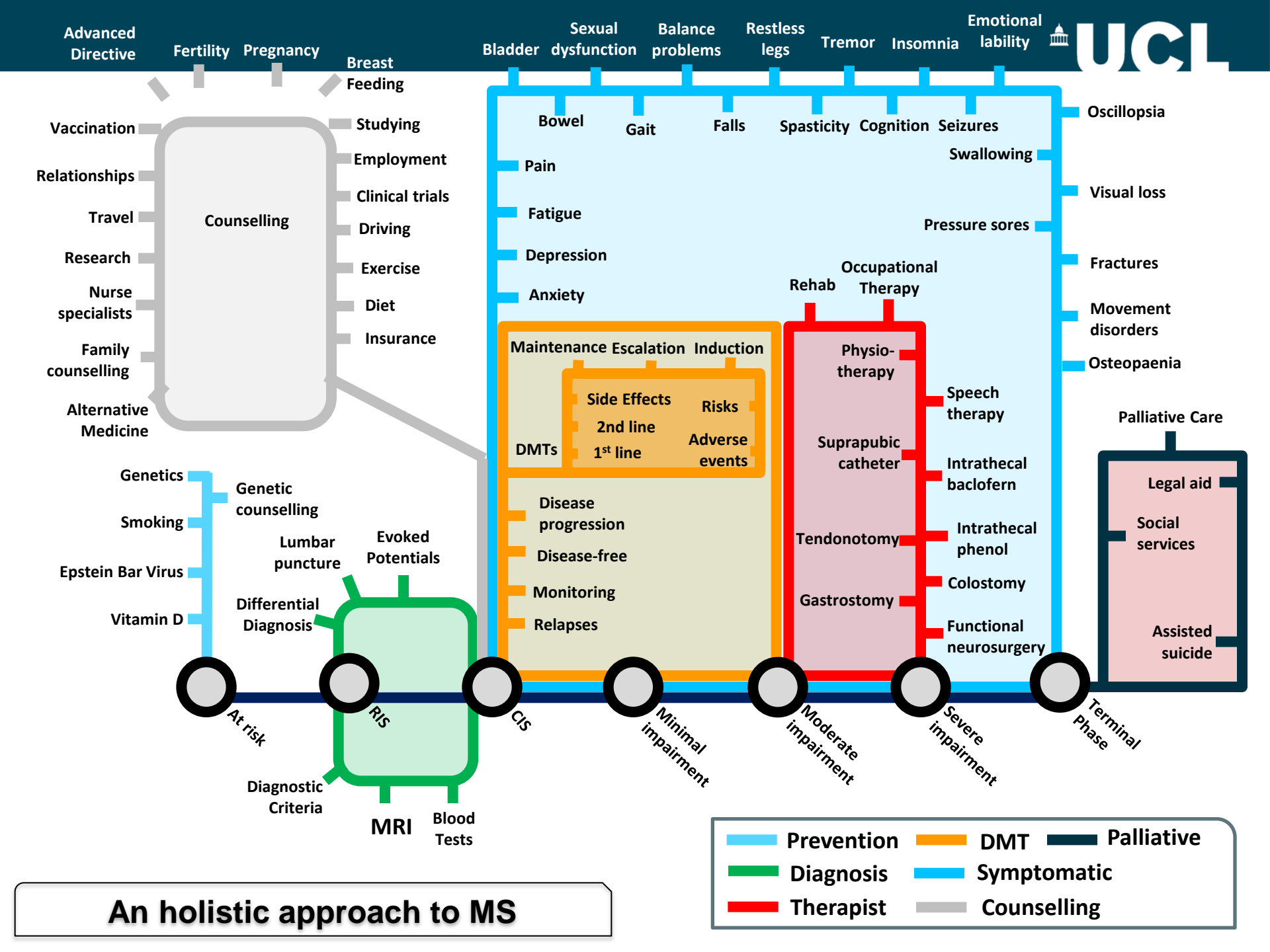
BR0040

MS Survey of 1,500 people with MS in 2015

- **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**

The unmet need is massive







m5 decisions

Treatments for Multiple Sclerosis

Who is eligible for Disease Modifying Drugs?

Not everyone with MS is eligible for Disease Modifying Drugs, and not everyone would benefit from having them. DMDs are prescribed by the NHS for people who meet certain criteria.

The criteria are based on the results of clinical trials of the drugs which indicate which patients would benefit. It all depends on how long you have had MS and which drug is being considered.

Who can be considered for interferon beta and glatiramer acetate?

Interferon beta and glatiramer acetate are well established DMDs. Interferon beta is a natural substance found in the body. Glatiramer acetate is a synthetic version of a protein found in the body. Both are used to treat MS.

Relapsing-remitting MS

The following criteria need to be met before you can be considered for treatment with interferon beta or glatiramer acetate:

- You have been diagnosed with MS
- You must be able to walk independently
- You must be at least 18 years old for interferon beta, meaning that you must be able to walk at least 10 metres with or without assistance
- You must be at least 18 years old for glatiramer acetate, meaning that you must be able to walk at least 10 metres without assistance
- You must have experienced at least two clinically isolated syndromes or relapses in the last 2 years

Clinically Isolated Syndrome (CIS) (interferon beta only)

CIS is a single episode of MS. It is the first episode of MS symptoms lasting at least 24 hours, but before a formal diagnosis of MS has been made. It is usually followed by a period of remission.

Secondary progressive MS (interferon beta only)

This criteria must be met for you to be eligible for treatment with interferon beta.

The young person's guide to MS

The central nervous system

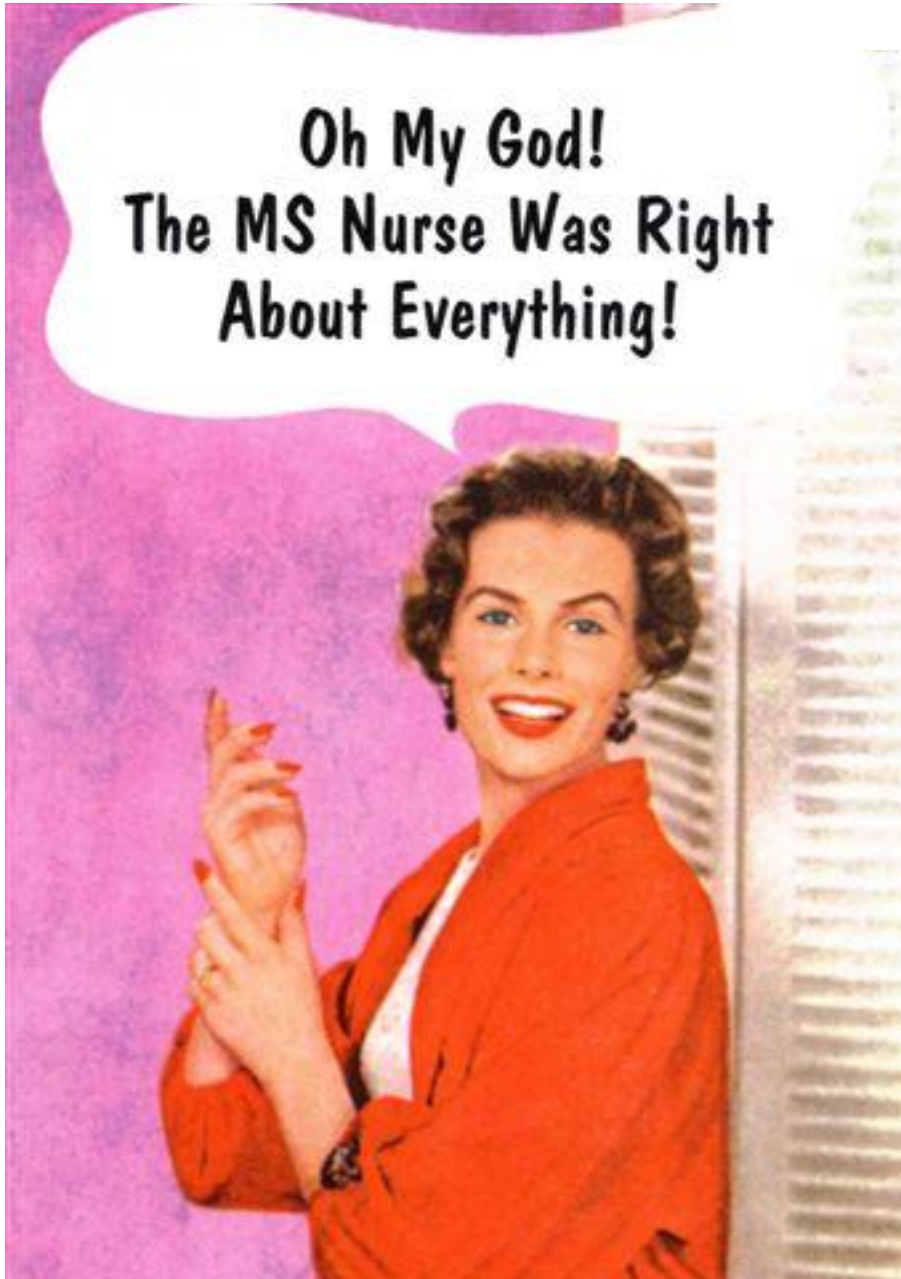
MS is a condition in which damage occurs to the central nervous system. The central nervous system is made up of the brain, spinal cord and optic nerves. It is responsible for controlling the body and sending messages to the rest of the body.

The central nervous system is divided into two main parts:

- 1. The brain
- 2. The spinal cord

The brain is the part of the central nervous system that controls the body and sends messages to the rest of the body. It is made up of billions of cells called neurons. The spinal cord is the part of the central nervous system that carries messages between the brain and the rest of the body. It is made up of a bundle of nerves.

**Oh My God!
The MS Nurse Was Right
About Everything!**



Guidelines in MS

NICE guidelines
NHS England
Association of British Neurologists

2014-2015

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

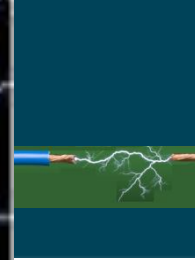
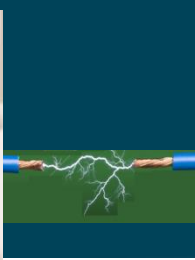


Management: Multidisciplinary approach

- 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 continence nurses
 - Psychologists and social care specialists
 - Dietitians

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



HEALTHCARE WITHOUT WALLS



NeuroDirect



NeuroView



NeuroMail



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.

Dimensions of Wellness



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

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

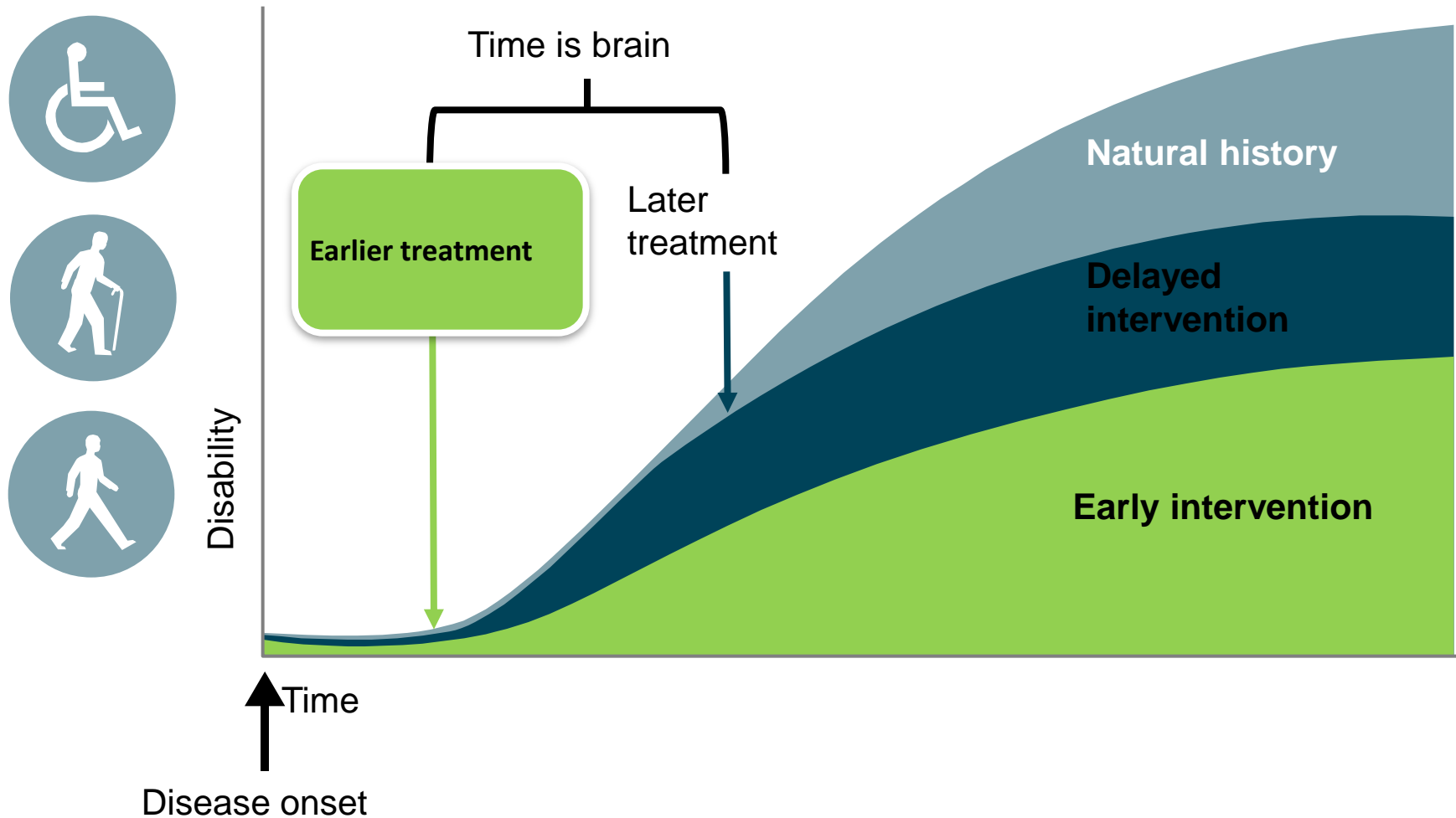
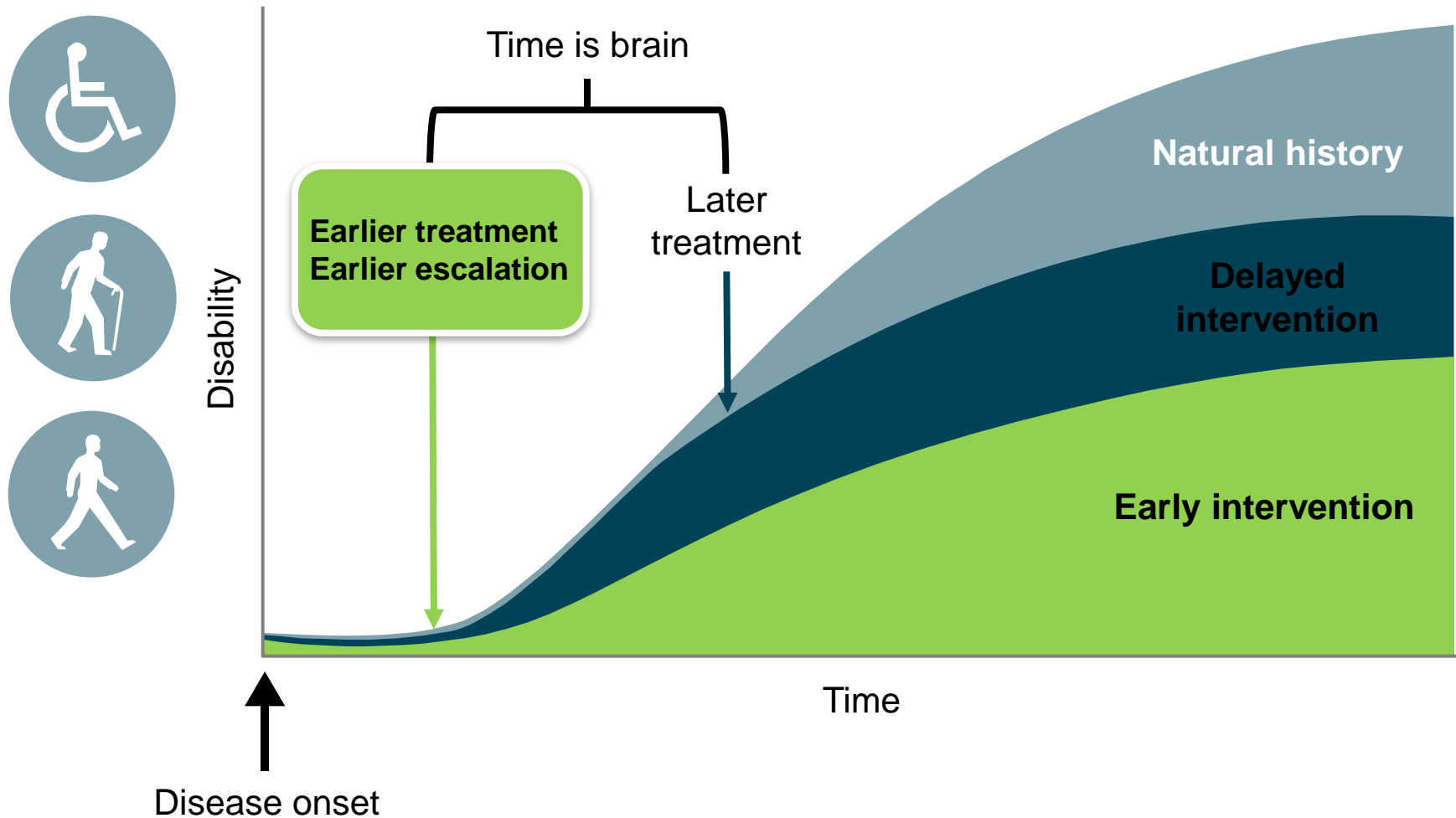


Figure: <http://multiple-sclerosis-research.blogspot.co.uk/2012/06/research-dmt-slow-onset-of-progression.html>
 Accessed 4 June 2013. Based on a review of Bergamaschi R *et al. Mult Scler* 2012

Early treatment seems to be desirable



Brain health

Time matters in multiple sclerosis

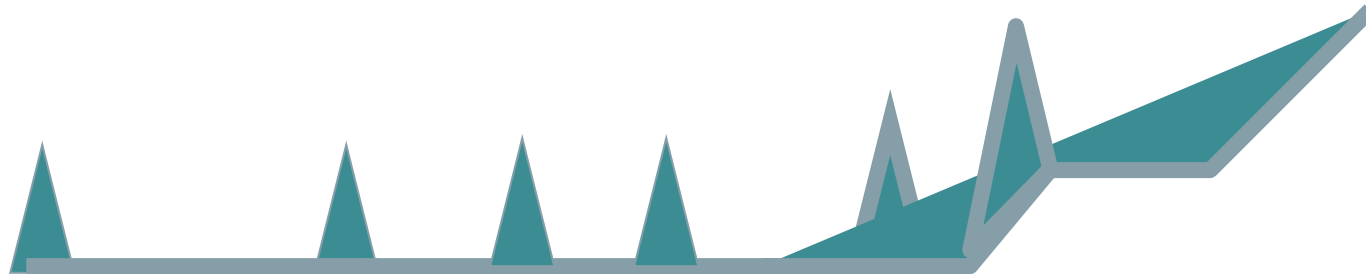
Gavin Giovannoni
Helmut Butzkueven
Suhayl Dhib-Jalbut
Jeremy Hobart
Gisela Kobelt
George Pepper
Maria Pia Sormani
Christoph Thalheim
Anthony Traboulsee
Timothy Vollmer



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



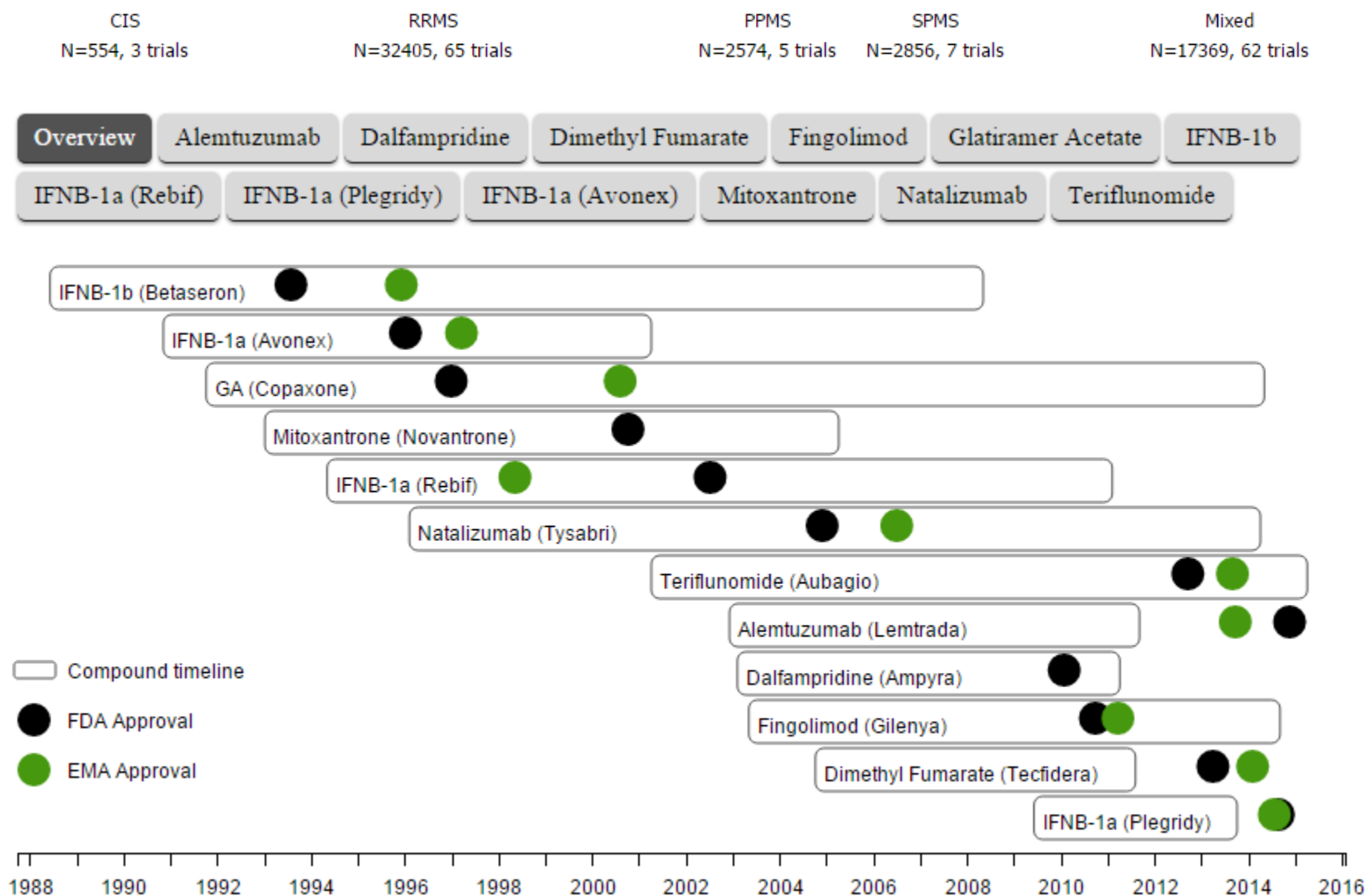
- ✓ Interferon beta 1a s.c.
- ✓ Interferon beta 1b s.c.
- ✓ Interferon beta 1a i.m.
- ✓ Glatiramer acetate
- ✓ Mitoxantrone
- ✓ Natalizumab
- ✓ Fingolimod
- ✓ Teriflunomide
- ✓ DMF
- ✓ Alemtuzumab

OTHER MOLECULES ARE COMING, SOME VERY SOON



- ✓ Interferon beta 1a s.c.
- ✓ Interferon beta 1 a 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



Treatment

Treatment & monitoring – DMD: First-line treatments

Drug, administration route	Reduction (%) in clinical activity (relapses) in clinical trials		Main side effects	Recommended safety monitoring
	Vs. placebo	Vs. first-line DMD		
Beta-interferon, SC or IM	30%	NA	<ul style="list-style-type: none"> -Flu-like symptoms -Mild-moderate lymphopenia -Elevated liver enzymes -Hypersensitivity 	<ul style="list-style-type: none"> -Regular blood tests -Regular brain MRI scans
Glatiramer acetate, SC	30%	NA	<ul style="list-style-type: none"> -Immediate post-injection reaction -Local injection-site skin reaction -Hypersensitivity 	<ul style="list-style-type: none"> -Regular brain MRI scans
Dimethyl fumarate, oral	45-50%	22%	<ul style="list-style-type: none"> -Flushing -Gastrointestinal events -Lymphopenia -Elevated liver enzymes 	<ul style="list-style-type: none"> -Regular blood tests -Regular brain MRI scans
Teriflunomide, oral	40-50%	No proved superiority of teriflunomide vs. SC beta-interferon	<ul style="list-style-type: none"> -Hair loss -Elevated liver enzymes -Leukopenia -Peripheral neuropathy -Elevated blood pressure 	<ul style="list-style-type: none"> -Regular blood tests -Regular brain MRI scans

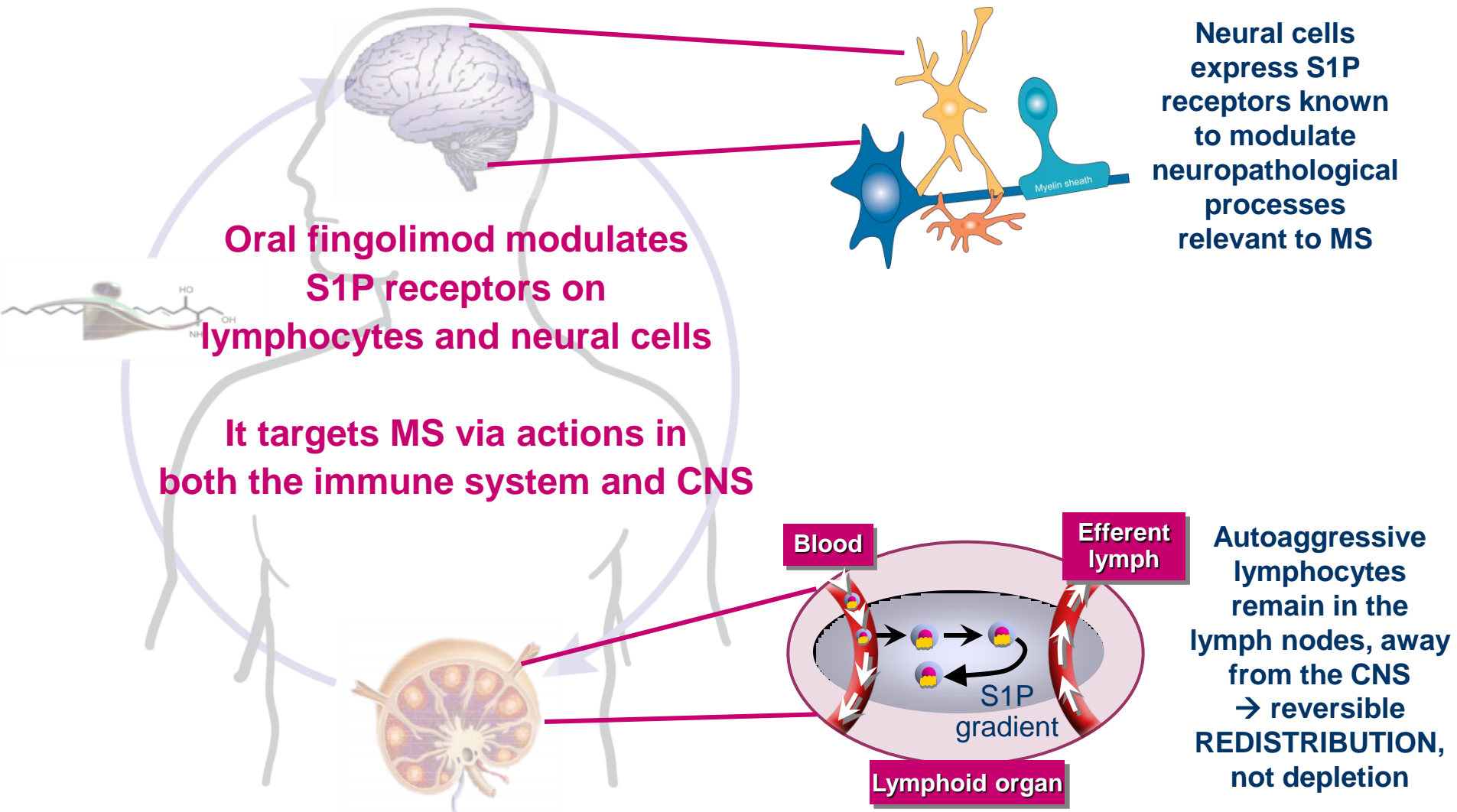
Treatment

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)

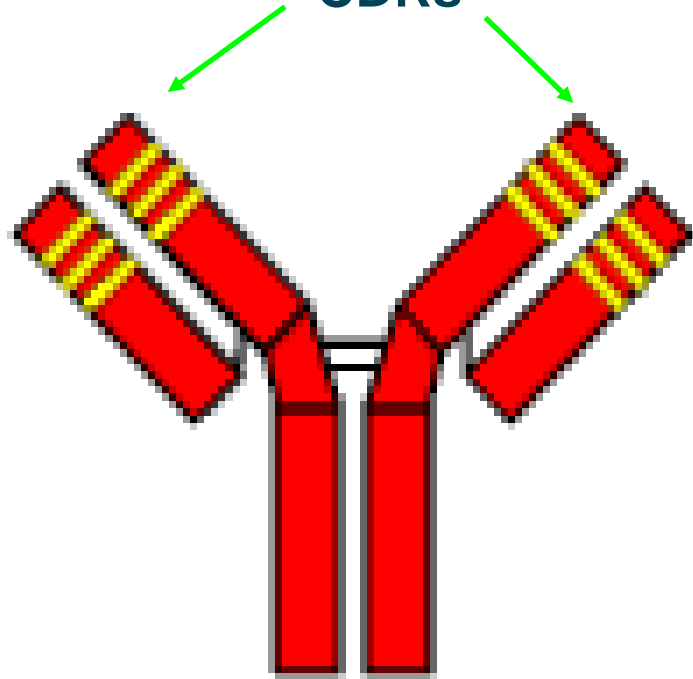
Oral fingolimod – mechanism of action



Natalizumab: A Humanized, Monoclonal Antibody (mAb) Against $\alpha 4$ Integrins

Complementarity-Determining Regions

CDRs

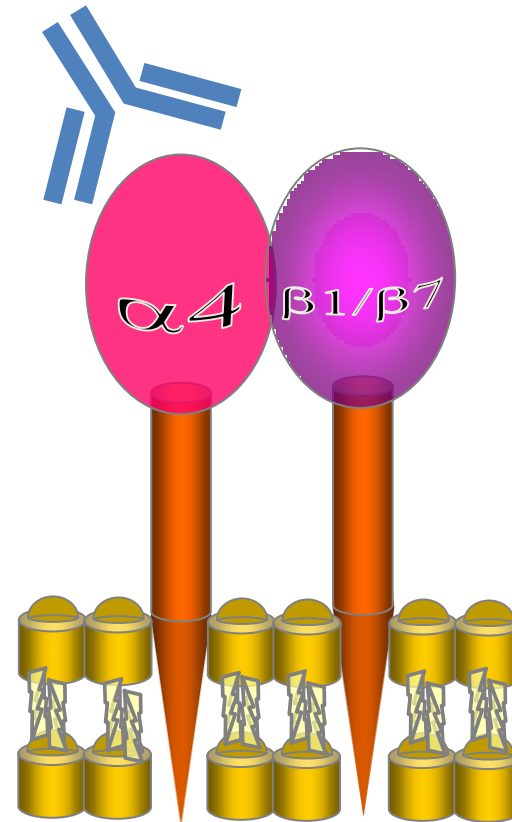


Framework

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

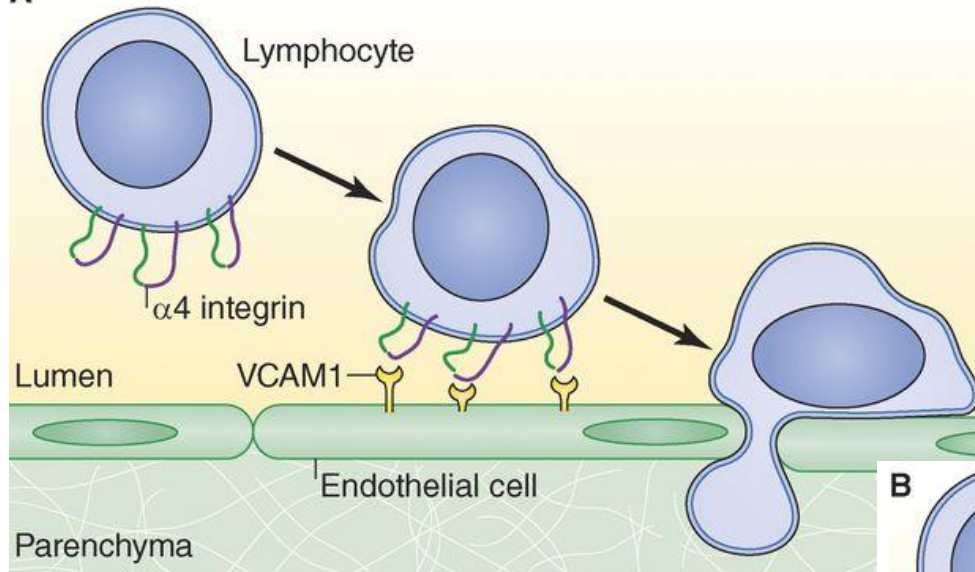
NATALIZUMAB

Natalizumab is a humanized ab against subunit α_4 of the integrins $\alpha_4\beta_1$ y $\alpha_4\beta_7$

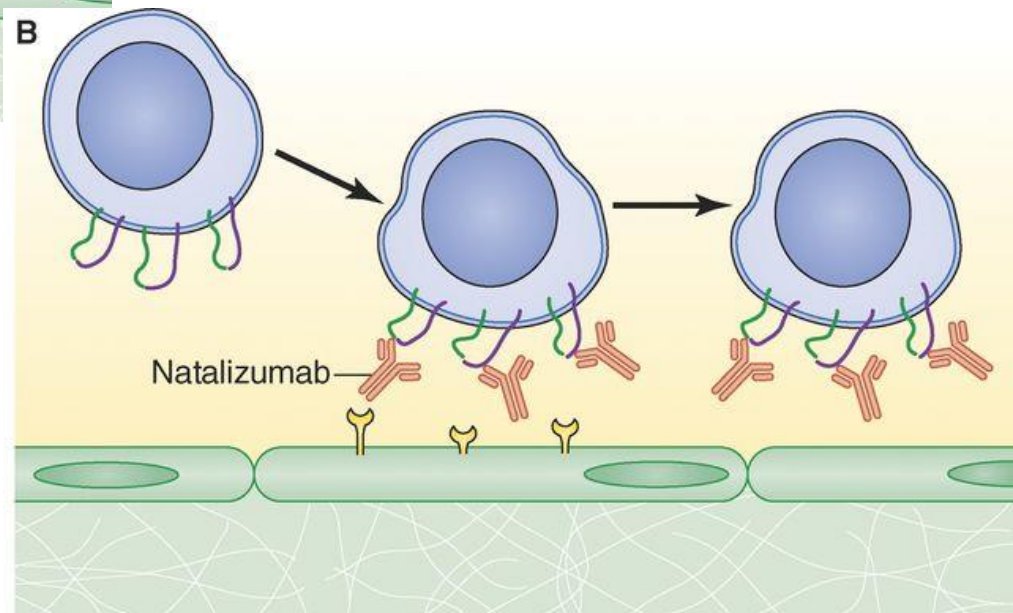


NATALIZUMAB

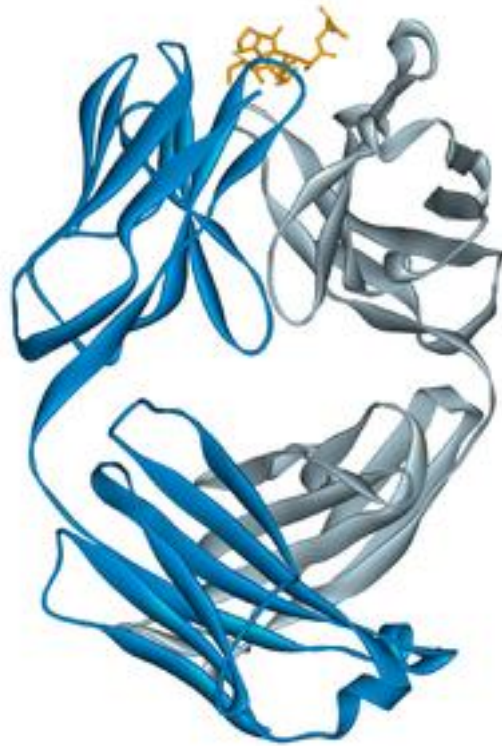
A



B



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



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



Adaptive immune system: Second line of defense against antigens

- T lymphocytes
- B lymphocytes

High CD52 expression



Alemtuzumab binding causes lysis and subsequent reduction of circulating T and B lymphocytes, resulting in decreased inflammation in the CNS



Alemtuzumab administration

Treatment

Treatment & monitoring – DMD: Second-line treatments

Drug, administration route	Reduction (%) in clinical activity (relapses) in clinical trials		Main side effects	Recommended safety monitoring
	Vs. placebo	Vs. first-line DMD		
Fingolimod, oral	55-60%	51-52%	<ul style="list-style-type: none"> -Bradycardia and other heart conduction abnormalities -Lymphopenia -Macular oedema -Elevated liver enzymes -Elevated blood pressure 	<ul style="list-style-type: none"> -Regular blood tests -Regular brain MRI scans -Continuous ECG monitoring during first 6 hours after first dose -OCT exam -Vaccination against VVZ is recommended before starting fingolimod treatment
Natalizumab, IV	68%	NA	<ul style="list-style-type: none"> -Perfusion reaction (nausea, vomiting, generally mild) -Hypersensitivity -Immunogenicity (antibodies against natalizumab) -Infections, including PML -Elevated lymphocyte count in peripheral blood 	<ul style="list-style-type: none"> -Regular blood tests -Regular brain MRI scans (i.e. every year or more frequently, every 6 or 3 months, if high risk of PML)
Alemtuzumab, IV	NA	55%	<ul style="list-style-type: none"> -Perfusion reaction (marked) -Marked lymphopenia -Infections -Secondary autoimmunity 	<ul style="list-style-type: none"> -Regular blood tests -Regular urine tests -Regular brain MRI scans

Treatment

Treatment & monitoring – DMD: Second-line treatments

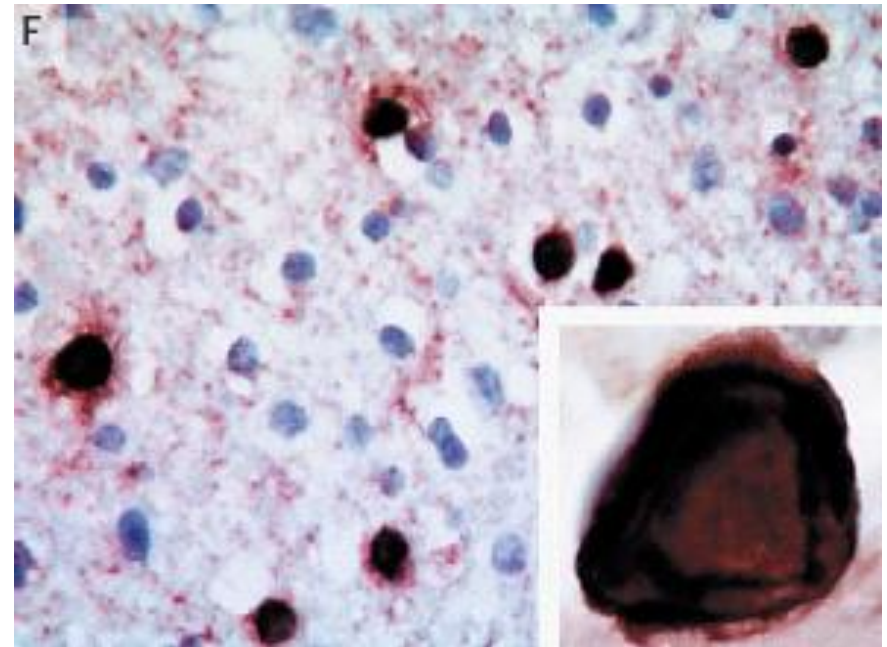
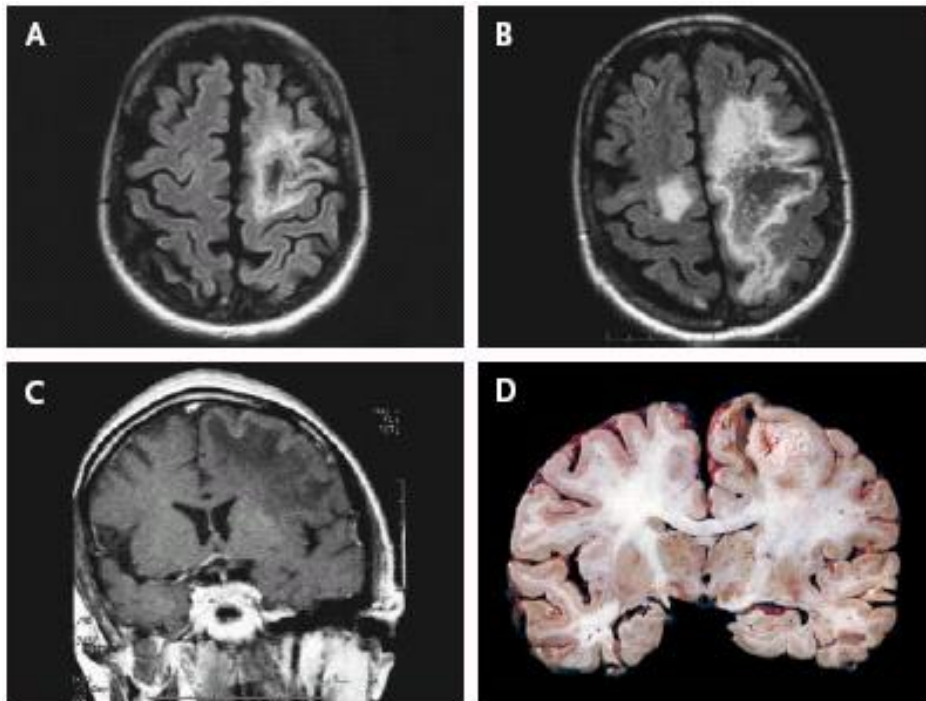
Indications

- 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

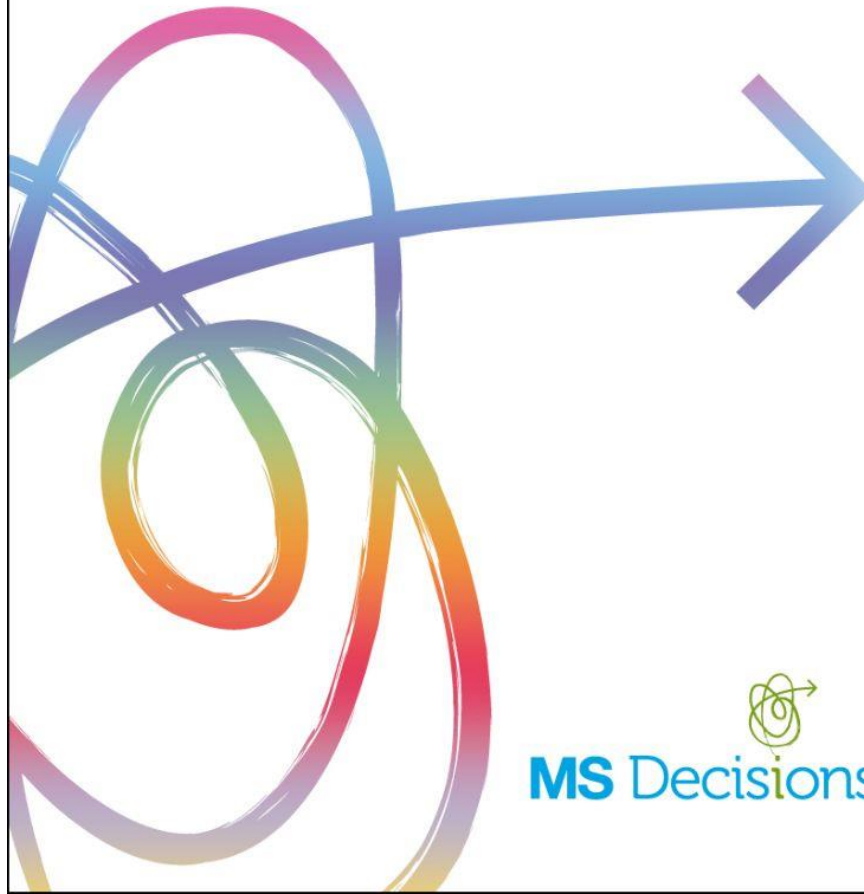
PML in association with Natalizumab

Cells with inclusions have positive nuclear signal for JC virus



Disease modifying drugs

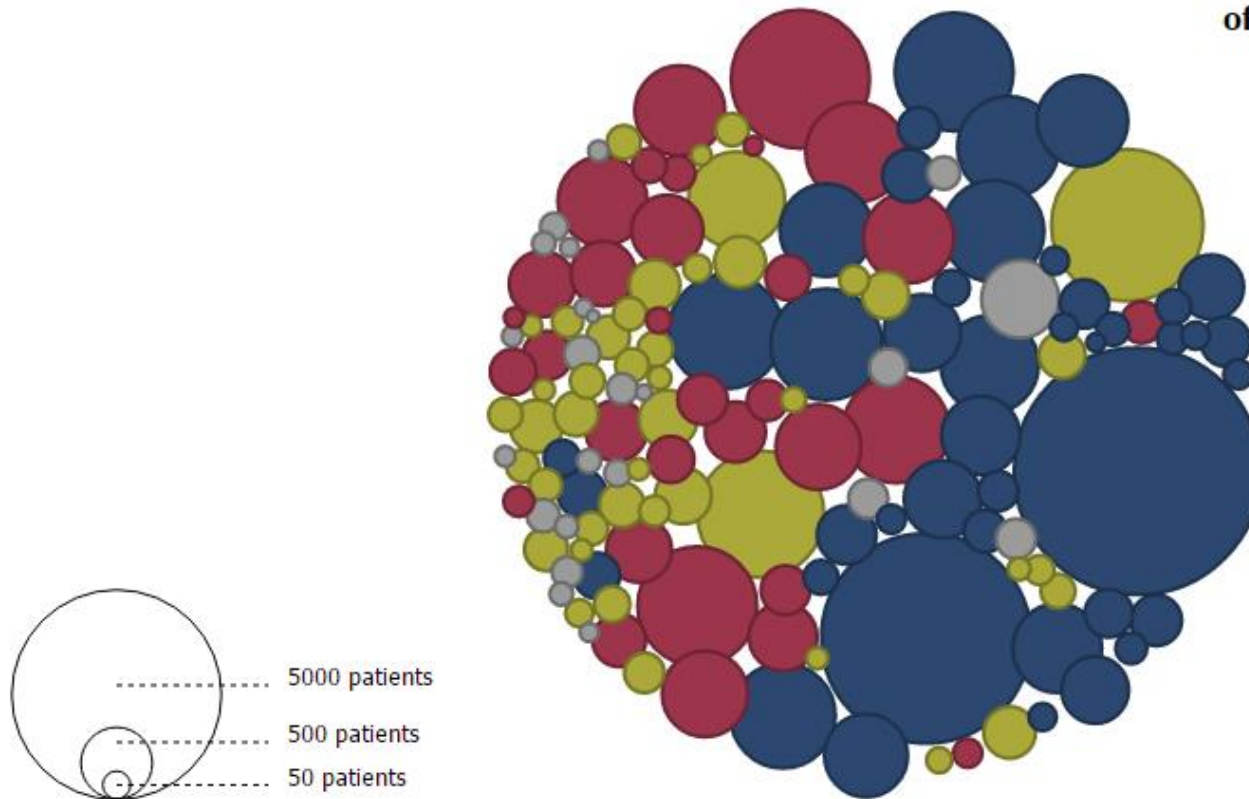
a guide to treatments
for relapsing MS




MS Decisions

Visual Map of MS Clinical Trials

142 ongoing clinical trials in MS
with a targeted total sample size
of **55758 patients.**



● Marketed for MS
 ● Marketed but not for MS
 ● Not Marketed
 ● Other

MS Trials by Patient Population

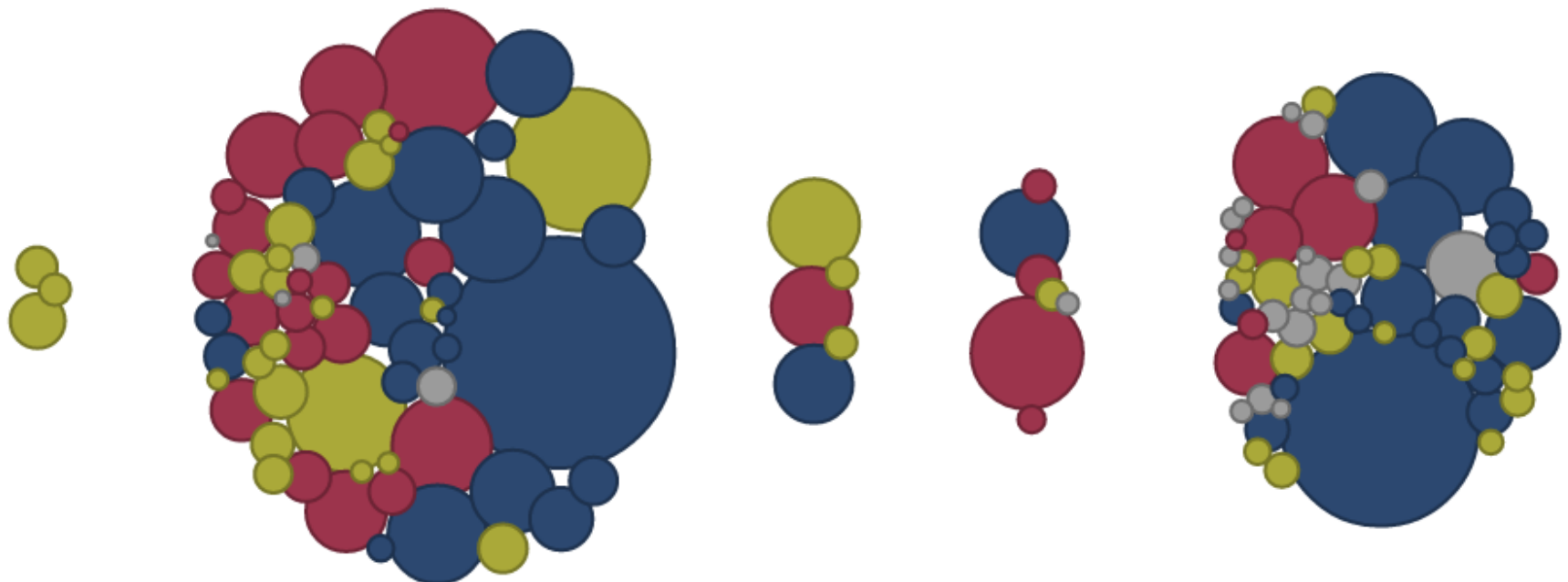
CIS
N=554, 3 trials

RRMS
N=32405, 65 trials

PPMS
N=2574, 5 trials

SPMS
N=2856, 7 trials

Mixed
N=17369, 62 trials



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

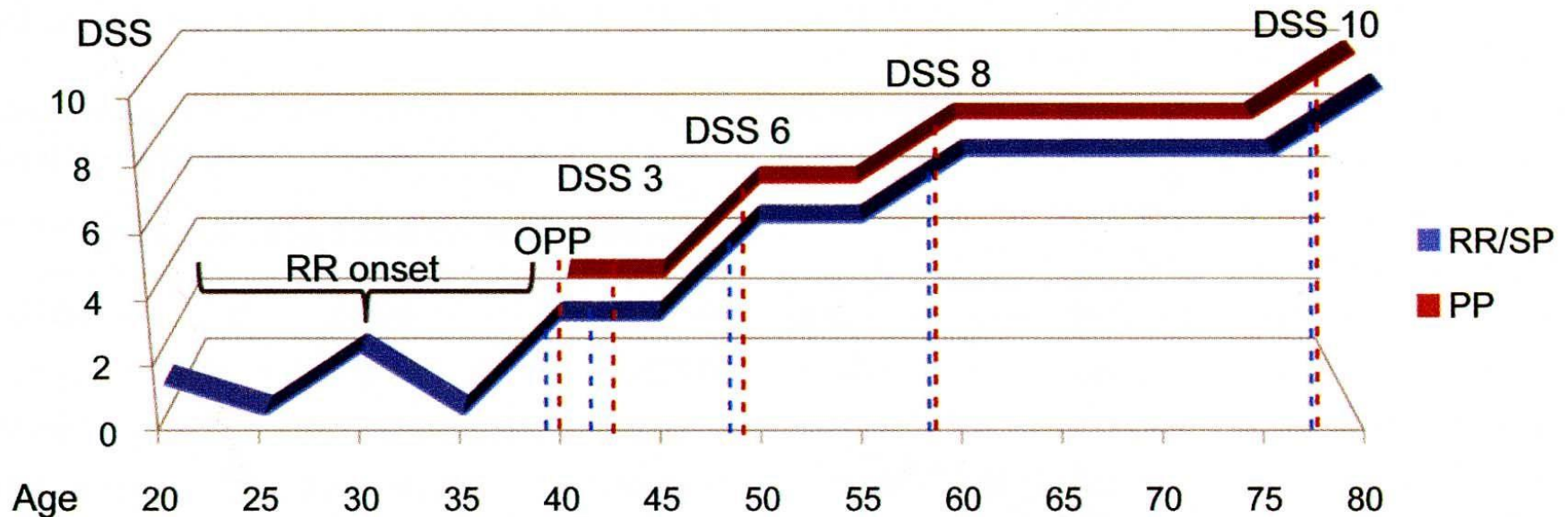
Urgent need to find solutions for people with Progressive MS

- Large worldwide impact: at least half of all (2.3million) 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

Age and disability accumulation in multiple sclerosis

Development of secondary progression is the dominant determinant of long-term prognosis, independent of disease duration and early relapse frequency

Figure 2 Ages at attainment of disability endpoints according to type of disease course



Age at	OPP	<i>p</i>	DSS 3	<i>p</i>	DSS 6	<i>p</i>	DSS 8	<i>p</i>	DSS 10	<i>p</i>
RR/SP	40.2 (39)	0.09	41.6 (41)	0.82	49.7 (48)	0.05	59.2 (58)	0.44	76.1 (78)	0.63
PP	38.6 (40)		42.3 (43)		48.0 (49)		58.4 (58)		73.8 (78)	

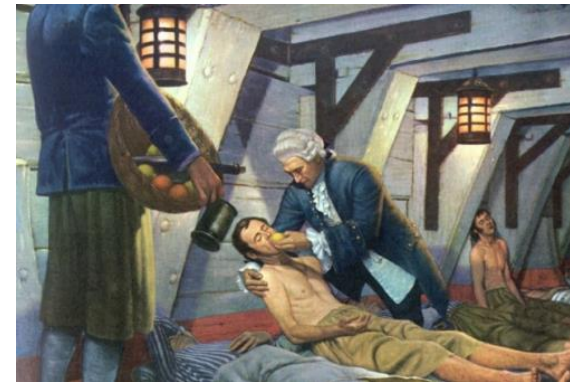
Onset of progressive phase determines disability

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.



The Top 10

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**

VIEWS & REVIEWS

Defining the clinical course of multiple sclerosis

The 2013 revisions

OPEN



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

Definitions (1)

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

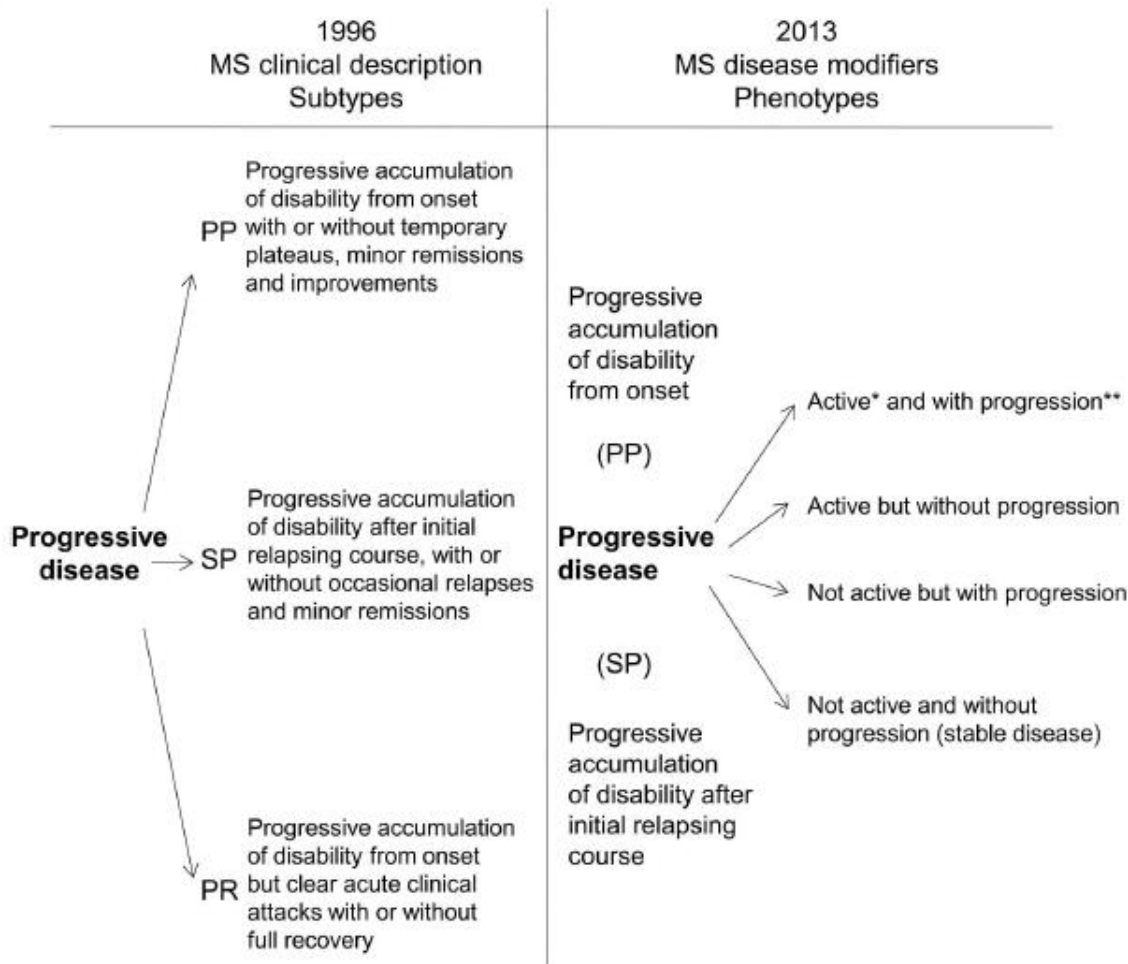
Clinical: steadily increasing objectively documented neurological dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur)

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

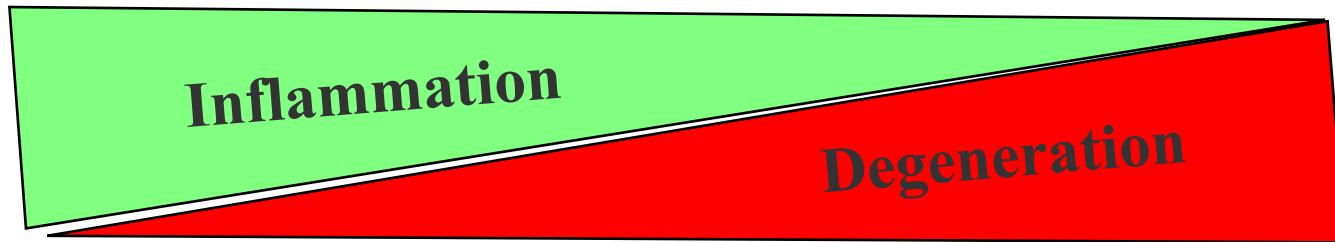
Figure 2 The 1996 vs 2013 multiple sclerosis phenotype descriptions for progressive disease



Lublin FD et al.
Neurology. 2014;83:1-9.

*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

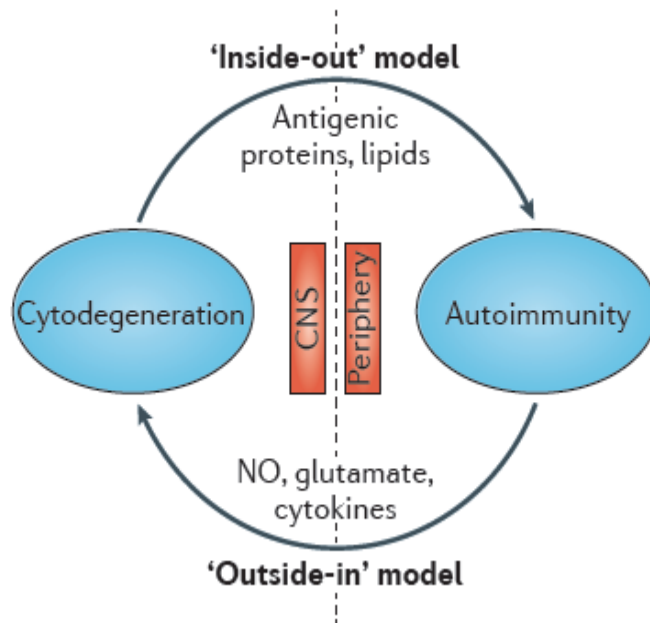


OPINION

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 cytodeneration, which is most faithfully reflected by primary progressive disease. SPMS, secondary progressive MS

Clinical Trials

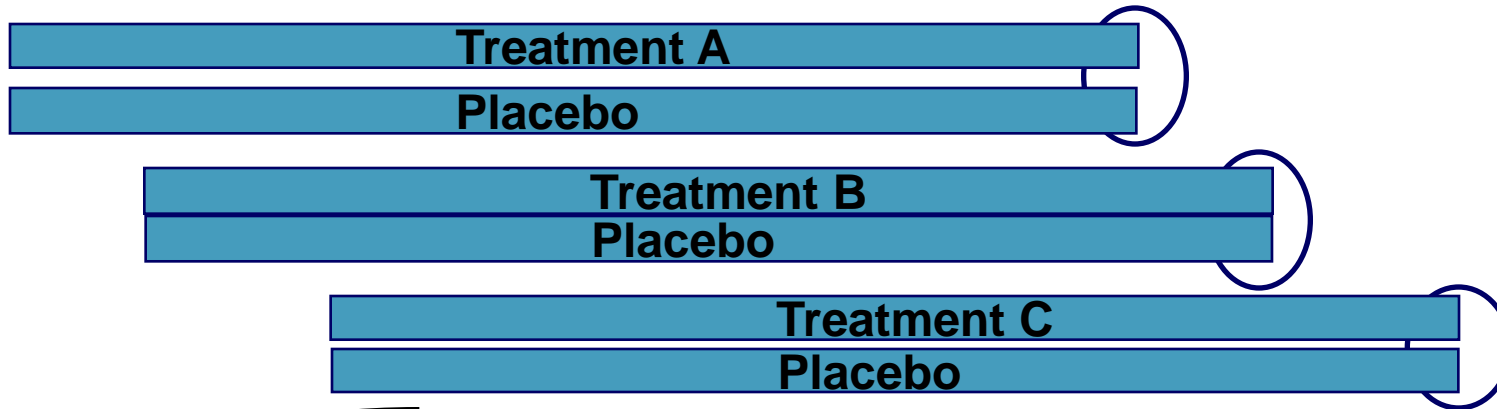
Conventional trial design

Large numbers, lengthy, very expensive

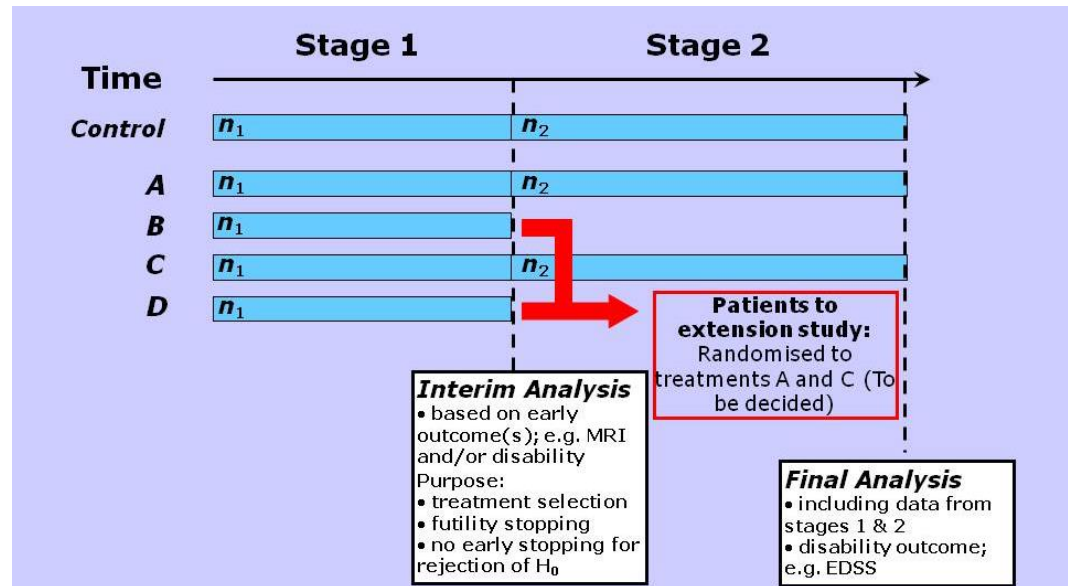
Targeting inflammation (largely)

=> Need to consider new trial designs

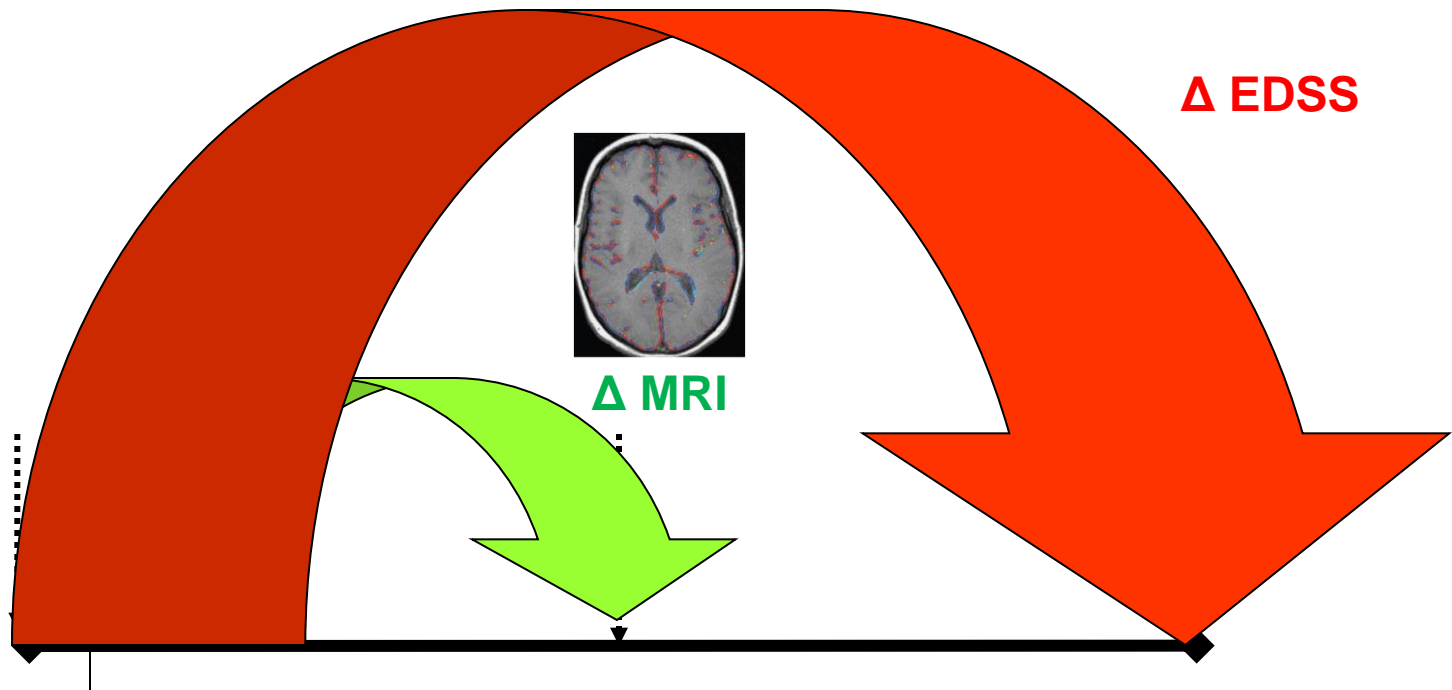
=> Need to focus on neuroprotection/repair?



Moving to adaptive trials



The interim measure



Research Paper

**MULTIPLE
SCLEROSIS
JOURNAL**



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

Jeremy Chataway^{1,2}, Richard Nicholas², Susan Todd³, David H Miller^{1,4}, Nicholas Parsons⁵, Elsa Valdés-Márquez³, Nigel Stallard⁵ and Tim Friede⁵

Multiple Sclerosis Journal

17(1) 81–88

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DOI: 10.1177/1352458510382129

msj.sagepub.com



Table 2 A: Trials in MS

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

Table 2 B: Current UK Trials in SPMS

Trial	N	Follow up Yrs	Entry EDSS	Active Treatment	Primary outcome measure	Reporting Date
CUPID (Phase III)	493	3	4.0-6.5	Tetra-hydrocannabinol	Time to confirmed EDSS worsening; MSIS29 mean change	2012
MS-STAT (Phase IIb)	140	2	4.0-6.5	Simvastatin	MRI brain atrophy	2012

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

Lancet 2014; 383: 2213–21

Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial



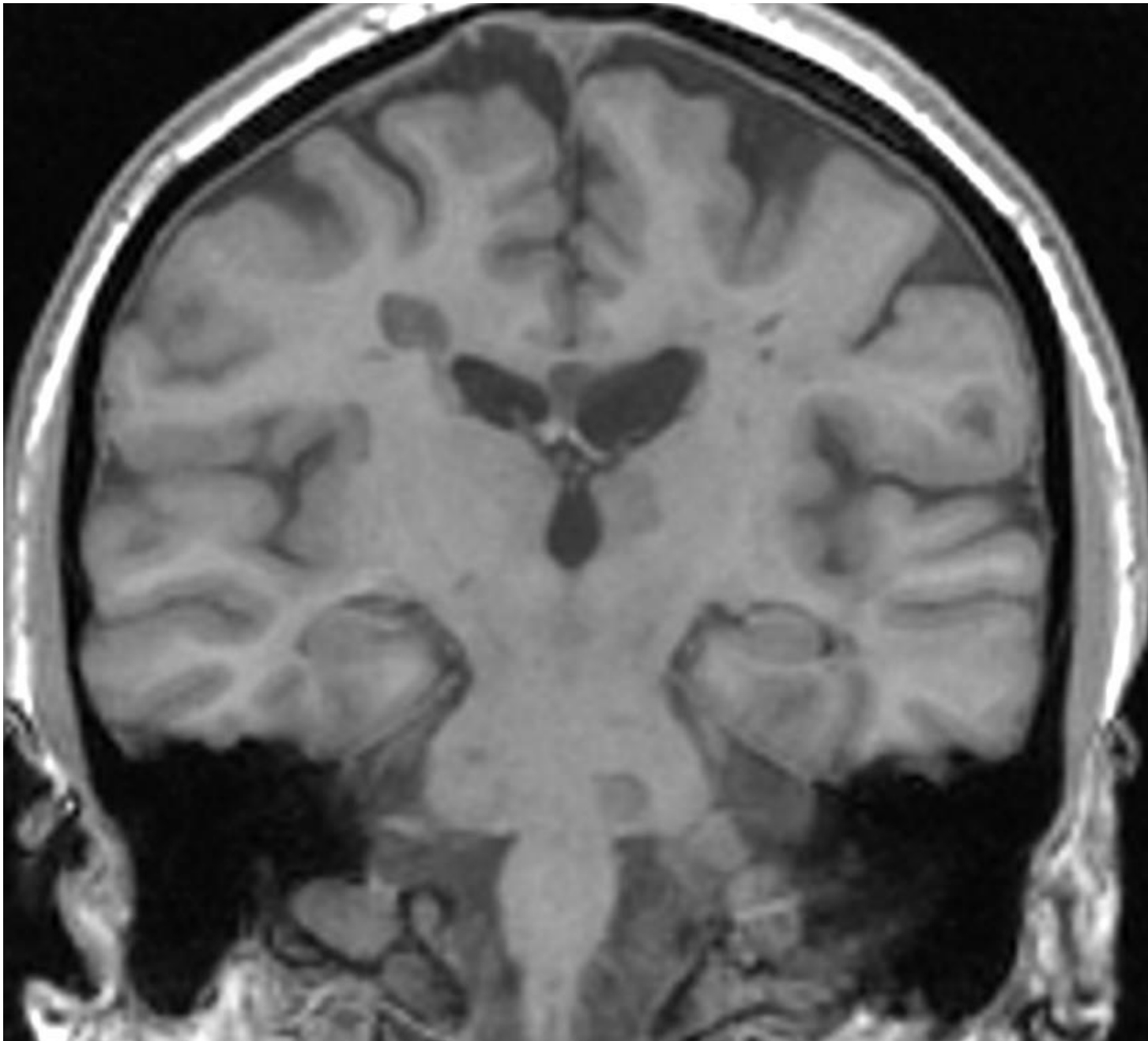
Jeremy Chataway, Nadine Schuerer, Ali Alsanousi, Dennis Chan, David MacManus, Kelvin Hunter, Val Anderson, Charles R M Bangham, Shona Clegg, Casper Nielsen, Nick C Fox, David Wilkie, Jennifer M Nicholas, Virginia L Calder, John Greenwood, Chris Frost, Richard Nicholas

- 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 >6months
 - Mitoxantrone >12 months
 - Never alemtuzumab/natalizumab

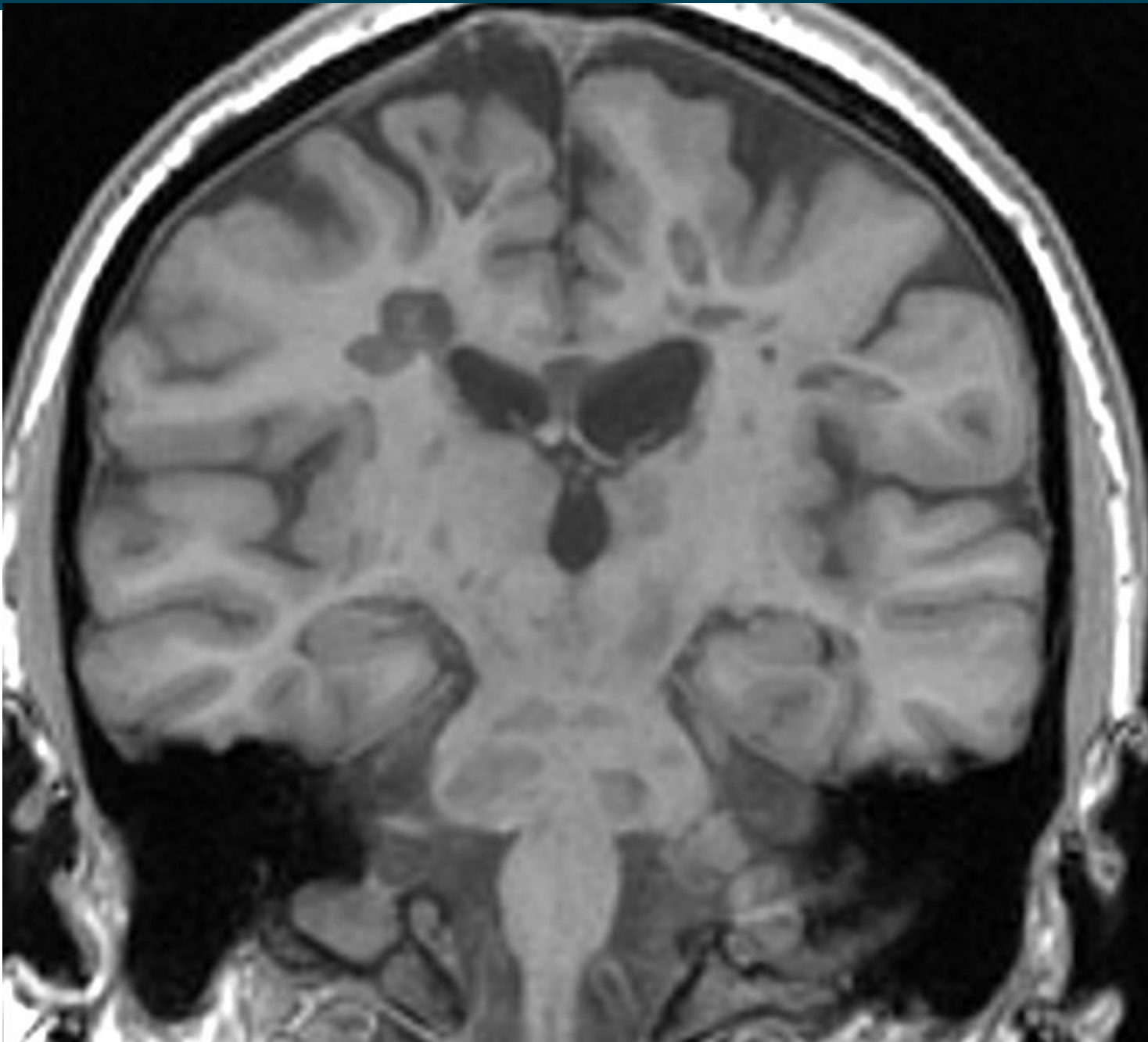
Outcomes

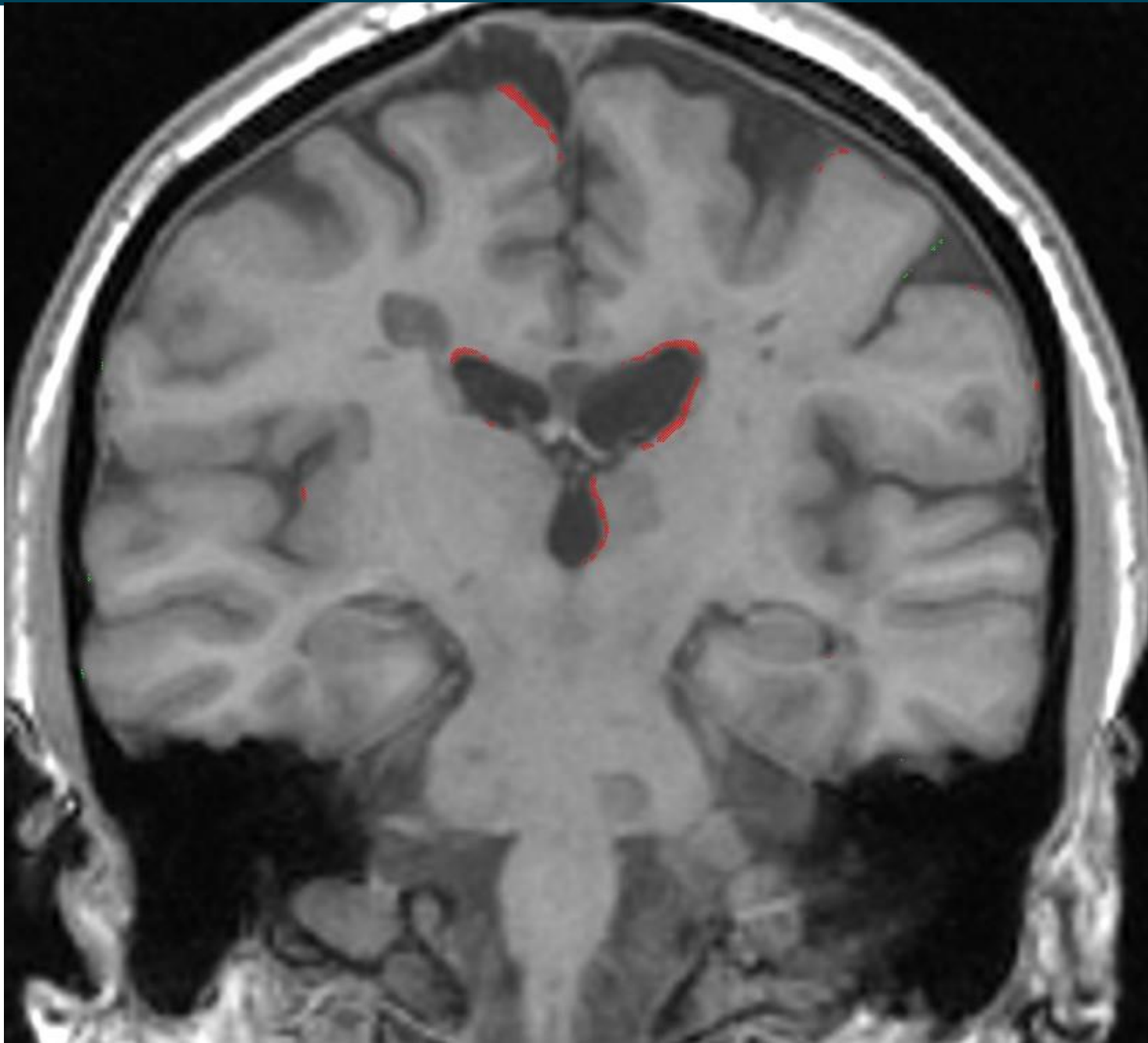
- Primary
 - Volumetric MRI BBSI
- Secondary
 - Disability (EDSS/MSIS-29v2/MSFC)
 - New and enlarging lesions T2 MRI
 - Relapses
 - Safety
- Other*
 - Neuropsychology
 - Immunology/Proteomics

Baseline



Registered
Year 2





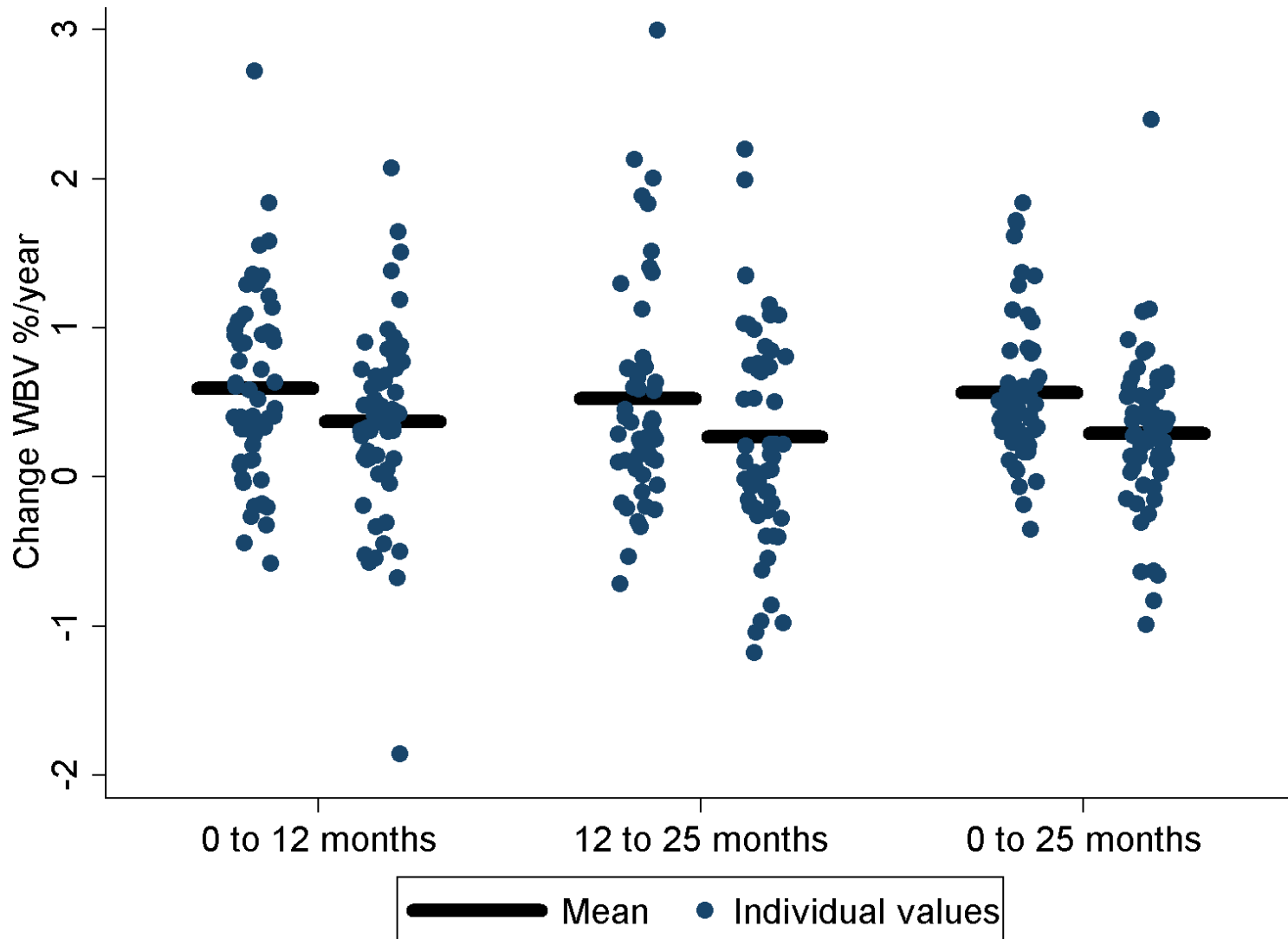
**Screening
showing
BBSI
colour
overlay**

Primary outcome: BBSI change in whole brain volume (%/year)

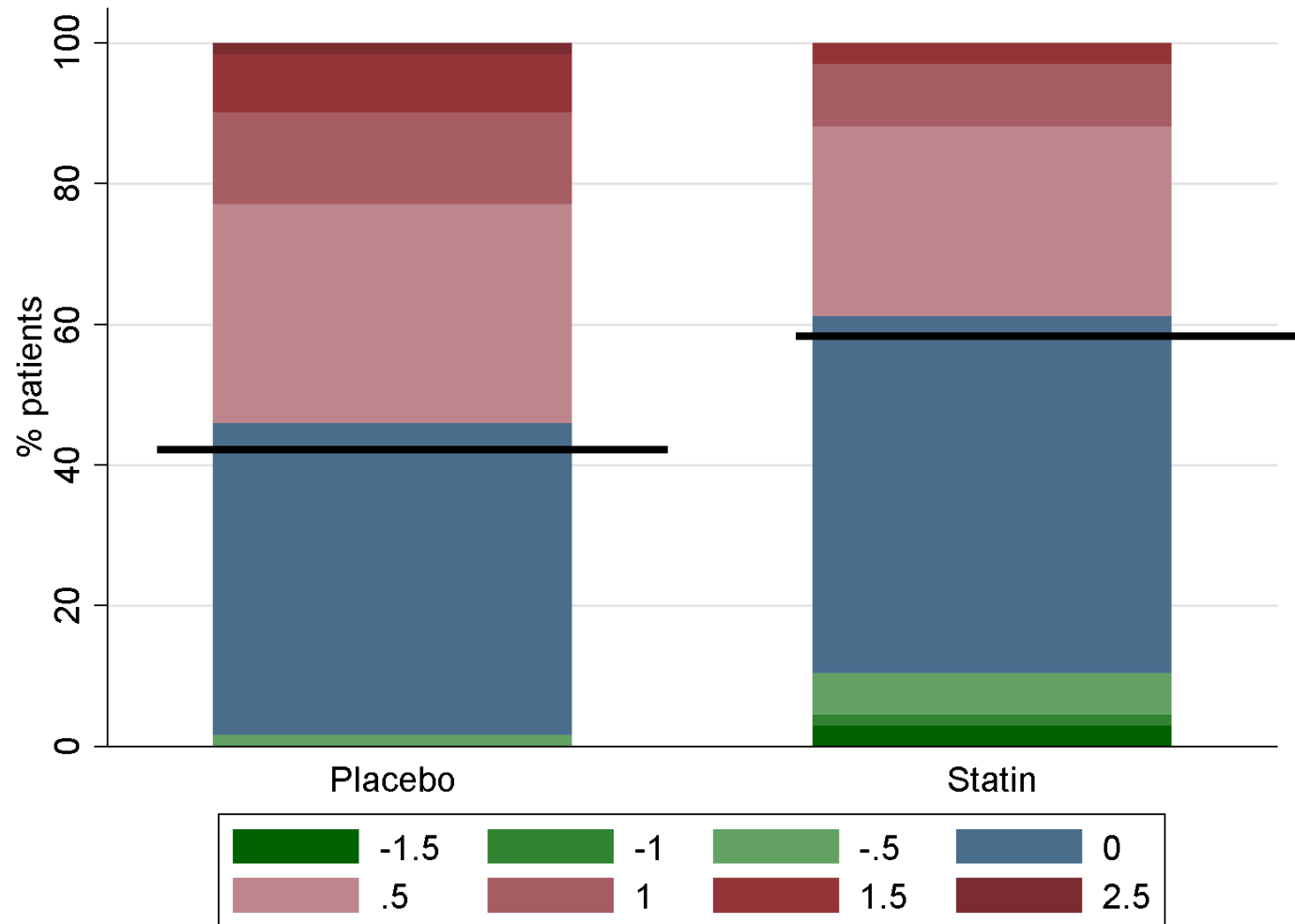
	Mean (SD) placebo	Mean (SD) simvastatin	Difference means (95% CI)*	in p-value
Change WBV (%/year)	0.589 (0.528)	0.298 (0.562)	-0.254 (-0.423 to -0.085)	0.003
Number patients evaluated	64	66		

*Adjusting for minimisation variables and MRI site

Change whole brain volume (%/yr)



Change in EDSS 0 to 24 months



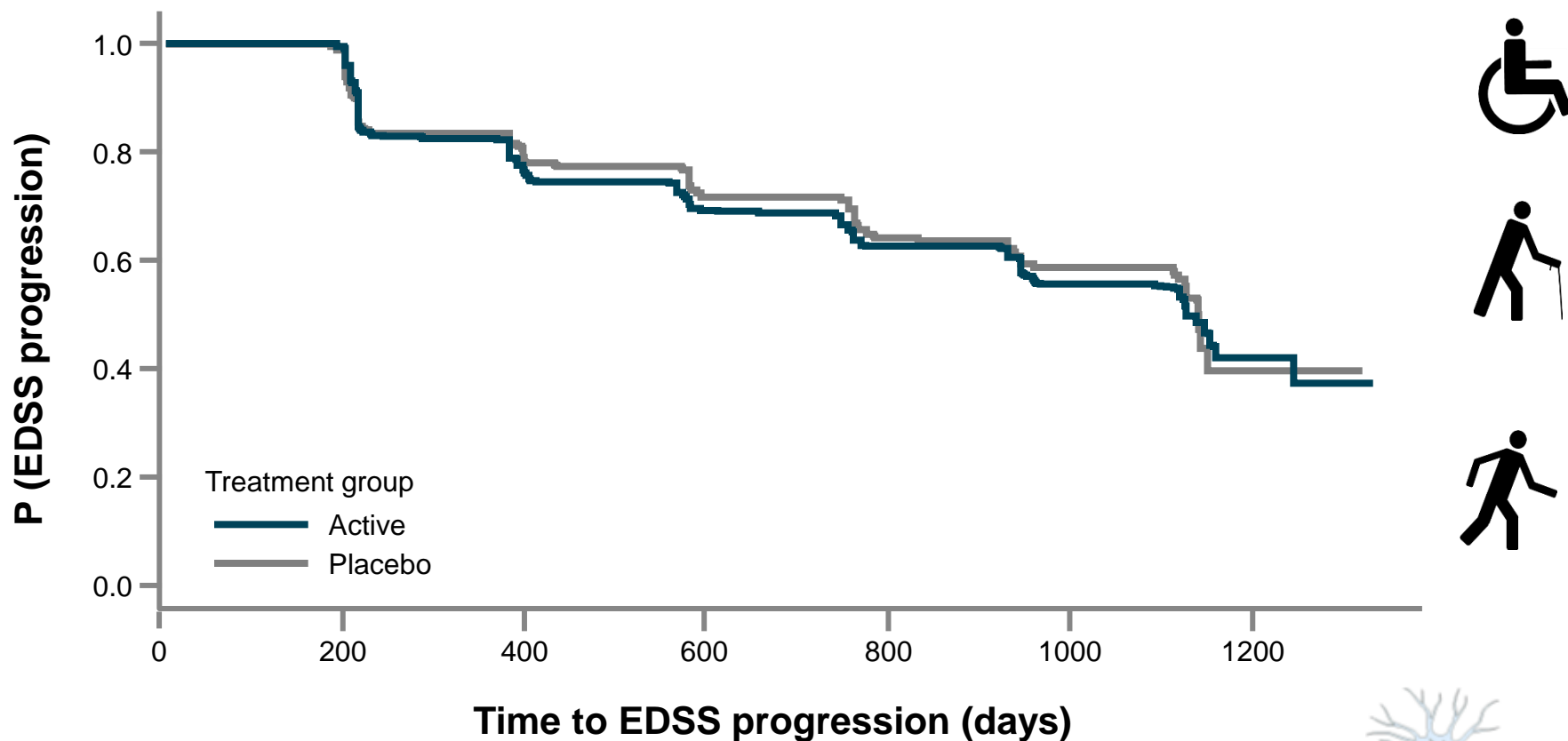


Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial

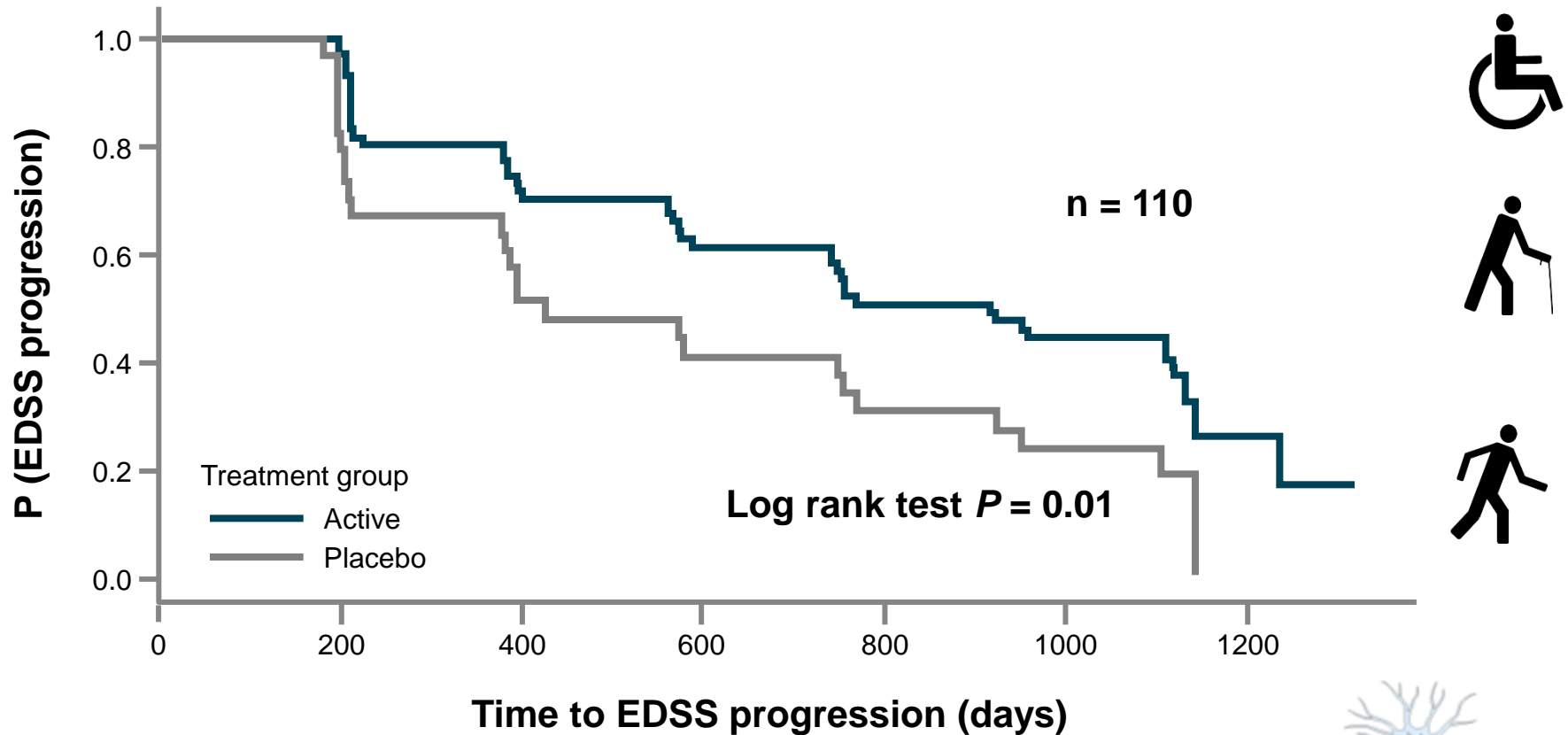
John Zajicek, Susan Ball, David Wright, Jane Vickery, Andrew Nunn, David Miller, Mayam Gomez Cano, David McManus, Sharukh Mallik, Jeremy Hobart, on behalf of the CUPID investigator group

- assess the value of Δ^9 -THC in slowing progressive MS over 3 yrs
- assess the safety of Δ^9 -THC over the long-term.
- improve research methodology; using new, patient-orientated methods.

CUPID (THC): EDSS progression over 3 years



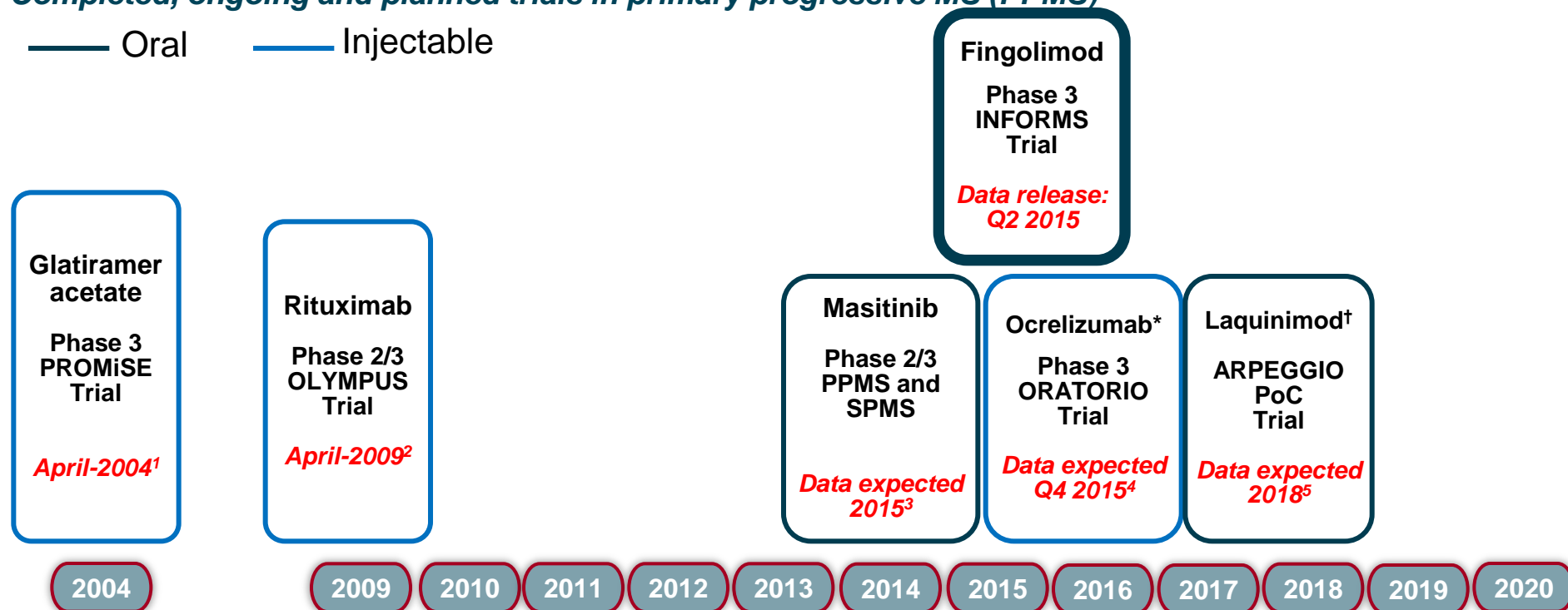
CUPID (THC): EDSS progression in patients with baseline EDSS <6 (post-hoc analysis)



Key PPMS clinical trials

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

— Oral — Injectables

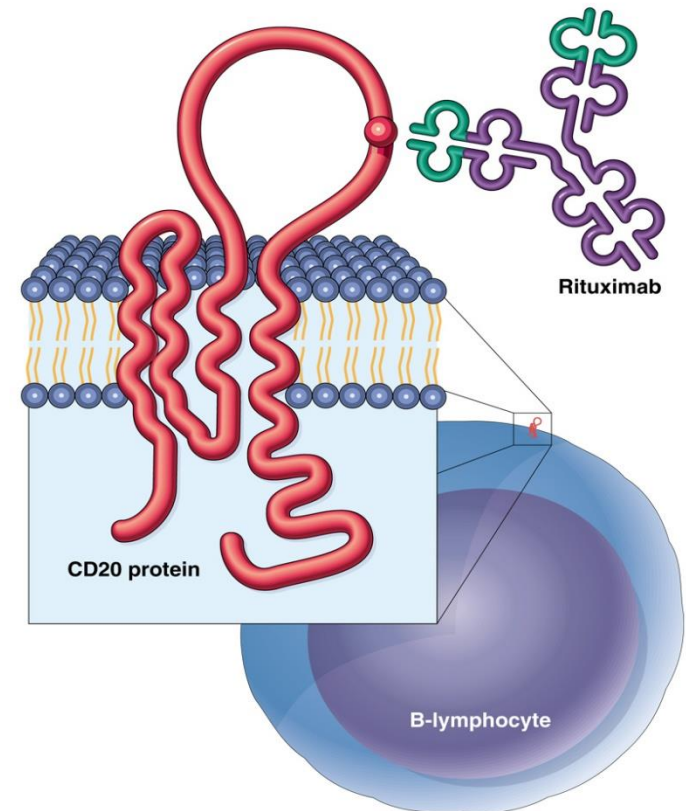


- PROMiSE (N=943) and OLYMPUS (N=439) are the two largest randomized trials in PPMS patients completed to date

Rituximab

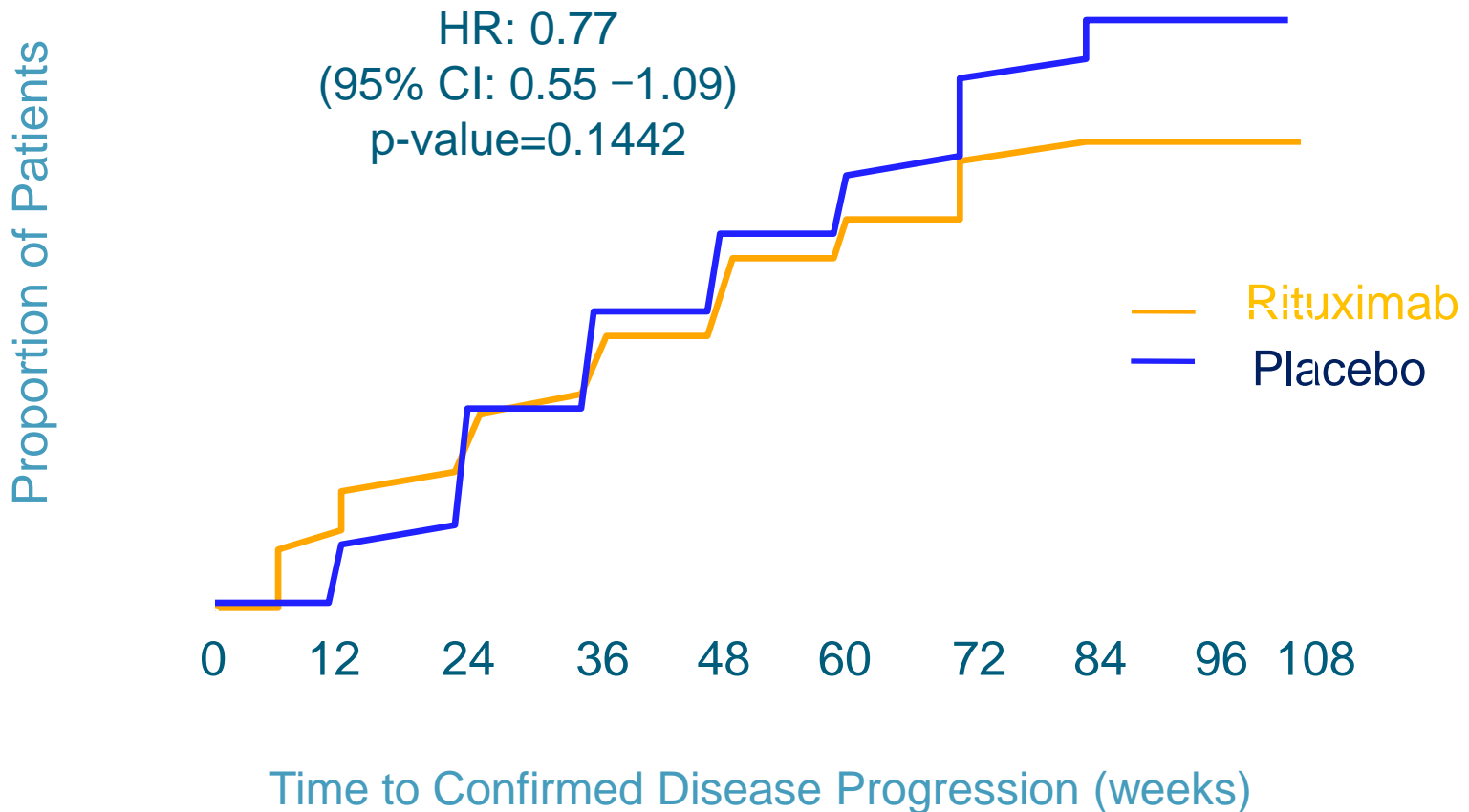
Anti-CD20 Monoclonal Antibody

- 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
- FDA approval for B-cell lymphoma (1997) and RA (2006)



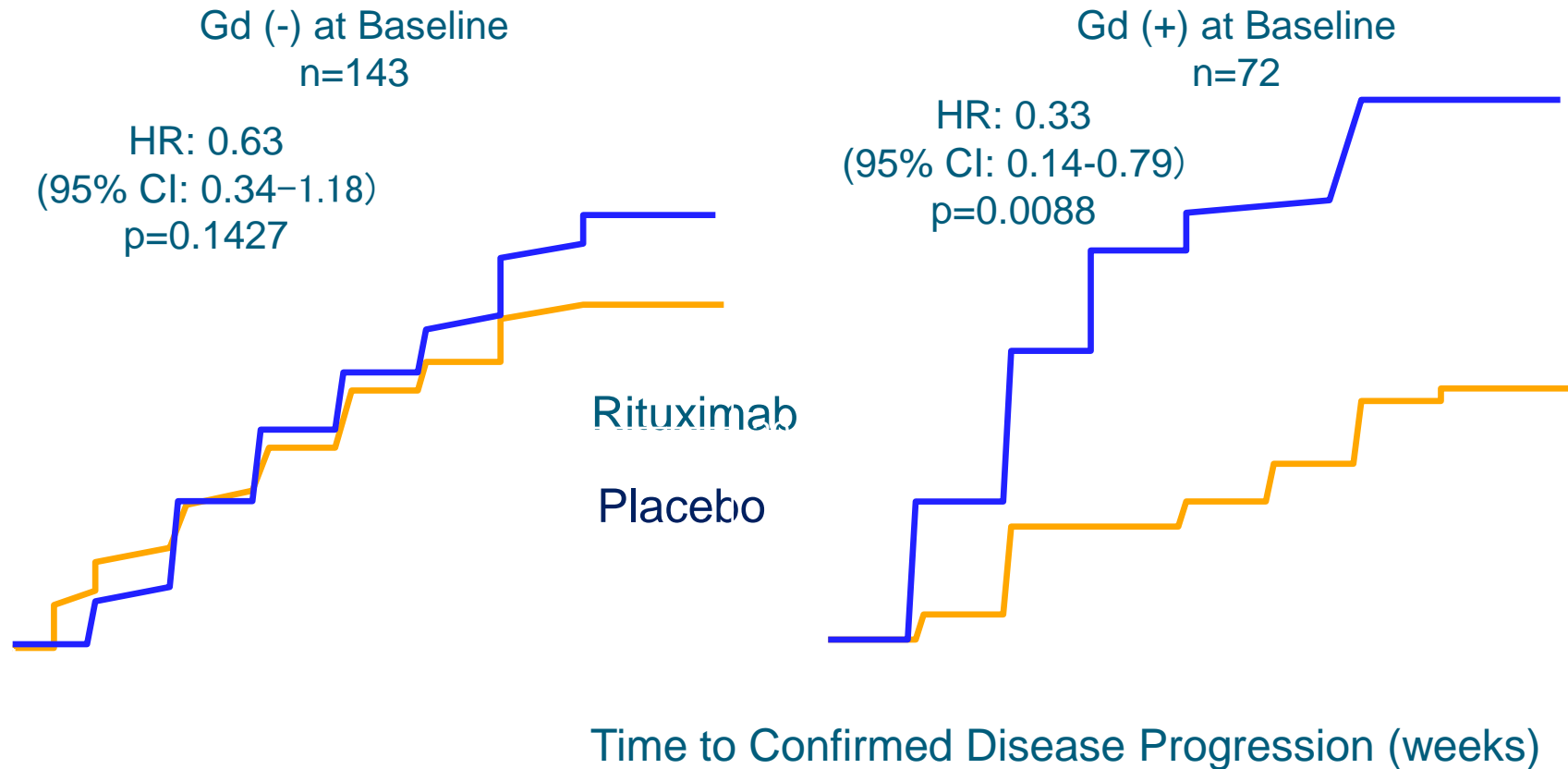
Time to Confirmed Disease Progression

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



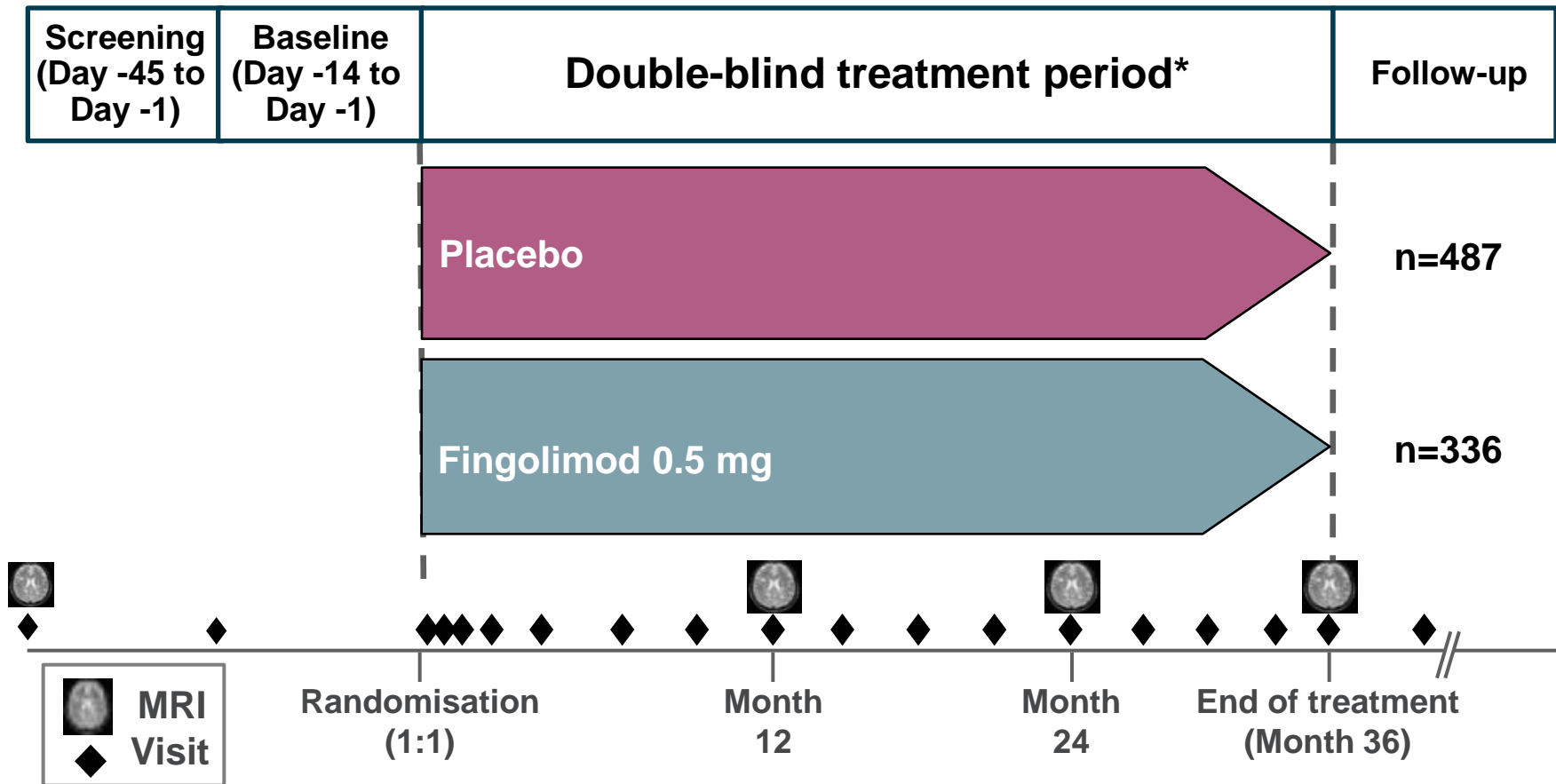
Time to Confirmed Disease Progression

Subgroup Analysis



INFORMS *Study design*

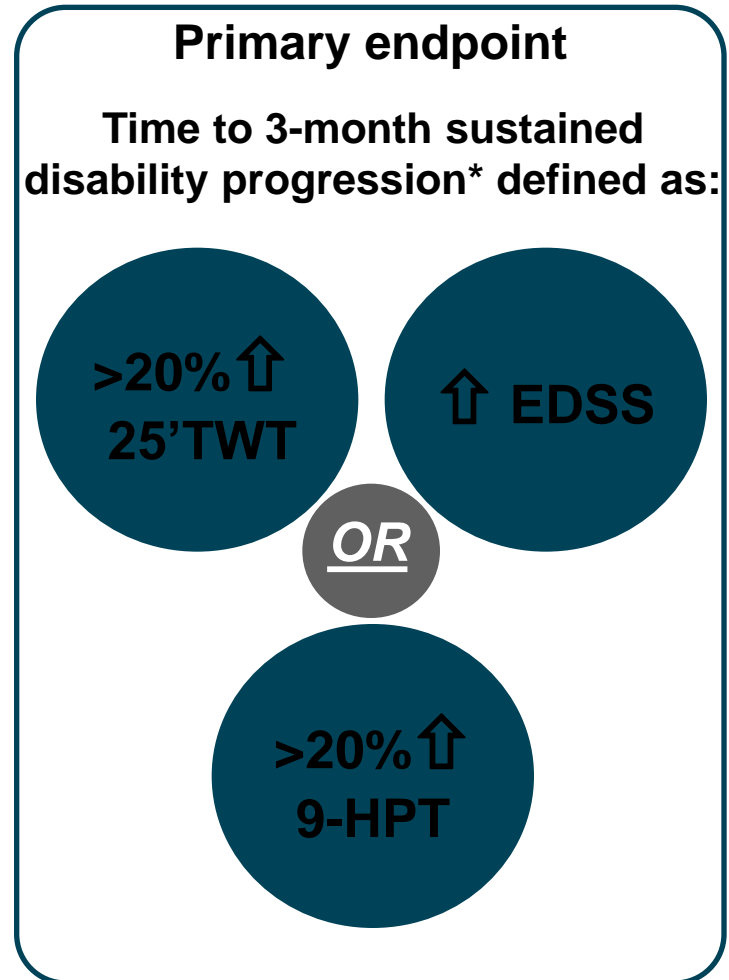
Randomised, multicentre, double-blind, placebo-controlled, parallel-group study in ~940 patients with PPMS



*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 $\geq 20\%$ from Baseline in the timed 25-foot walk test (25'TWT) **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**OR**
 - 3-month sustained increase of $\geq 20\%$ from Baseline in the 9-hole peg test (9-HPT)



*Defined as an increase of $\geq 20\%$ 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 $\geq 20\%$ 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

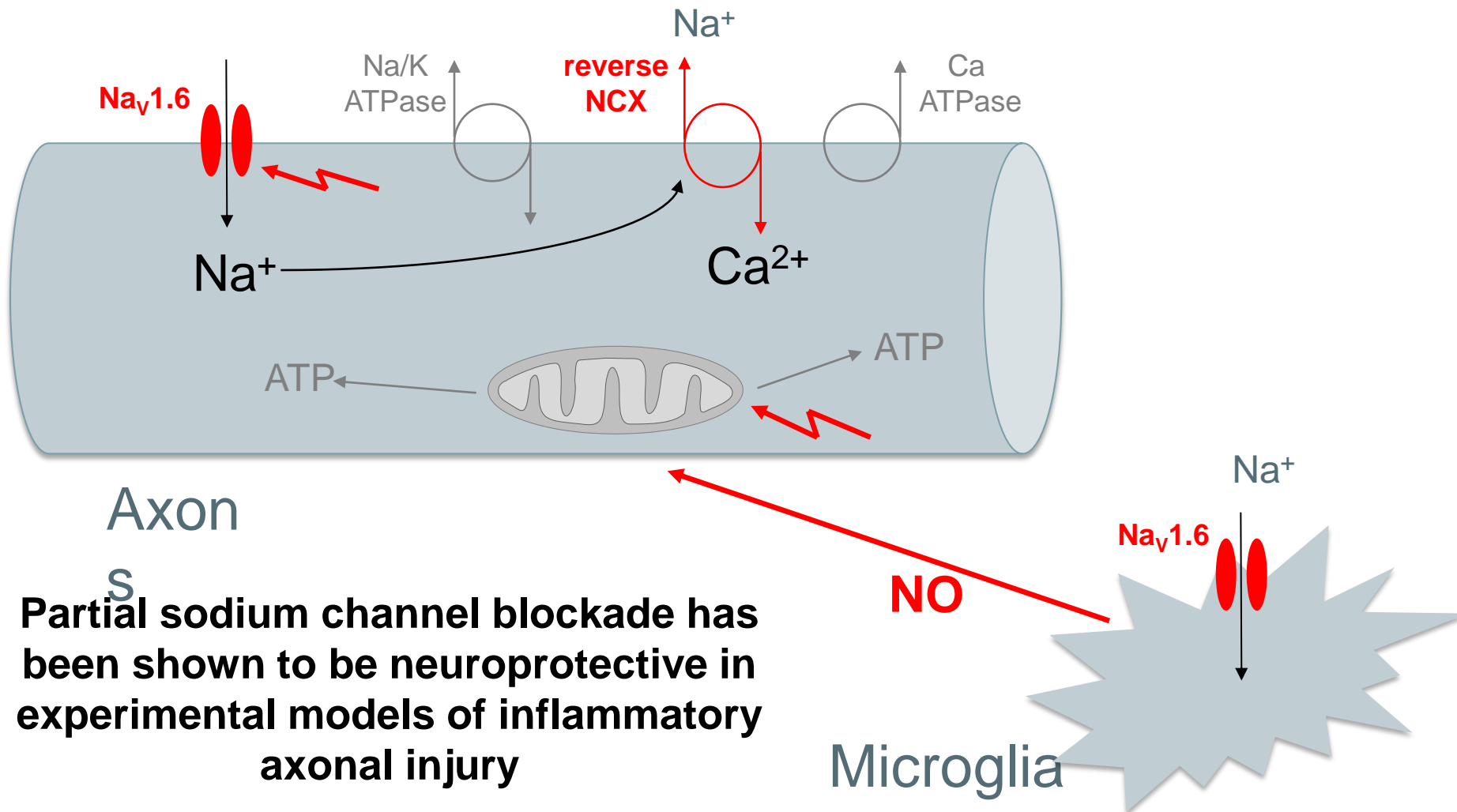
Lifestyle

Rehabilitation

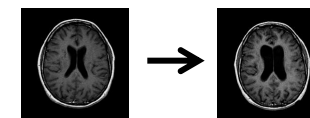
Enhancing plasticity

Treatment target

Neuroprotection: sodium channel blockers



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 (SD -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)70131-9

See *Reflection and Reaction*

page 647

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raj.kapoor@uclh.nhs.uk

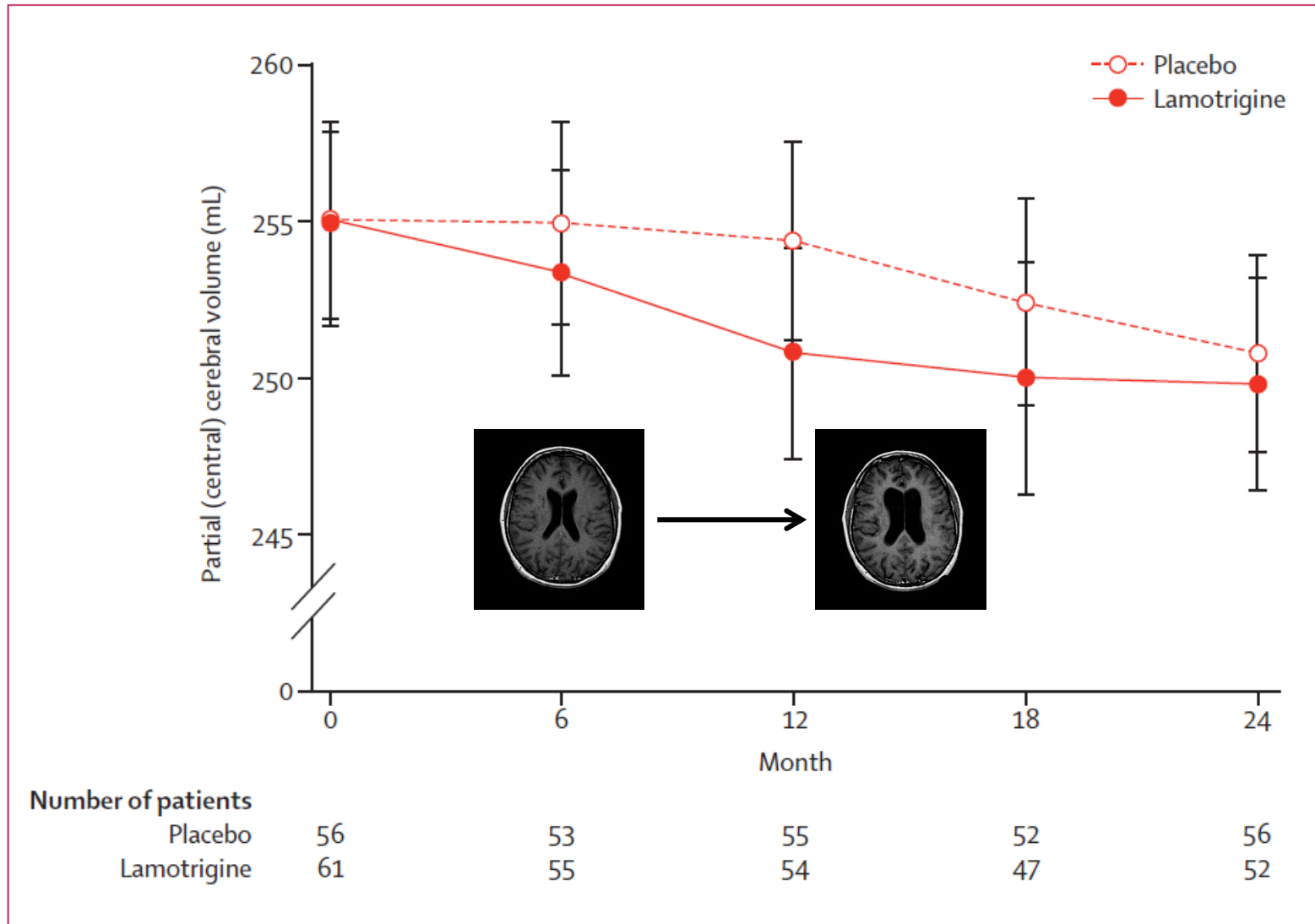
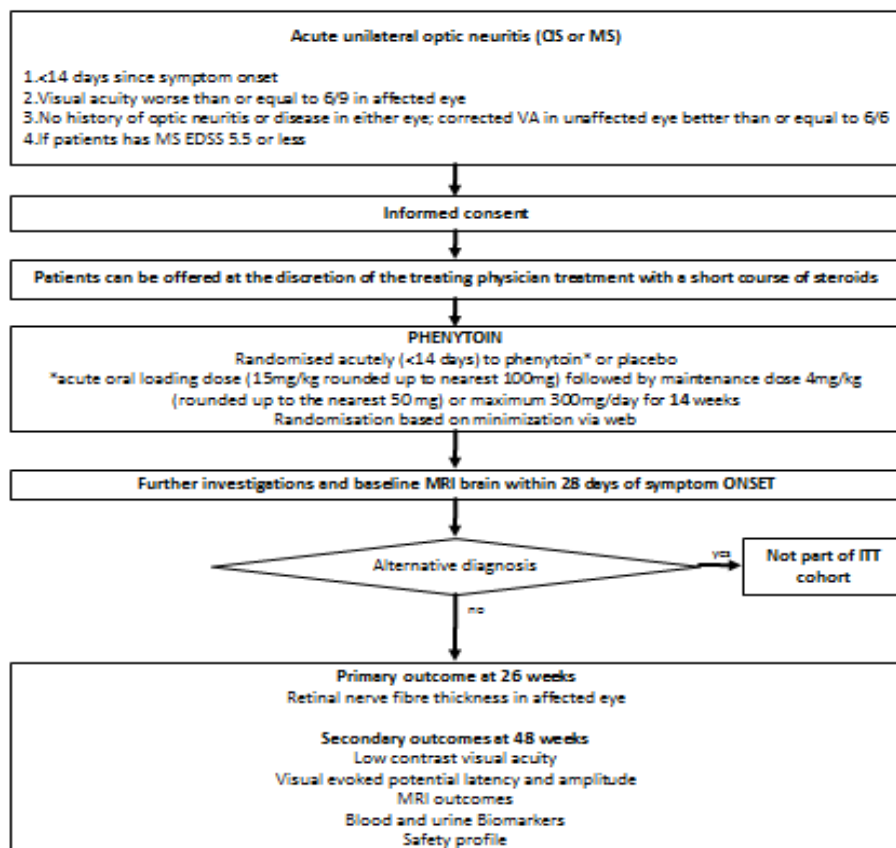


Figure 2: Primary outcome

Mean partial (central) cerebral volume by intention-to-treat comparison, including numbers of valid 6-monthly observations. Bars=SE.

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

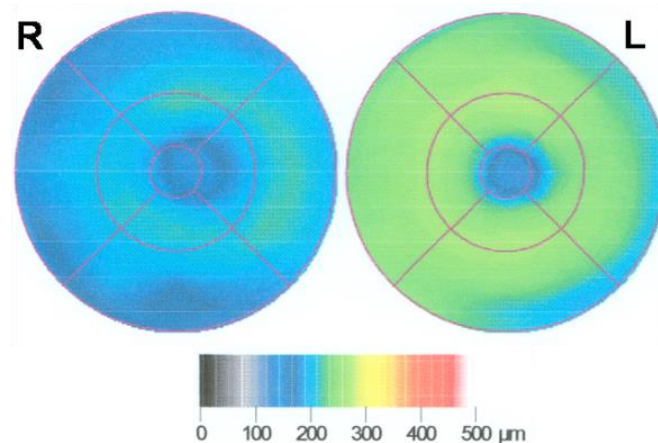
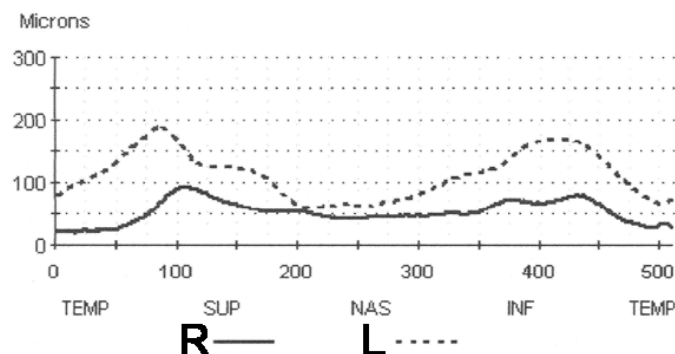


Estimated power calculations*

Clinical Classification	Placebo 1	Phenytoin	
Alternative diagnosis	?	?	?
ITT population	45	45	90
	45	45	?

* Data from a longitudinal study of OCT findings obtained in 22 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 Henderson, D Altmann, D Ganjuji-Waith and CW Miller, unpublished). was used to calculate the sample size, based on the most efficient analysis of data on the primary outcome. A power of 80% to detect a treatment effect of 30% at 5% significance level, allowing for a combined loss to follow-up and non-adherence of 20%.

Acute neuroprotection



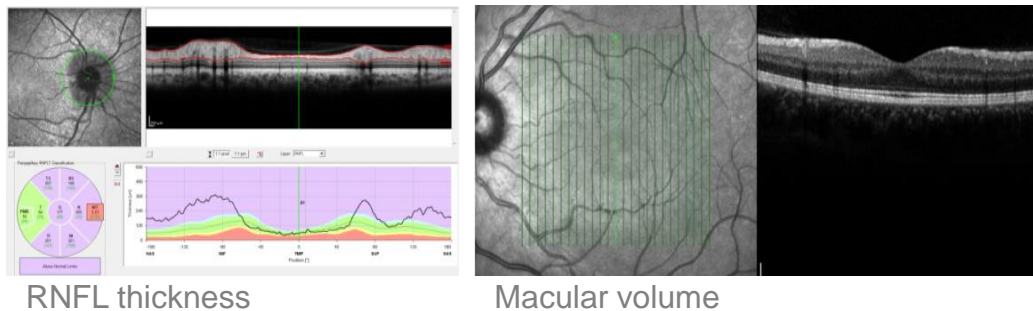
Phenytoin is neuroprotective in acute optic neuritis: Results of a phase 2 randomized controlled trial

R Kapoor^{1, 2}, R Raftopoulos^{1,2}, S Hickman⁴, A Toosy^{1,2}, B Sharrack⁴, S Mallik^{1,2}, D Altmann², P Malladi¹, M Koltzenburg^{1,2}, 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

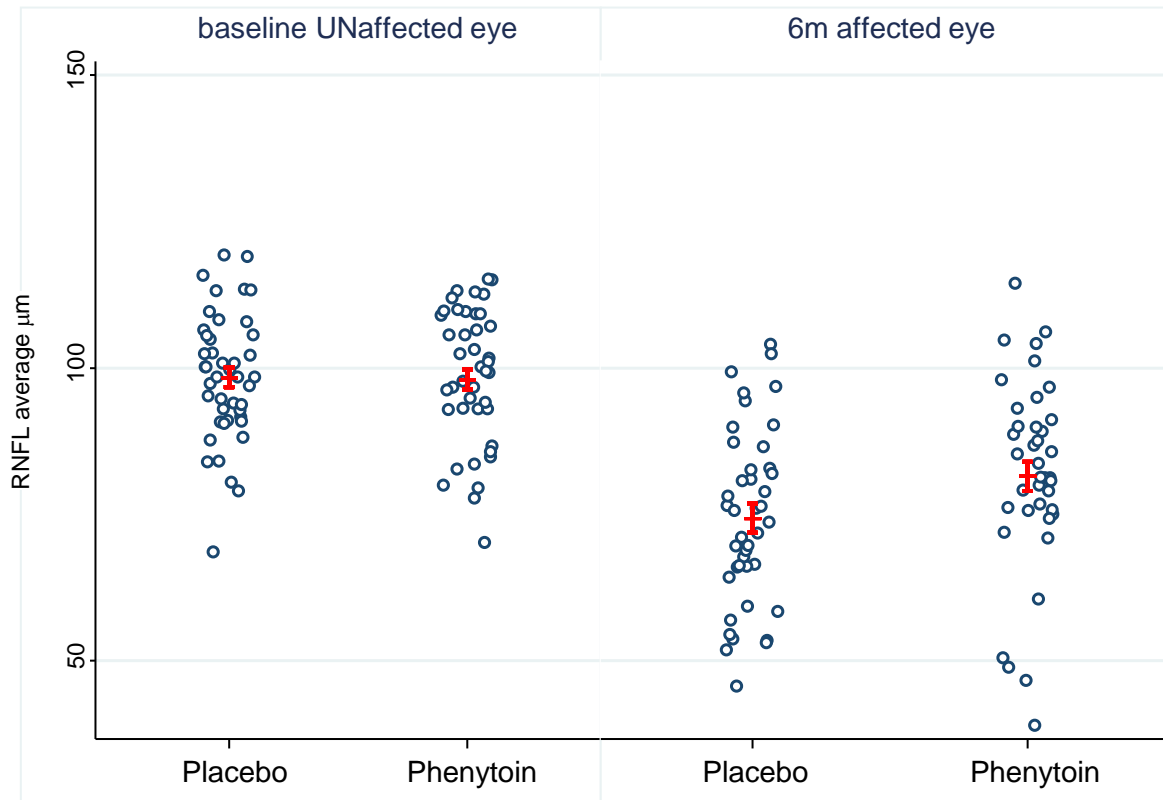


	50%	
40%		60%
55	35	25

- 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



Bars are standard errors around the unadjusted group means

- 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 $p=0.03$)

Lamotrigine in SPMS

Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial

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

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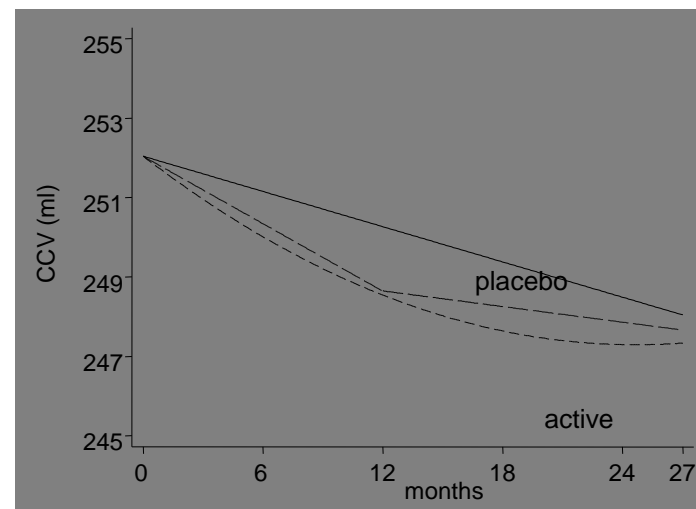
Methods Patients with secondary progressive multiple sclerosis who attended the National Hospital for Neurology and Neurosurgery or the Royal Free Hospital, London, UK, were eligible for inclusion in this double-blind, parallel-group trial. Patients were randomly assigned via a website by minimisation 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.

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See Reflection and Reaction
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Suggestion of slower volume loss in year 2

Rate of change of speed (1/T25FW) (%/mo X10 ³)	active	placebo	
ITT comparison	-0.38	-0.88	p=0.02
PP comparison	-0.20	-0.88	p=0.01

Slower deterioration of timed walk

OPEN ACCESS Freely available online

PLOS ONE

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

Sharmilee Gnanapavan^{1*}, Donna Grant¹, Steve Morant², Julian Furby¹, Tom Hayton¹, Charlotte E. Teunissen³, Valerio Leoni⁴, Monica Marta⁵, Robert Brenner⁶, Jacqueline Palace⁷, David H. Miller¹, Raj Kapoor¹, Gavin Giovannoni⁵

¹Department of Neuroinflammation, UCL Institute of Neurology, London, United Kingdom, ²Independent Statistician, Haddenham, Bucks, United Kingdom, ³Department of Clinical Chemistry, VU University Medical Center Amsterdam, Amsterdam, The Netherlands, ⁴Laboratory of Clinical Pathology and Medical Genetics, Foundation IRCCS Neurology Institute "Carlo Besta", Milano, Italy, ⁵Blizard Institute, Queen Mary University London, London, United Kingdom, ⁶Department of Clinical Neuroscience, Royal Free Hospital, London, United Kingdom, ⁷University Department of Clinical Neurology, Radcliffe Infirmary, Oxford, United Kingdom

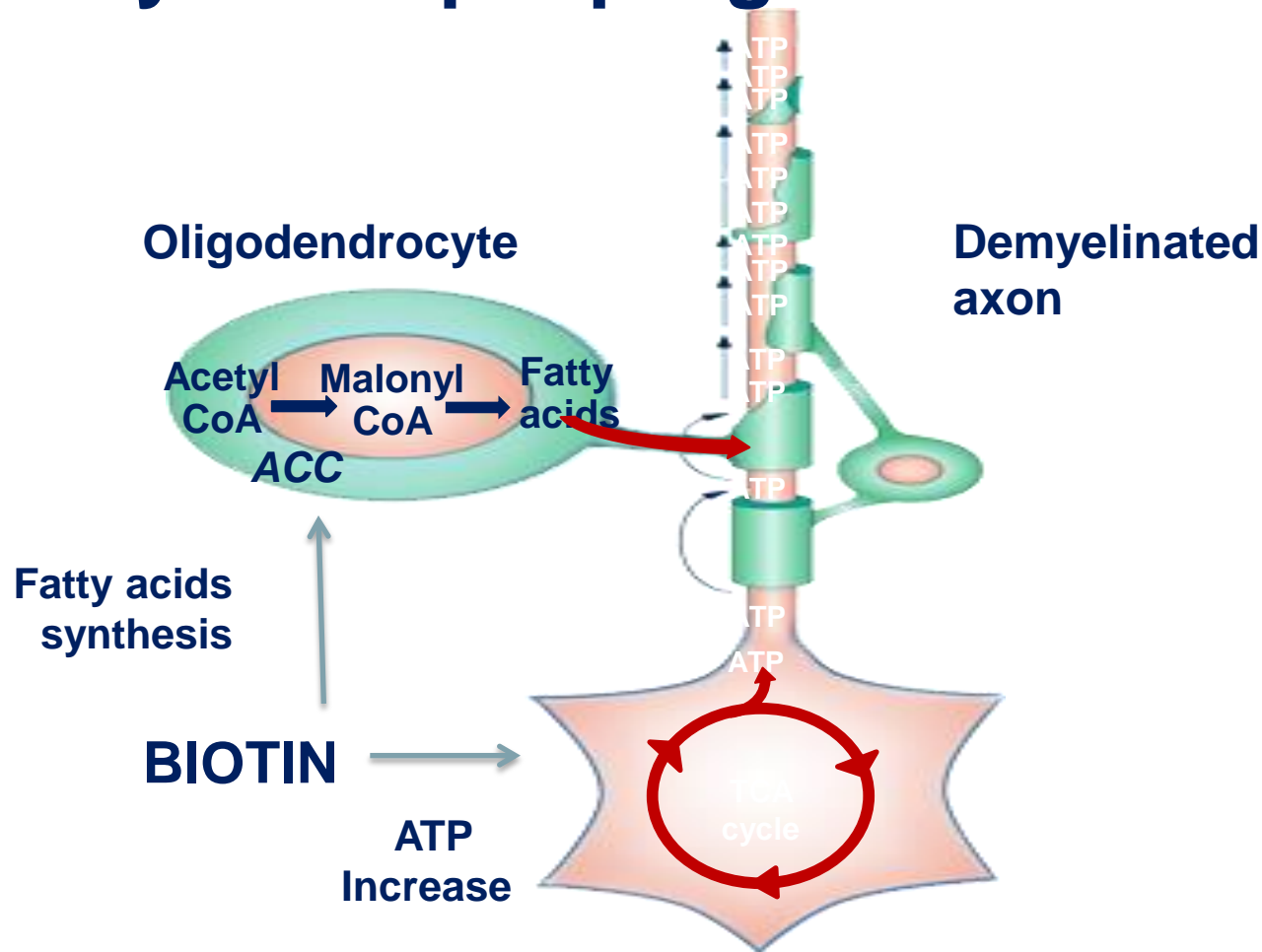
Positive NfH response in adherent group

Effect of MD1003 (High Doses of Biotin) in Progressive Multiple Sclerosis: Results of a pivotal phase III Randomized Double Blind Placebo Controlled Study

A. Tourbah, C. Lebrun-Frenay, G. Edan,
M. Clanet, C. Papeix, S. Vukusic, J. de Sèze, M. Debouverie,
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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



ACC: acetyl CoA carboxylase

Baseline Characteristics (154 patients)

	MD1003 n=103	Placebo n=51	
Female (%)	51.5	58.8	NS
Age, years, mean (SD)	51.8 (9.1)	50.7 (8.4)	NS
PPMS (%)	40.8	25.5	NS
SPMS (%)	59.2	74.5	NS
MS duration, years, mean (SD)	14.8 (8.9)	17.4 (10.3)	NS
EDSS, mean (SD)	5.98 (0.8)	6.2 (0.5)	NS
Concomitant DMT (%)	40.8	41.2	NS
Treatment with fampridine (%)	41	54.9	NS

Primary endpoint: Proportion of patients with improvement at M9 confirmed at M12

- Definition of improvement:
EDSS \searrow by at least by 1 point if baseline EDSS 4.5-5.5 and 0.5 point if baseline EDSS 6-7 or
Timed 25-Foot Walk (TW25) \searrow 20% compared to baseline
- Baseline values: best EDSS and TW25 between M-1 and M0



Primary Endpoint results

	MD1003 n(%)	Placebo n(%)	p-value ¹
ITT population	N=103 13 (12.62%)	N=51 0 (0.0%)	0.0051
Per protocol population	N=87 13 (14.9%)	N=42 0 (0.0%)	0.0093

(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

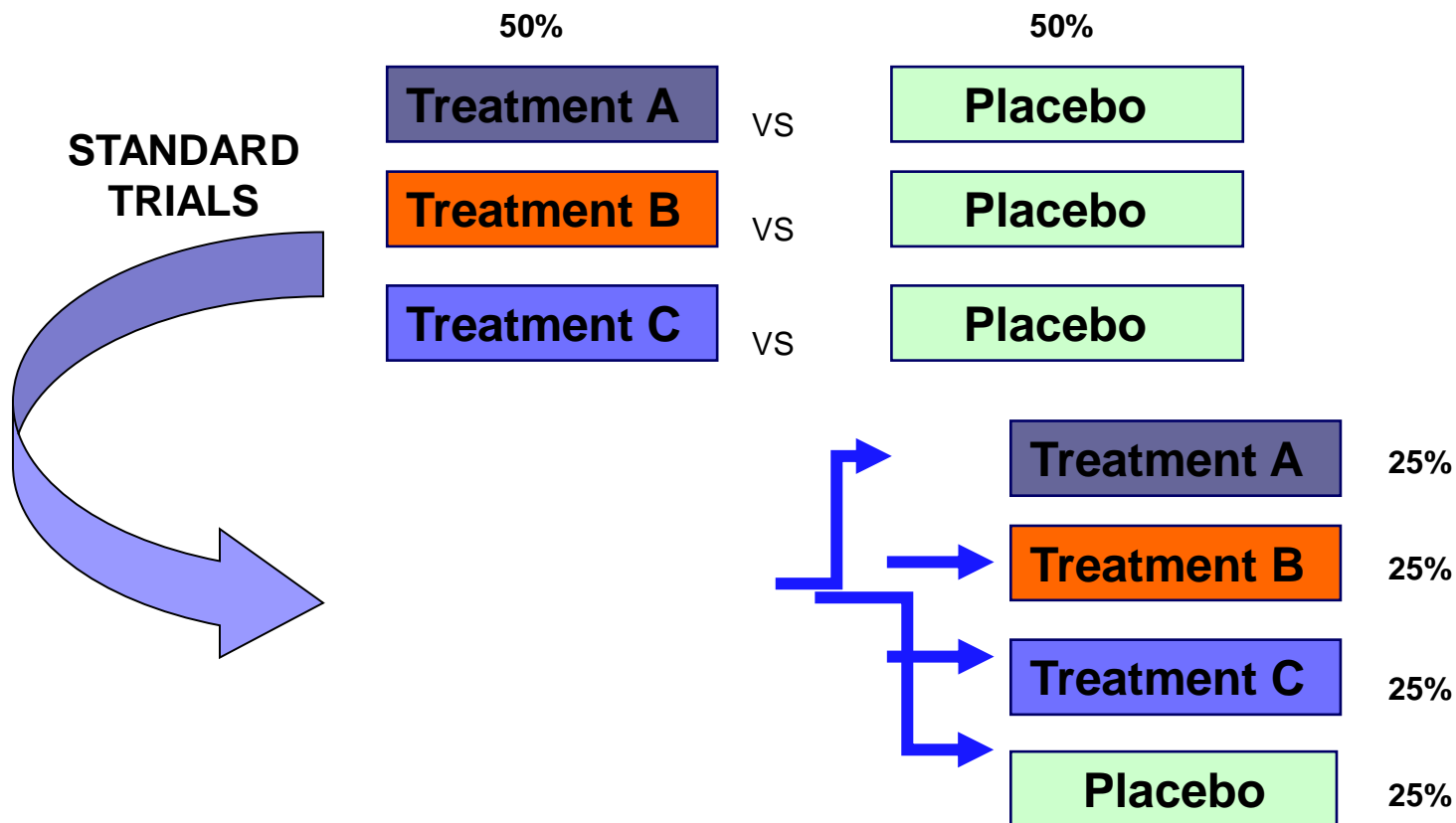
Dr Jeremy Chataway

"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."



Efficacy and Mechanism Evaluation Programme

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- β 1 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



MSC Treatment of Multiple Sclerosis

Reference	Indication	Patients	MSC Source
Connick 2012	SPMS	10	Autologous culture-expanded BM MSCs administered IV
Karussis 2010	RR, SP, PP MS	15	Autologous culture-expanded BM MSCs administered IV and IT
Liang 2009	PP MS	1	Allogeneic umbilical cord MSCs administered IV and IT after CTX
Mohyeddin Bonad 2007	Treatment-refractory MS	10	Autologous culture-expanded BM MSCs administered IT
Rice 2010	Chronic MS	6	Fresh BM cells enriched for MSCs
Riordan 2009	Treatment-refractory MS	3	Autologous non-expanded adipose MSCs
Yamout 2010	SPMS	10	Autologous culture-expanded BM MSCs administered IT

Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study

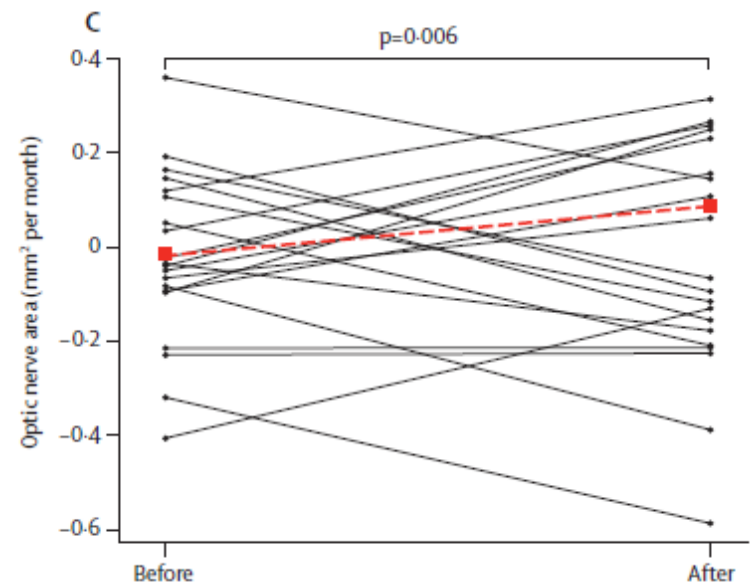
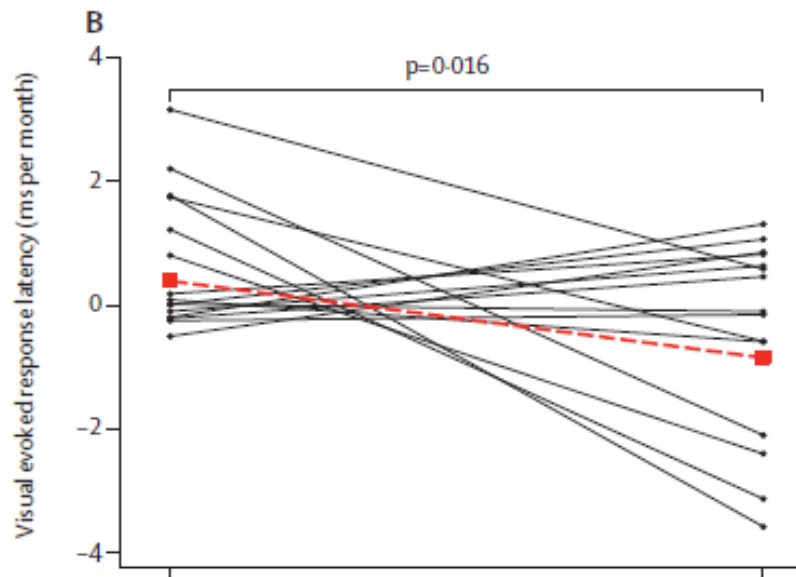
**Peter Connick, Madhan Kolappan, Charles Crawley, Daniel J Webber,
Rickie Patani, Andrew W Michell, Ming-Qing Du, Shi-Lu Luan,
Daniel R Altmann, Alan J Thompson, Alastair Compston,
Michael A Scott, David H Miller, Siddharthan Chandran**

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)
 - \downarrow VEP latency ($p=0.016$) & \uparrow optic nerve area ($p=0.006$)





IMSCTSG

International Mesenchymal Stem Cell
Transplantation Study Group

- 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*



New Perspectives

MULTIPLE
SCLEROSIS
JOURNAL

MSJ

Setting a research agenda for progressive multiple sclerosis: The International Collaborative on Progressive MS

Multiple Sclerosis Journal
0(0) 1–7

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msj.sagepub.com



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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 Hohlfield, 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

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

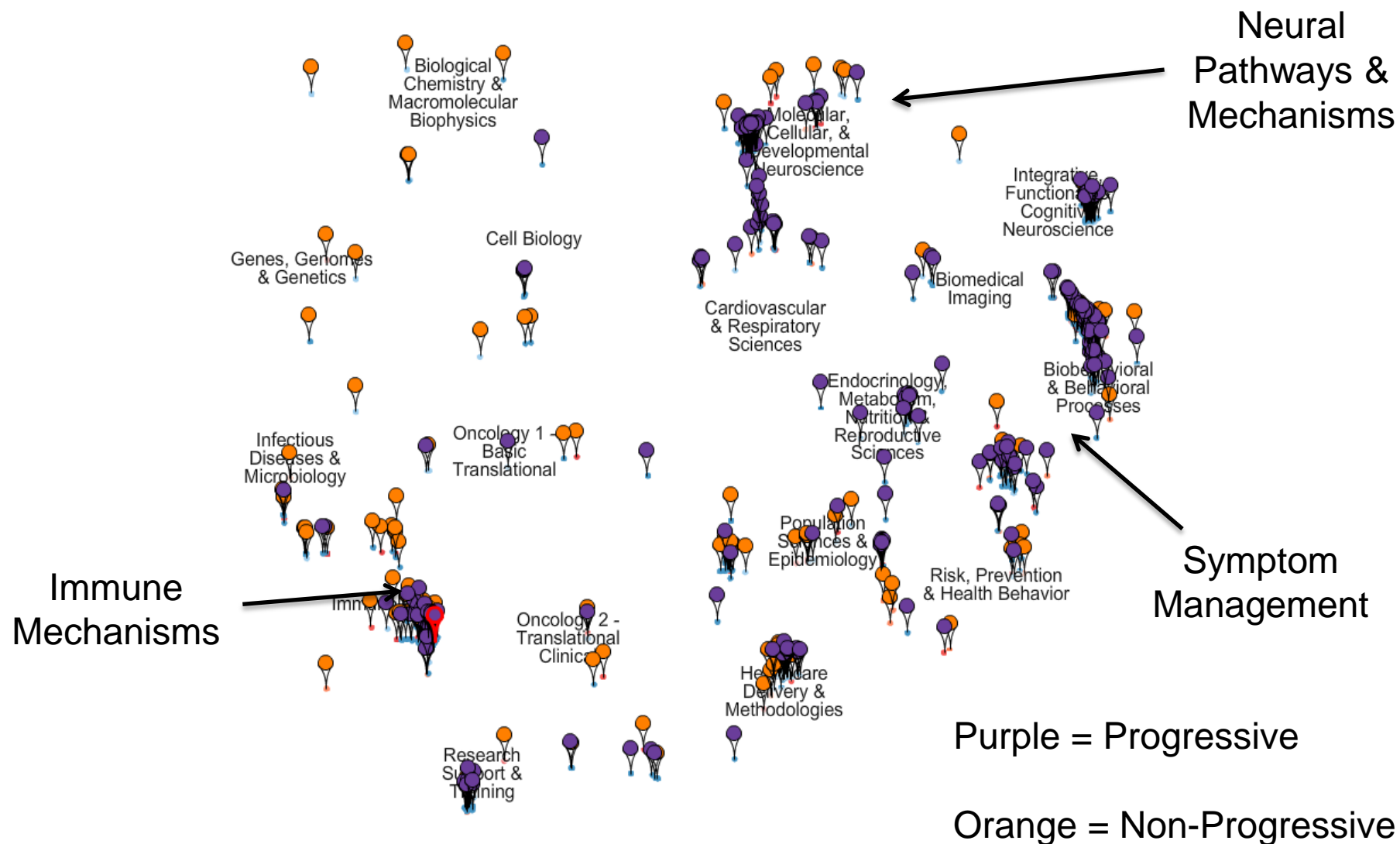
Global Research Funders

- Government
 - NIH, CDMRP, Medical Research Council (UK), CIHR (Canada)
- MS Societies
- Private foundations
 - Hilton Foundation, Wellcome Trust
- Pharmaceutical companies

Global Progressive MS Projects - Pushgraph™ Analytics

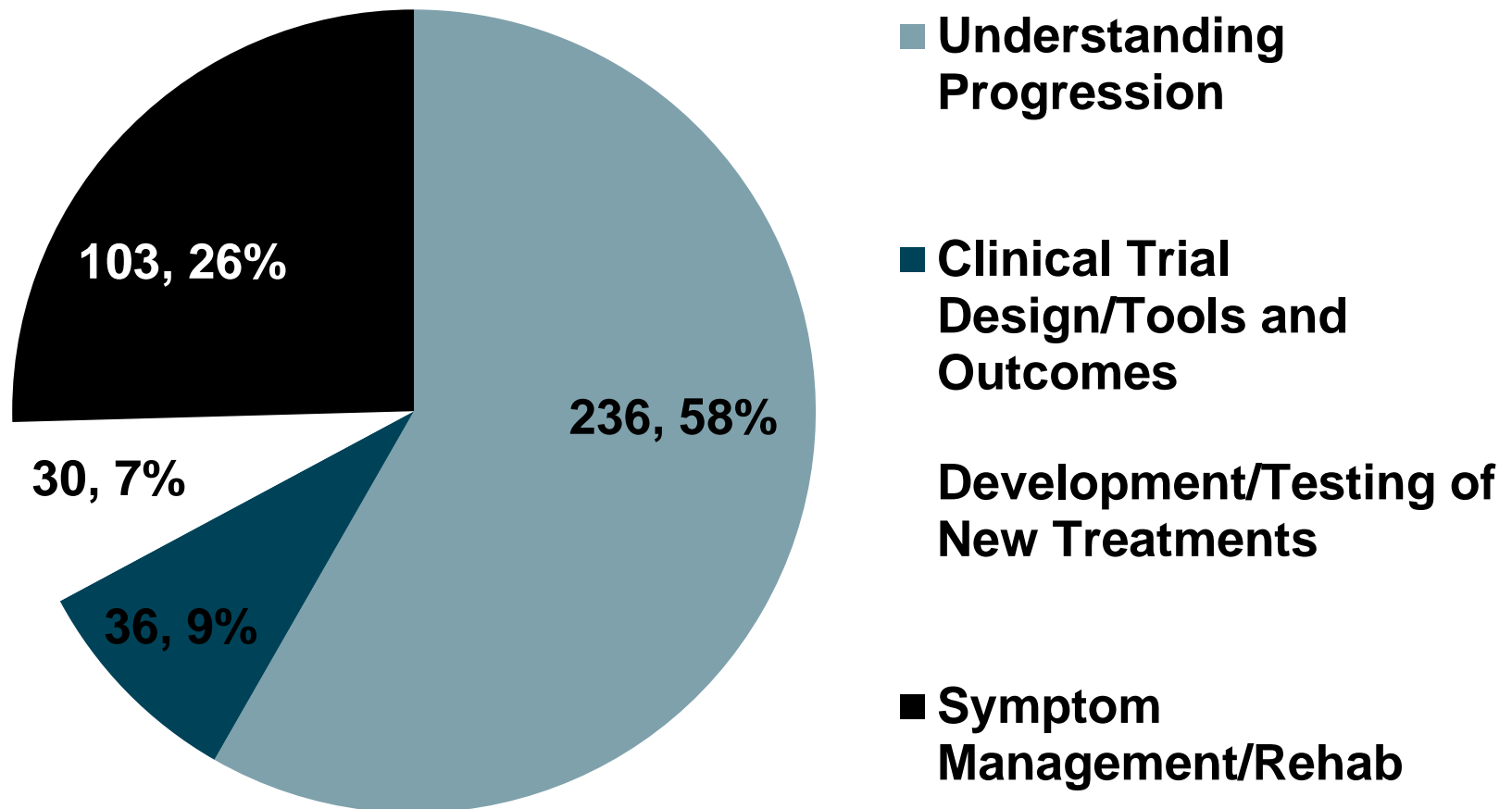
- 405 projects (out of 707) identified as relevant to progressive MS
- Total Multi-Year Commitment = \$132,608,598

Progressive MS Map



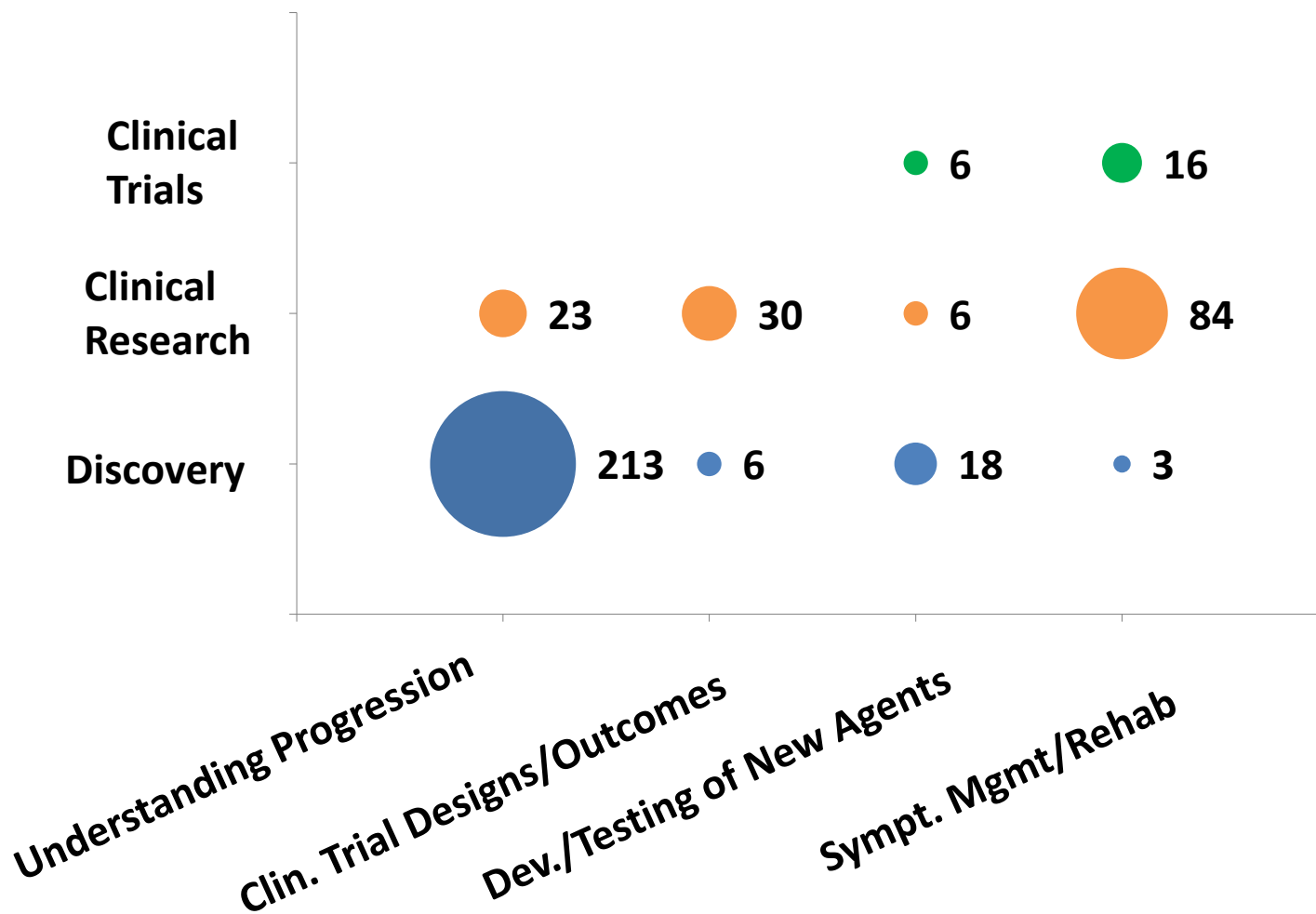
Global Progressive MS Portfolio

Distribution of Projects by Alliance Priority



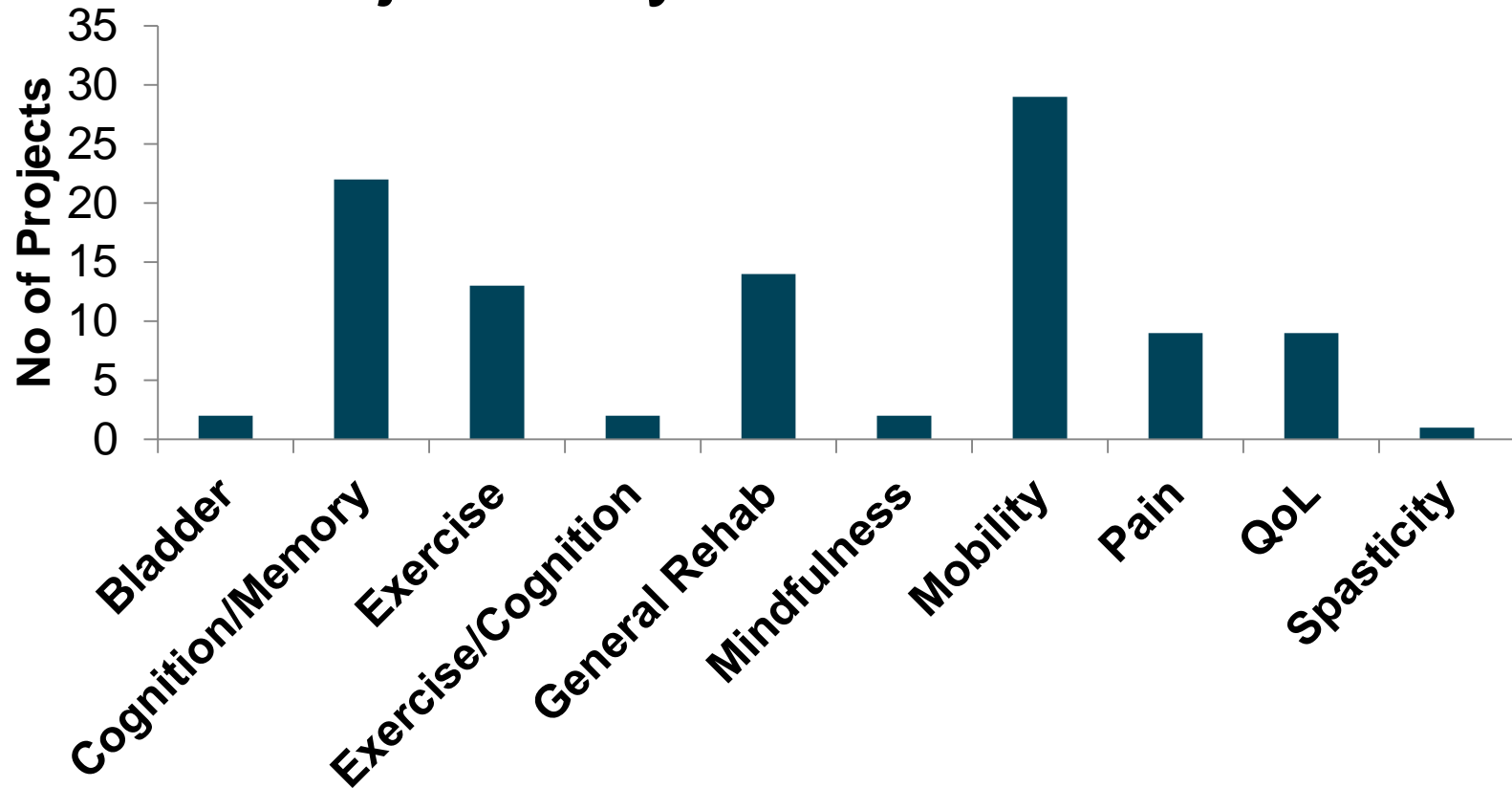
Global Progressive MS Portfolio

Distribution of Projects by Priority/Stage



Symptoms/Rehab Priority

Projects by Area of Focus



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 ACCELERATE RESEARCH**

Scientific Strategy Timeline

Sept 2013

Sept 2014

Sept 2015

Sept 2016

Science
Strategy
Meeting

RFA 1 – Challenge & Infrastructure

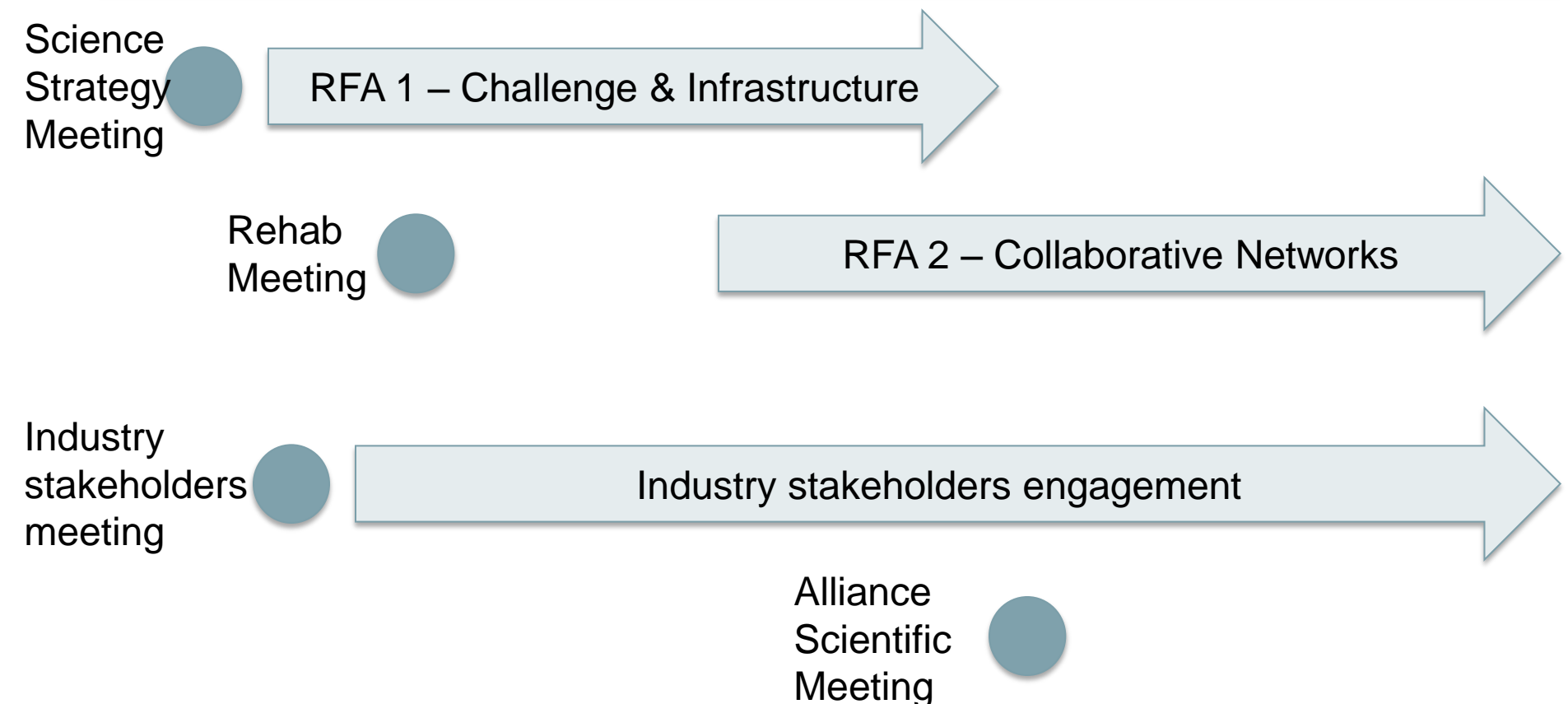
Rehab
Meeting

RFA 2 – Collaborative Networks

Industry
stakeholders
meeting

Industry stakeholders engagement

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**

Multiple Sclerosis Journal

1–9

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1352458515603802

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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

Series

Progressive multiple sclerosis 1

Pathological mechanisms in progressive multiple sclerosis



Lancet Neurol 2015; 14: 194-207

Series



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

Series



Progressive multiple sclerosis 3

Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives

Daniel Ontaneda, Robert J Fox, Jeremy Chataway

THE LANCET Neurology



Lancet Neurol 2015; 14: 208-23

Challenges ahead

- Understand relevant aspects of human MS pathology
 - Validate a pre-clinical model that emulates human pathology
 - Develop high through-put 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

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.

