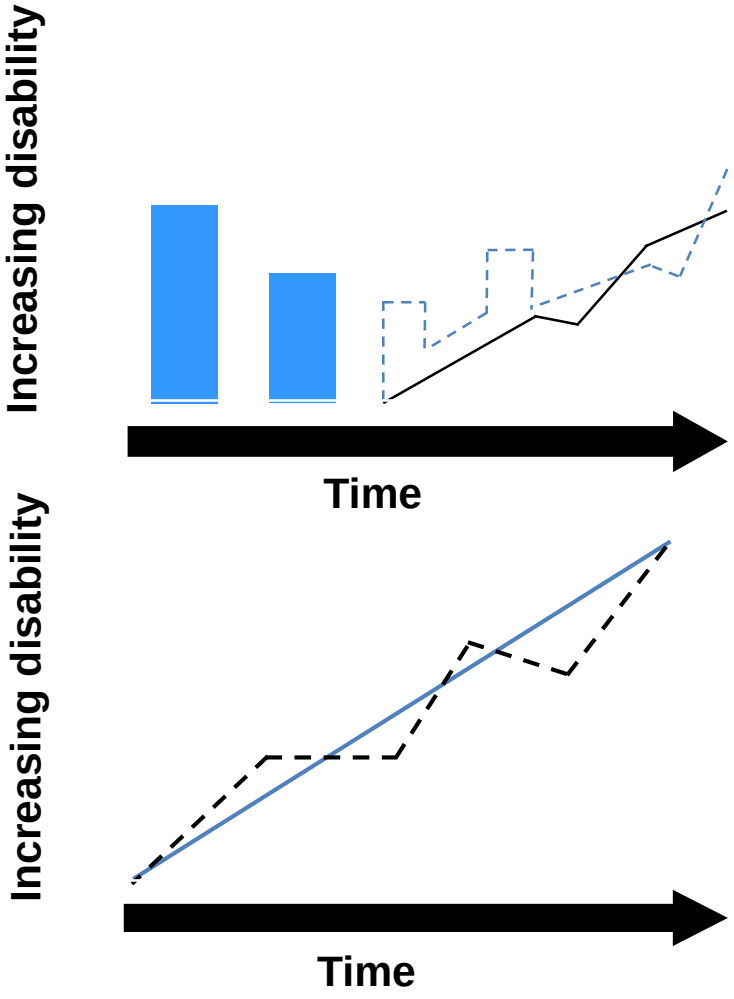
International **P**rogressive **M**ultiple **S**clerosis **C**ollaborative : Update on Research Strategy

Progressive Forms of MS



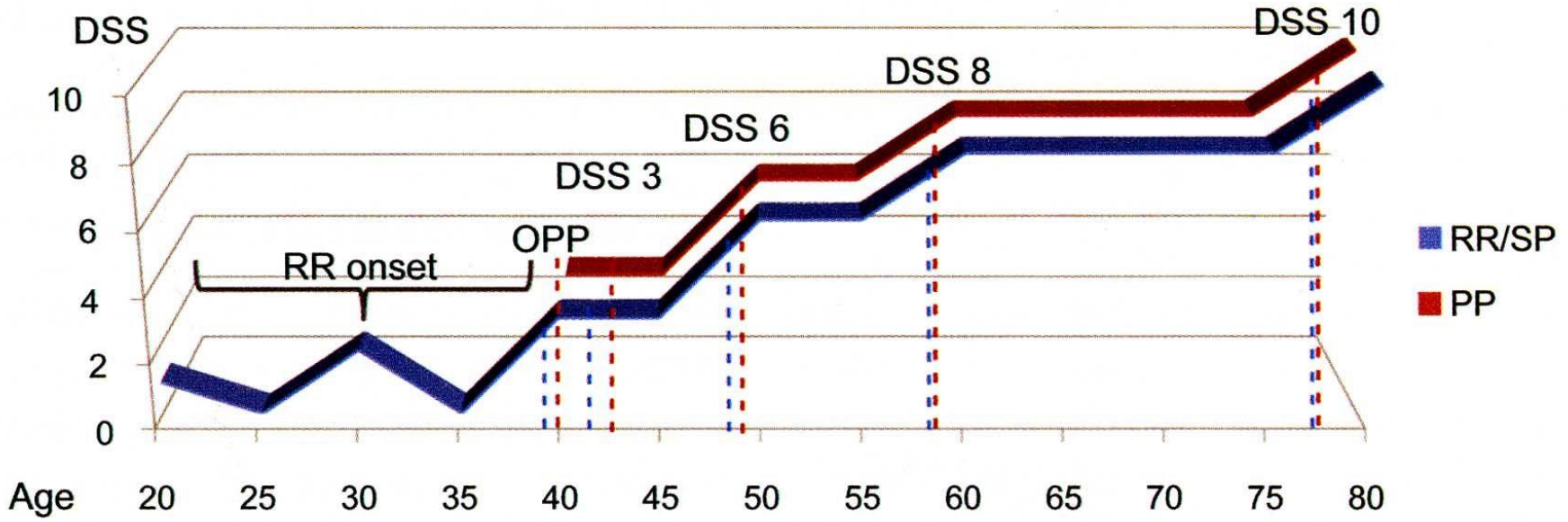
- Many MS patients begin with a relapsing form and convert to a progressive form
- A small percentage of MS patients have nearly continuous progression of disability with no distinct relapses

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

Scalfari et al Neurology 2011

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



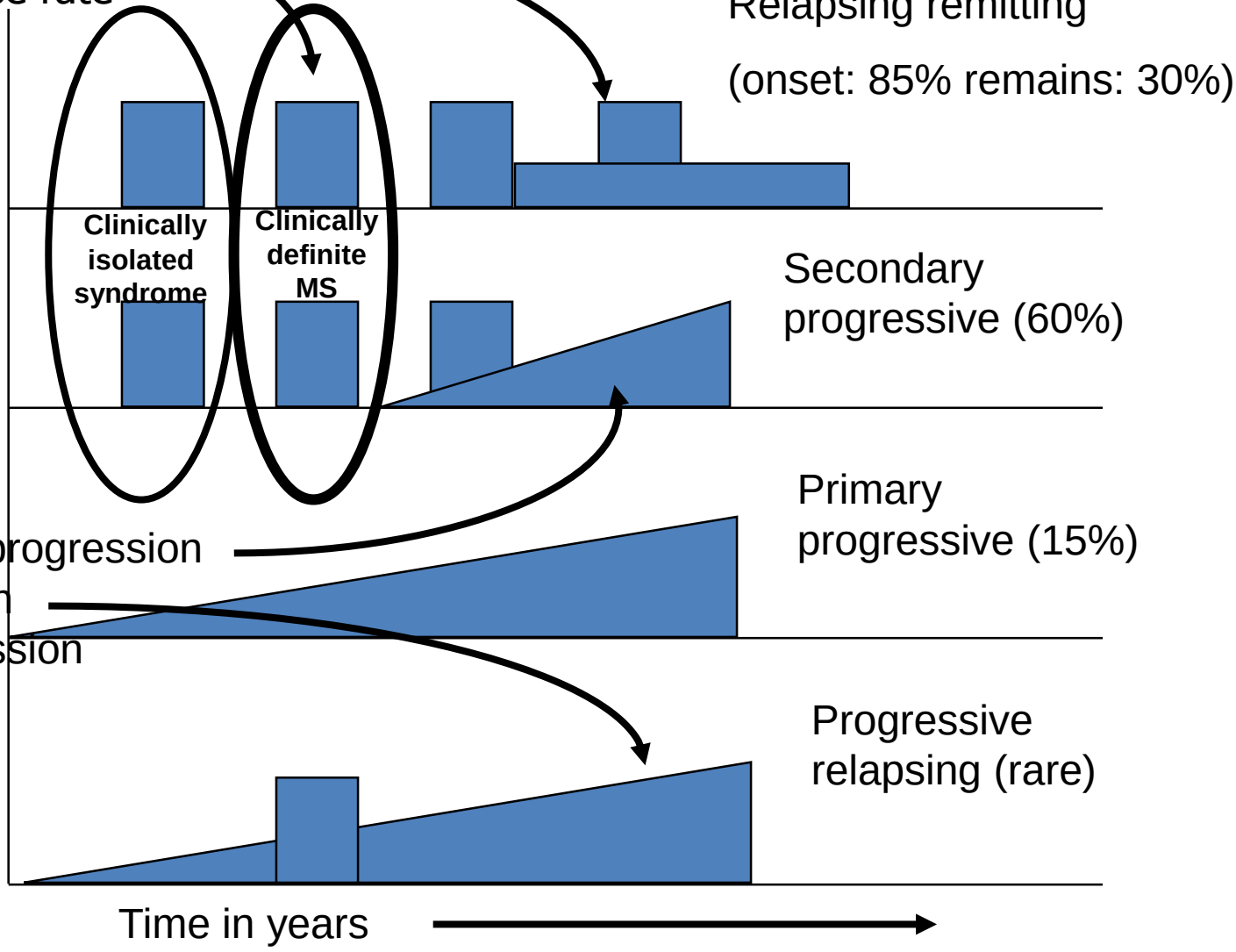
Age at	OPP	*p*	DSS 3	*p*	DSS 6	*p*	DSS 8	*p*	DSS 10	*p*
RR/SP	40.2 (39)	0.09	41.6 (41)	0.82	49.7 (48)	0.05	59.2 (58)	0.44	76.1 (78)	0.63
PP	38.6 (40)		42.3 (43)		48.0 (49)		58.4 (58)		73.8 (78)	

Onset of progressive phase determines disability

Scalfari et al Neurology 2011

Goals of treatment

1. Reduce relapse disability
2. Reduce relapse rate



3. Reduce rate of progression
4. Stop progression
5. Reverse progression

Many new drugs available/coming very soon

- Prevention of T cell circulation and transmigration
  - Natalizumab
  - Fingolimod

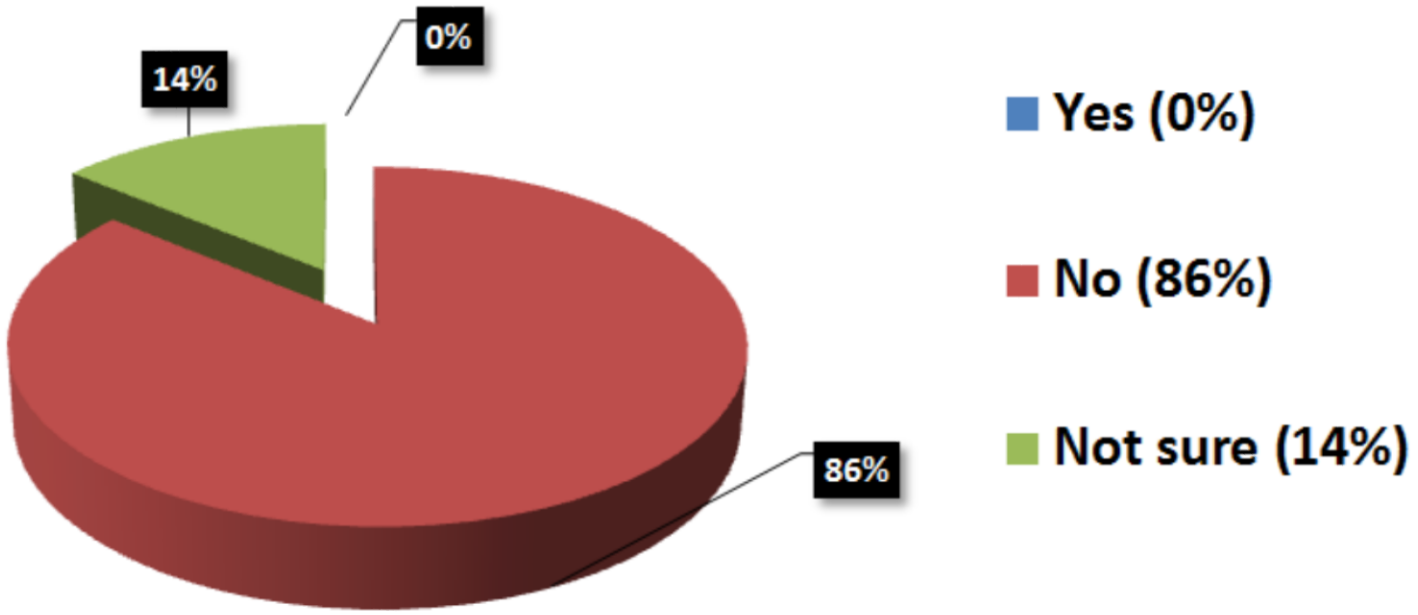
- Anti-metabolities - Teriflunomide

- Leukocyte depletion
  - Alemtuzumab
  - Daclizumab [Phase III]

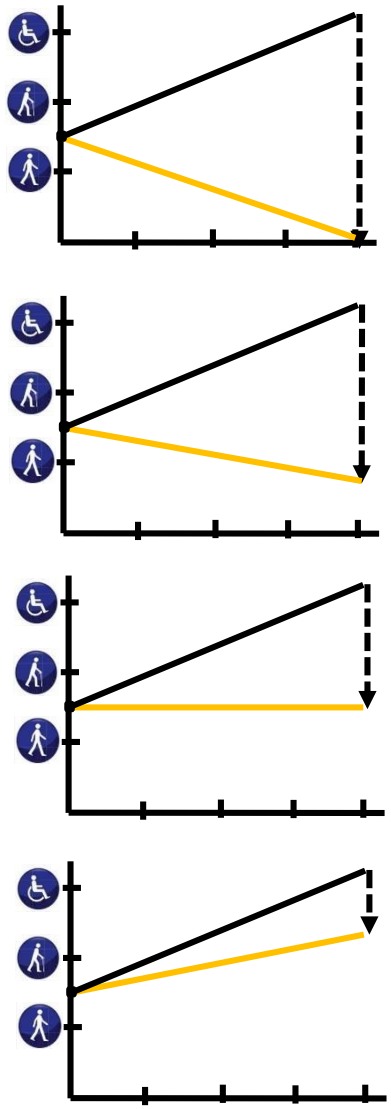
- B-cell directed therapies - Ocreluzimab [Phase III]

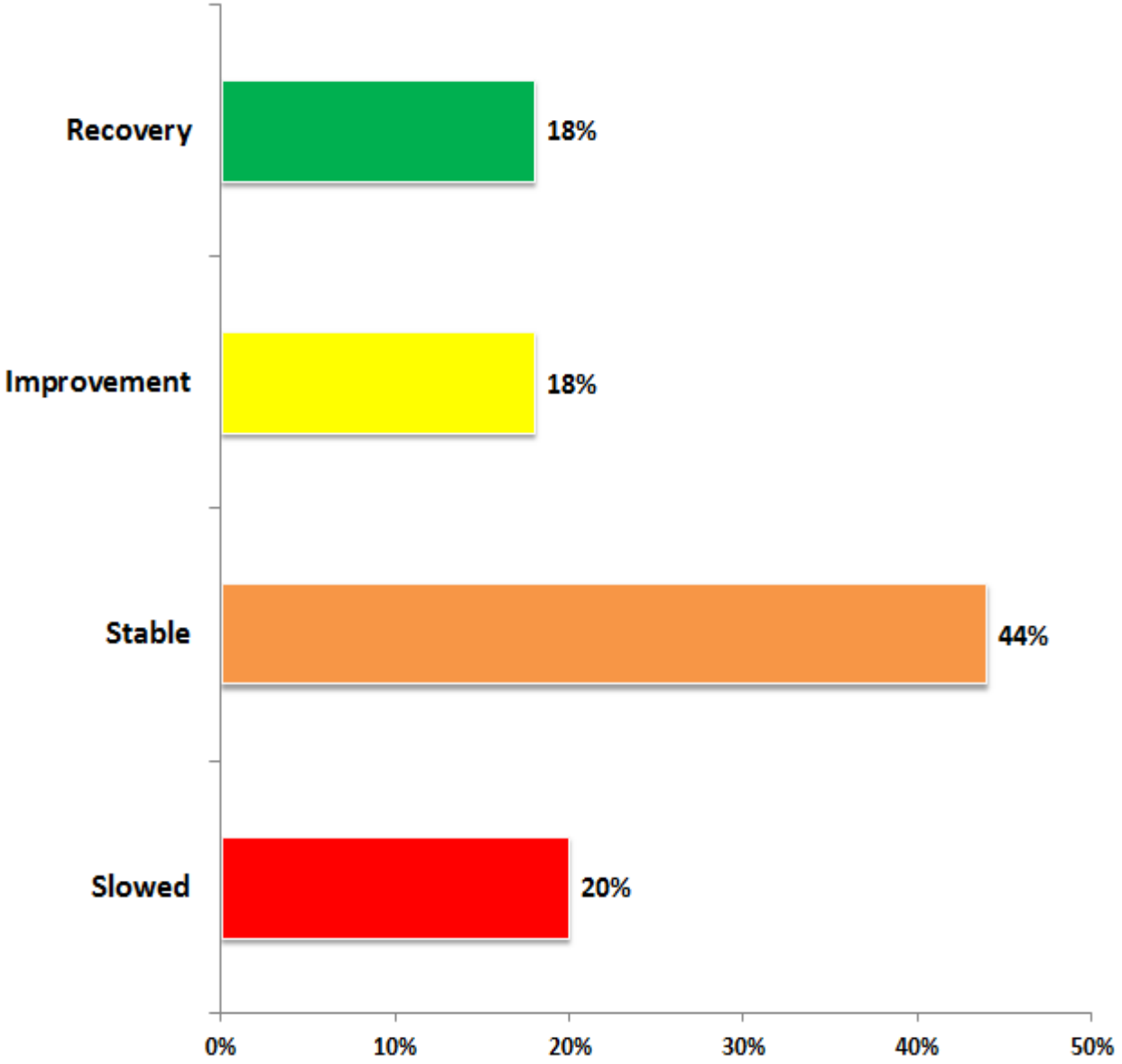
  - Laquinomod , Fumarate

Do you think we are doing enough to address the needs of MSers with progressive disease?

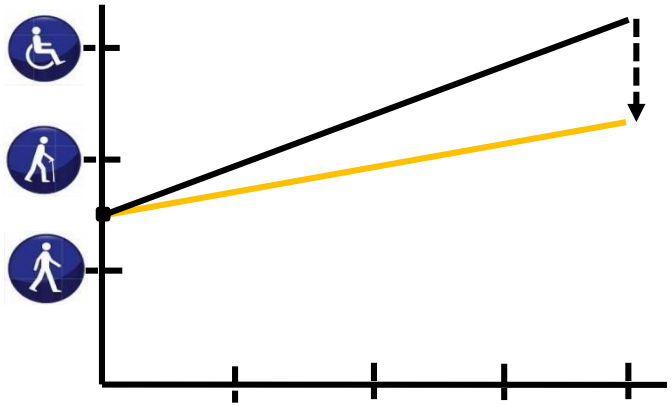


WHAT ARE YOUR EXPECTATIONS OF A THERAPY FOR PROGRESSIVE MS?

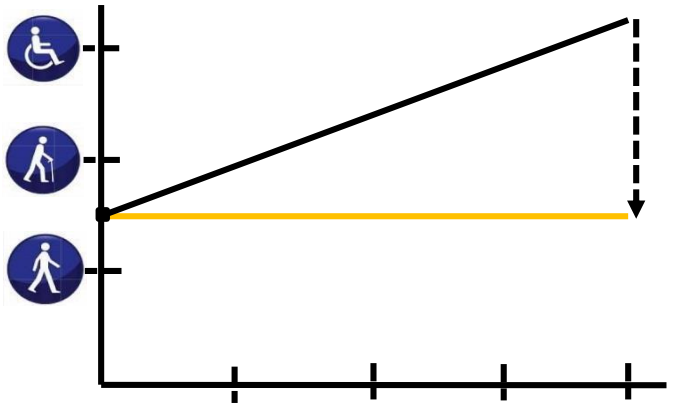




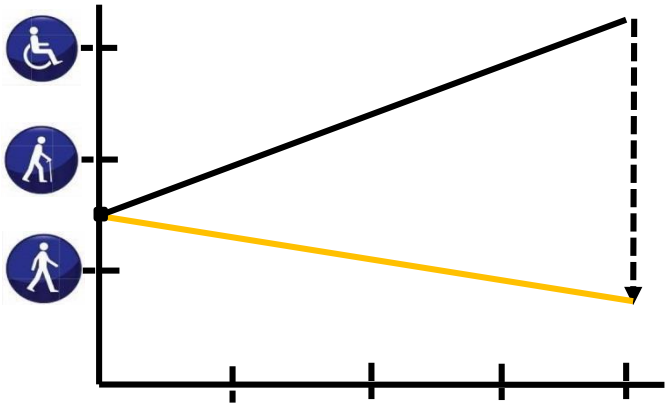
1. Delayed Progression



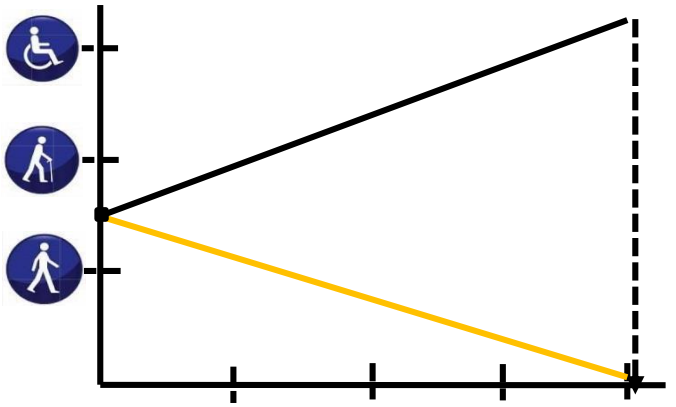
2. Stabilised Progression



3. Improved Function



4. Recovered Function



MAJOR UNMET NEED

Background to the IPMSC

- Think-tank - Boston December 2010
- Societies convened to explore possibility of an international consortium - July 2011
- Kick off Steering committee - January 2012
- Presentation to MSIF Board - October 2012
- Working group meeting in London
- Followed by Steering committee - November 2012

International **P**rogressive **MS** **C**ollaborative

Mission

to expedite the development of therapies for effective disease modification and symptom management in progressive MS

What Do We Hope to Achieve?

- To build on existing research investments to create an integrated, multidisciplinary, collaborative research effort.

- To rally the research community and bring additional worldwide resources to propel this effort forward.

New Perspectives

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–7

DOI: 10.1177/1352458512458169
msj.sagepub.com
SAGE

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

Robert J. Fox[1], Alan Thompson[2], David Baker[3], Peer Baneke[4], Doug Brown[5], Paul Browne[4], Dhia Chandraratna[4], Olga Ciccarelli[2], Timothy Coetzee[6], Giancarlo Comi[7], Anthony Feinstein[8], Raj Kapoor[9], Karen Lee[10], Marco Salvetti[11], Kersten Sharrock[12], Ahmed Toosy[2], Paola Zaratin[13] and Kim Zuidwijk[14]

Multiple Sclerosis Society of Canada

MS RESEARCH

Multiple Sclerosis Society

SCLEROSI MULTIPLA associazione italiana un mondo libero dalla SM

MS National Multiple Sclerosis Society

multiple sclerosis international federation

International **P**rogressive **MS** **C**ollaborative

Initial discussions identified 5 priority areas:

- Experimental Models
- Target pathways and drug repurposing
- Proof of concept trials
- Phase III clinical outcome measures
- Symptom management and rehabilitation

Previous trials

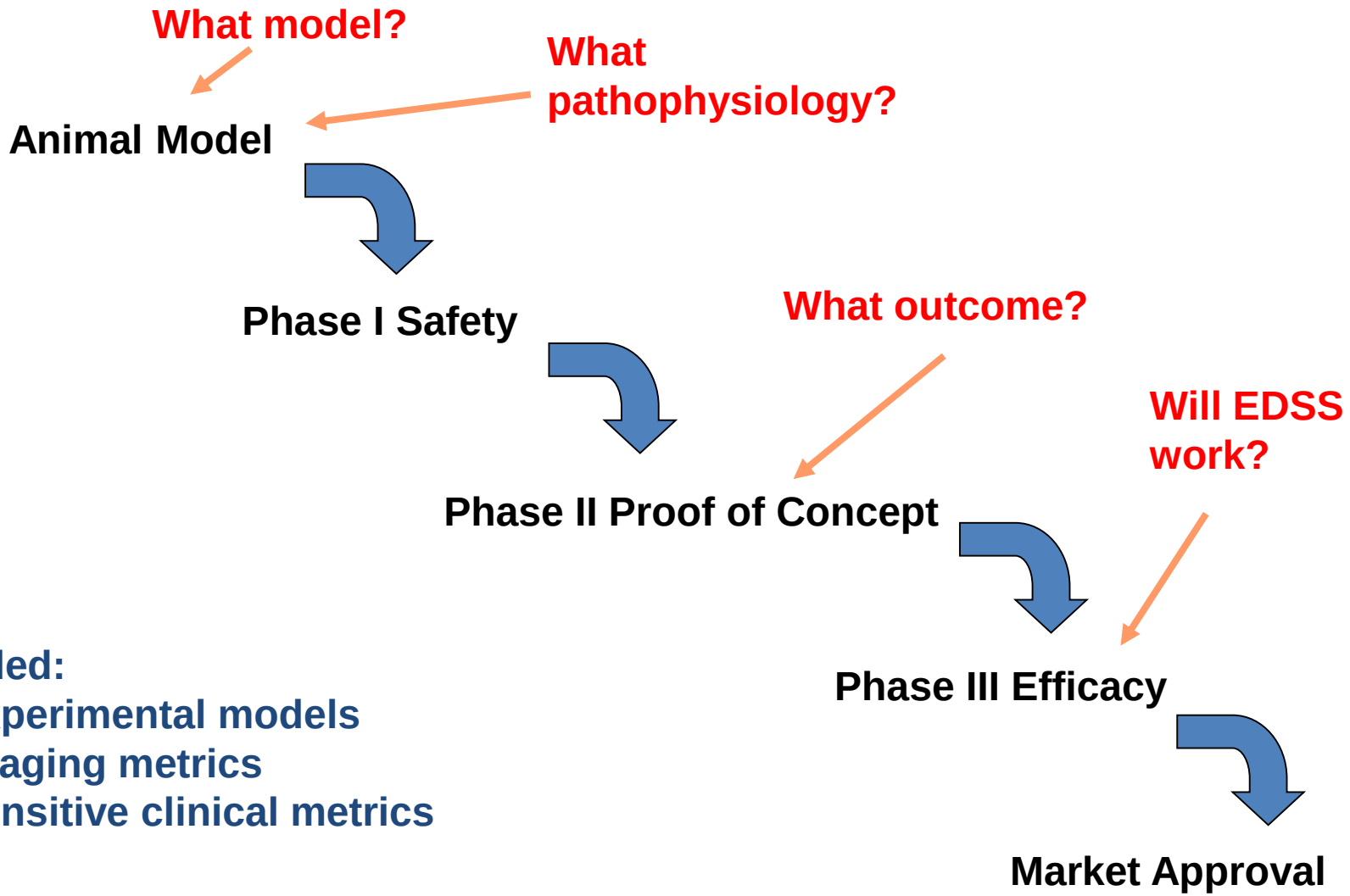
Table 2 A: Trials in MS

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); activites 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

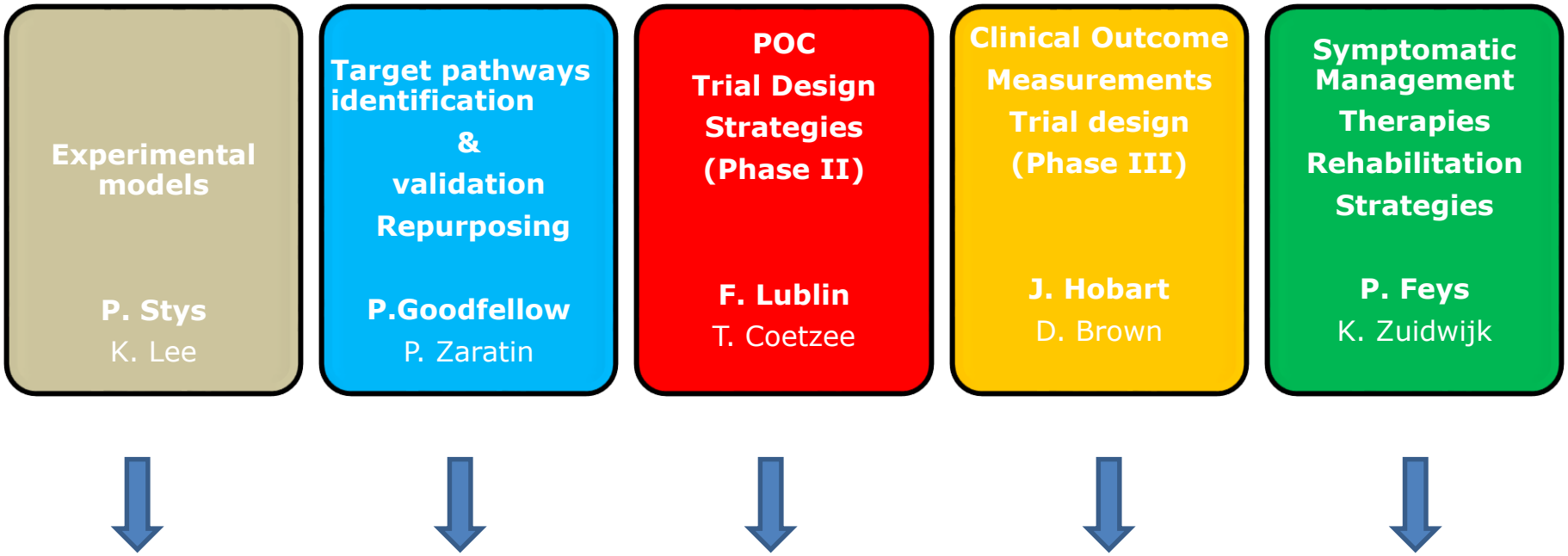
Trial	N	Follow up Yrs	Entry EDSS	Active Treatment	Primary outcome measure	Reporting Date
CUPID (Phase III)	493	3	4.0-6.5	Tetra-hydrocannabinol	Time to confirmed EDSS worsening; MSIS29 mean change	**2012**
MS-STAT (Phase IIb)	140	2	4.0-6.5	Simvastatin	MRI brain atrophy	**2012**

Challenges in drug development for progressive MS



Needed:
1. Experimental models
2. Imaging metrics
3. Sensitive clinical metrics

International Progressive MS Collaborative



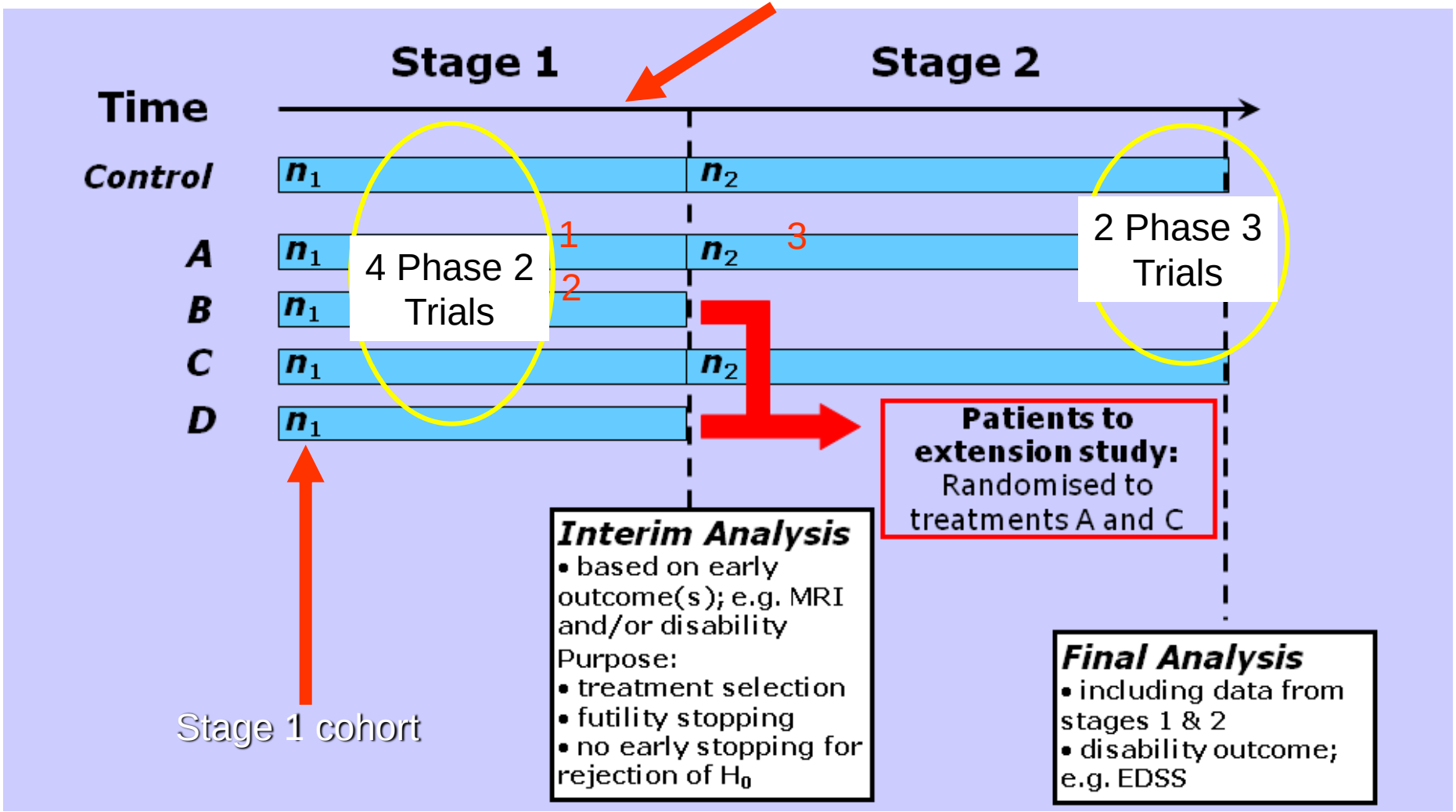
COMMUNITY ENGAGEMENT
TO IDENTIFY RESEARCH GAPS
TO PROPOSE FUNDING STRATEGIES AND COLLABORATIVE MODELS

Why These Five Priority Areas?

- Addresses gaps in understanding about progressive MS
- Creates the tools and resources needed to accelerate research
- Builds on existing research investments

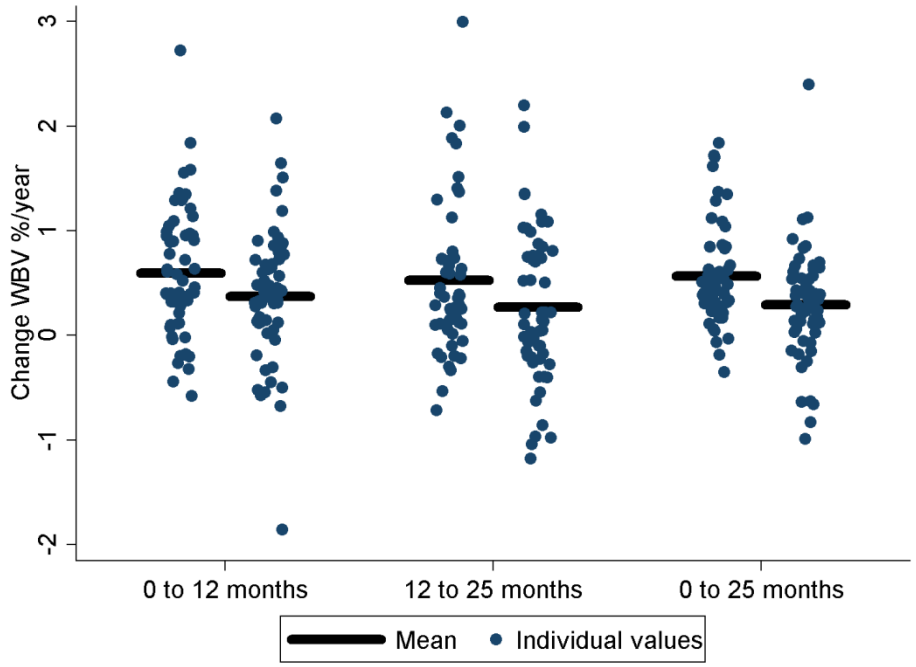
Adaptive Trial Design

- 4 test treatments and 1 control (placebo)



MS-STAT trial

High dose oral Simvastatin in Secondary Progressive Multiple Sclerosis



Scientific Activities – Oct 2012 to date

- **Five working groups develop ideas in each priority area**
  80+ scientific leaders engaged to develop priorities

- **Research Strategy paper developed and endorsed by member societies**
  - Priority research areas
  - Logistics, budget and timeline for first RFAs
  - Criteria for funding and management of projects

- **First Annual IPMSC Meeting – Milan, Feb 2013**
  - More than 170 MS researchers, clinicians, and PwMS.
  - Academics & Industry partners
  - Recommendations for each priority area presented by working group chairs

Scientific Leadership - International Effort

Countries represented: Argentina, Austria, Australia, Belgium, Canada, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Switzerland, United Kingdom, United States

First Annual IPMSC Meeting - 2013

- Overall attendees rated the meeting highly
- Reinforced the importance of the initiative
- Attendees initiated collaborations as a result of the meeting (e.g. Fox / Chataway Trials)
- Great momentum, now need to keep it moving
- Need for clear goals/priorities to focus community

Alignment with Other Initiatives

- The Multiple Sclerosis Outcome Assessments Consortium (MSOAC)
- The International Advisory Committee on Clinical Trials in MS Committee (ICTC)
- UK MS Society Clinical Trials network
- SUMMIT Risk Factors for Progression study
- CENTERS (Centro Neurologico Terapie Sperimentali, Rome): repurposing of existing drugs

A New MS Consortium for A New MS Clinical Outcome Measure

Nicholas G. LaRocca, Ph.D.
Richard Rudick, M.D.
Lynn Hudson, Ph.D.
Co-Directors, MSOAC

U.S. Food and Drug Administration
April 1st, 2013

CRITICAL PATH INSTITUTE

National Multiple Sclerosis Society

Multiple Sclerosis Outcome Assessments Consortium (MSOAC)

The Mission of MSOAC

The Multiple Sclerosis Outcome Assessments Consortium (MSOAC), funded by the NMSS, aims to:

Evaluate existing clinical trial data to qualify a new primary clinical outcome measure for disability in MS clinical trials.

MSOAC Members

- MSOAC Leadership

  Lynn Hudson, PhD; Nick LaRocca, PhD; Richard Rudick, MD
- Academic Investigators
- Industry
- Patient Advocacy Groups
  - NMSS, Italian MS Society, MS Society of UK
  - Alberta MS Research Foundation
  - Consortium of MS Centers
- Regulators and Government Funding Agencies
  - FDA
  - EMA
  - NINDS

Organizational Activities to support Research Strategy

- Steering committee guides overall scientific activity – staff and volunteers
- NMSS acting as project manager for science - support provided by AISM, MSSC, & MSIF
- Infrastructure available through NMSS for first call for proposals

Next Steps

- Steering Committee meets May 20
  - to decide on priorities
  - issue call for proposals

- Additional scientific community and industry engagement
  - workshops
  - focused initiatives.

Progressive MS

- Greatest challenge for patients and researchers
- Improved understanding which will provide greater potential to identify new targets
- More innovative trial design & encouraging recent data
- **Greater international collaboration essential to raise profile and accelerate progress**

The Lancet Neurology

Setting new standards in multiple sclerosis care and research

In the run up to the 2012 European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting in Lyon, France, two important new multiple sclerosis (MS) initiatives are making progress. The International Collaborative on Progressive MS published its agenda of research priorities in late August, while the European MS Platform (EMSP) is due to roll out the next stage of MS Nurse Professional (MS Nurse PRO), a programme to standardise training for MS nurses across Europe, in Barcelona, Spain, at the end of September. Despite taking very different approaches, these initiatives have the potential to benefit many of the estimated 2·5 million people worldwide who have MS.

About 10–15% of people with MS present with primary progressive disease and 80% of the rest develop secondary progressive MS within 20 years. But, despite relative success in the development of treatments for relapsing-

the European Rehabilitation in MS (RIMS) network and the International Organization of Multiple Sclerosis Nurses (IOMSN), which already provides international training for MS nurses. MS Nurse PRO will be based on five core modules: epidemiology and pathophysiology, clinical presentation, diagnosis and assessment, management of MS, and patient care and support. Despite the desire for standardisation, the training will accommodate national differences in the availability of drugs and the needs of employers of MS nurses, which can include charities, health-care providers, and pharmaceutical companies. The scheme has already run a pilot in Malta, and the Spanish launch with be the first test in a language other than English; MS Nurse PRO should also be available in German, Italian, and Czech by the end of 2012 and rolled out to other European countries from 2013 onwards.

Collaboration between organisations in different

For more on **ECTRIMS** see http://www.congrex.ch/ectrims2012.html

For the **progressive MS research agenda** see *Mult Scler* 2012: published online Aug 23. DOI: 10.1177/1352458512458169

For more on the **EMSP** see http://www.emsp.org/

For more on **MS Nurse PRO** see http://www.mstrust.org.uk/professionals/information/wayahead/articles/16032012_06.jsp

For more on **neurological specialist nurses** see InContext *Lancet Neurol* 2012; **11:** 210–11

For the **MS-NEED results** see *Eur Neurol Rev* 2011; 6: 106–09

For more on the **IOMSN** see http://www.iomsn.org/

People with progressive MS still lack effective disease modifying treatments. MS Societies, academia, industry and other stakeholders have to identify a new operative model to collaborate to revitalize innovation and help to introduce disease modifying treatments for progressive MS.

International **P**rogressive **M**ultiple **S**clerosis **C**ollaborative : Update on Research Strategy