PCORI Workshop on Treatment for Multiple Sclerosis

Breakout Group Topics and Questions – Draft 3-27-15

Group 1 - Comparison across DMTs, including differential effects in subgroups

Consolidated straw man questions

1.a	What are the comparative harms and benefits of the different disease-modifying therapies in newly diagnosed relapsing, remitting multiple sclerosis in terms of disease progression and disability?
1.b	Among MS patients receiving a disease modifying therapy who experience a relapse, what are the benefits and harms of continuing the same therapy versus switching to a new medication or a similar medication (e.g., interferon) with a different dosage and administration frequency?

Considerations

Subgroups (examples)

- Relapsing remitting, primary progressive, secondary progressive
- Degree of underlying disease activity
- Low socioeconomic status or poor access to healthcare
- Sex
- Newly-diagnosed vs. established disease

Original (refined) questions

1.1	How do the currently-approved DMTs compare in terms of slowing the progression of people living with MS from the relapsing-remitting (RR) form of the disease to the secondary-progressive (SP) form of the disease?
1.2	What is the comparative effectiveness of the various DMTs to treat symptoms and regenerate or enhance remyelination?
1.3	What is the effect of MS or its treatments on susceptibility to other autoimmune disorders? What is the effect of DMTs upon the risk of infections or malignancies?

1.4	Conduct a 3-5 year randomized, controlled trial to compare Glatiramer acetate (Copaxone), Fingolimod (Gilenya), Dimethyl fumarate (Tecfidera), Interferon Beta-1a (Avonex and Rebif), and Peginterferon beta-1a (Plegridy) in newly diagnosed relapsing, remitting multiple sclerosis for effects on disease progression and disability.
1.5	In patients with relapsing multiple sclerosis, what is the impact of step therapy for medications on relapse rates, patient daily function, and disability progression?
1.6	Among MS patients receiving a disease modifying therapy who experience a relapse, what are the benefits and risks of continuing same therapy versus switching to a new mechanism or similar mechanism with different dosage, i.e. low dose / low frequency vs. high dose / high frequency interferons?
1.7	In people with a diagnosis of relapsing MS, what are the comparative benefits of the current disease modifying therapies on disability progression, cognitive function, depression, and quality of life.
1.8	In patients with MS on Tysabri is there efficacy - by clinical relapses, disability progression, MRI activity - and safety of extended dosing of Natalizumab (NTZ)? OR What are the comparative benefits and risks of extended vs FDA approved dosing?
1.9	What is the risk of PML in patients on extended dosing of Natalizumab (NTZ) compared with FDA approved dosing?
1.10	In persons with relapsing-remitting MS, study the comparative effectiveness of currently approved therapies on MS symptoms such as 1) cognitive impairment, 2) fatigue, 3) pain, or 4) spasticity in RR-MS patients who experience such symptoms.
1.11	Once diagnosed with MS (any type), how should the patient be treated to help them return to normal or to be as functional as possible (QOL)?
	Questions about subgroups
1.12	Compare intensity of Primary Progressive symptoms and co-morbidities across ethnic and socio-economic groups before and after “effective” treatment of the comorbidity.
1.13	What is the risk/benefit of a given DMD (same as DMT) for patients by degree of underlying disease activity?

1.14	Compare outcomes for each of the DMDs in terms of QoL, job productivity, etc., in patients who are progressing due to an aggressive, malignant relapsing MS (e.g., having breakthrough relapses) versus patients who are primary progressive MS (i.e., experiencing disability but not having any relapses)
1.15	For people who are Medicaid beneficiaries who have MS; who have mental health and substance abuse diagnoses what is the rate of progression of their MS?
1.16	What is the comparative effectiveness of DMTs on MS-related symptoms in patients with MS? Does this effectiveness differ for different subgroups of MS patients (i.e. those with relapsing, remitting MS, those with secondary progressive MS, or those with primary progressive MS)?
1.17	Do DMTs or symptomatic treatments differ in effectiveness or safety by patient characteristics, MS type or other disease characteristics, genetic differences, or other patient subgroups?

Group 2 - Care strategies

Consolidated straw man questions

2.a	In patients with relapsing-remitting, secondary progressive, and primary progressive, what are the comparative benefits and harms, in terms of both clinically-assessed outcomes and patient-reported outcomes, of treatment by either an MS specialist, general neurologist or other clinician?
2.b	What are the comparative benefits and risks, in terms of both clinically-assessed outcomes and patient-reported outcomes, of treating to a standard of "no-evidence of disease activity" (NEDA) compared with other strategies in people with relapsing-remitting MS?
2.c	What are the effects of different care strategies (e.g., solo practitioner, collaborative care, interdisciplinary care teams) in effectively treating MS-related symptoms in MS patients with and without comorbidities?

Considerations

What healthcare systems modifications would be useful, in terms of technology, personnel, or care models?

Original (refined) questions

2.1	What are the comparative benefits and risks of MS specialist center vs. Community Neurologist based care for patients with progressive MS (SPMS/ PPMS)? This question should look at outcomes that include symptoms of depression, cognition, mobility, sphincter disturbance and employability.
2.2	What are the comparative benefits and risks of MS specialist center vs. Community Neurologist based care for patients with RRMS (EDSS 0-5.0)? This question should look at long term (3+ years) outcomes that include mobility, cognition, mood and employability.
2.3	In patients with MS and visual impairment, what is the effect on medication compliance of use of alternative prescribing instructions suitably for the visually impaired?
2.4	In patients with MS with mobility challenges, what is the effect on use of preventive screening and patient experience by providing accessible exam equipment, such as exam table scales, compared to usual care?
2.5	Compare intensity of Primary Progressive symptoms and co-morbidities across ethnic and socio-economic groups before and after "effective" treatment of the comorbidity.

2.6	What are the comparative benefits and risks, in terms of both clinically-assessed outcomes and patient-reported outcomes, of treatment by either an MS specialist, general neurologist or other clinician for people with RRMS, Secondary-Progressive MS (SPMS) or Primary-Progressive MS (PPMS)?
2.7	What are the comparative benefits and risks of MS specialist center vs. Community Neurologist based care for patients with progressive MS (SPMS/ PPMS)? This question should look at outcomes that include symptoms of depression, cognition, mobility, sphincter disturbance and employability.
2.8	What are the comparative benefits and risks, in terms of both clinically-assessed outcomes and patient-reported outcomes, of treating to a standard of NEDA compared with other strategies in people with relapsing-remitting MS? (Treating to a NEDA standard means changing/escalating treatment upon evidence of disease activity in the form of relapses, disability progression, and/or MRI lesion activity.)
2.9	Of the currently approved disease modifying drug therapies how can doctors help patients select the best, meaning maximum benefit and lowest risk, drug for their form or stage of MS? Should disease modifying therapies be just the start of treatment? Or should these drugs be used in conjunction with OT, PT, ST, and exercise therapy to help reduce de-conditioning and more progressive stages of MS?
2.10	What existing tools, or as-yet not developed tools, effectively measure MS-related symptoms? How can these tools be used to identify best practices to mitigate the impact of these symptoms on patients' quality of life?
2.11	What are the comparative safety and effectiveness of strategies to help patients engage in key self-management behaviors for managing MS or MS-related symptoms?
2.12	How do people with MS find, assess, and integrate treatment information to manage their health?
2.13	What kind of information do people with MS seek to inform their self-care or shared decision making with their healthcare providers?
2.14	What is the comparative effectiveness of annual (once per annum) vs. semi-annual (twice per annum) cranial magnetic resonance imaging scanning for the management of MS disease modifying therapy in people with relapsing MS?

Group 3 - Non-pharmacologic and non-DMT therapy for specific symptoms and overall health

Consolidated straw man questions

3.a	For persons with MS who have moderate to severe fatigue, compare strategies for fatigue management education, including individual, group, online, medication vs aerobic exercise to counteract deconditioning for their effects on fatigue and quality of life.
3.b	In people with relapse-remitting MS who are already receiving disease modifying therapies (DMT), compare the effectiveness of DMT alone or DMT plus physical rehabilitation interventions and other adjunctive therapies for decreasing the rate and accumulation of disability.

Considerations

Specific symptoms (examples): • Fatigue • Depression • Disability • Cognitive impairment
In patients with multiple sclerosis and [specific characteristics], what is the comparative effectiveness of the following (examples): • Rehabilitation for impairments, mobility, and function • Different levels of exercise on prevention of disability and restoration of function • Complementary and alternative medicine, occupational therapy, physical therapy, massage, and speech therapy • Standard pharmacologic therapy compared to appropriate non-pharmacologic therapy • Nutritional supplements • Mind and body approaches, such as mindfulness meditation, relaxation exercises, yoga, and tai chi

Original (refined) questions

3.1	In people with relapse-remitting MS who are already receiving disease modifying therapies (DMT), compare the effectiveness of DMT alone or DMT plus physical rehabilitation interventions for decreasing the rate and accumulation of disability. Rehabilitation Interventions can include an integrated, comprehensive team approach that can be defined and measured, or can compare specific physical interventions designed to address impairments, mobility and function.
3.2	In people with progressive forms of MS, compare the effectiveness of low, moderate, and high intensity exercise on health measures, prevention of disability and restoration of function.
3.3	Compare the effectiveness of standard therapy (pharma, CAM, PT, OT) for symptoms and/or relapse intensity and/or frequency in R/R MS across ethnic and socio-economic groups.
3.4	Compare the effectiveness of standard therapy (pharma, CAM, PT, OT) for progression to secondary progressive MS across ethnic and socio-economic groups.
3.5	What are the comparative benefits and risks of occupational or physical therapy vs. pharmaceutical treatments for patients with primary progressive MS?
3.6	What are the comparative benefits and risks of nutritional supplements vs. not using nutritional supplements in patients with primary progressive MS?
3.7	What are the harms and benefits of the disease modifying therapies with and without adjunctive treatments of OT, PT, ST, and exercise therapy to reduce de-conditioning in patients in the more progressive stages of MS? How does the form or stage of MS affect these results?
3.8	What is the comparative effectiveness of complementary and integrative approaches – in particular massage, manipulation, or physical therapy for MS patients with chronic pain?
3.9	What are the comparative benefits and risks of mind and body approaches (mindfulness meditation, relaxation exercises, yoga, tai chi, etc.) interventions on emotional health and quality of life of MS patients?
3.10	What are the comparative benefits and risks of early wellness interventions (mind and body approaches, diet and exercise) on mental health outcomes (depression, anxiety) of MS patients?

3.11	In patients with MS, what are the best screening tools to evaluate the presence and severity of MS-related cognitive impairment?
3.12	Among MS experiencing depression, what are the comparative benefits and risks of treatment with antidepressants with or without counseling?
3.13	What are the comparative benefits and risks of pharmacological and non-pharmacological treatments for depression in people with a diagnosis of MS? Target population: diagnosis of MS, between the ages of 18 – 55, depression determined by BDI) score >13. Primary outcomes: change in BDI score from baseline to 3,6,12 months, comparison of side effects, comparison of risk perception of the various interventions
3.14	For persons with MS who have moderate to severe fatigue (average score of 4 or higher on Fatigue Severity Scale), compare strategies for fatigue management education (individual, group, online, medication vs aerobic exercise to counteract deconditioning) for their effects on Fatigue Impact (U-FIS), Quality of Life (FACT-G or SF-36), Self-Efficacy (SEPESCA) and energy conservation behavioral change (ECSS).
3.15	For MS patients with specific symptoms (pain, spasticity, partial or complete paralysis, muscle weakness, fatigue, cognitive dysfunction, etc.) compare strategies to reduce these symptoms, both short and long term?
3.16	What are the comparative benefits and risks of individual fatigue management education, fatigue medication, and aerobic exercise for persons with MS and fatigue?
3.17	What is the comparative effectiveness of therapies other than DMTs (e.g., exercise therapy, CAM therapies, non-DMT pharmacologic therapies) on MS-related symptoms in patients with MS? Does this effectiveness differ for different subgroups of MS patients (i.e. those with relapsing, remitting MS, those with secondary progressive MS, or those with primary progressive MS)?
3.18	How does the use of therapies other than DMTs for patients with MS impact the effectiveness of DMTs in patients with MS?
3.19	In patients with MS who are experiencing cognitive impairment, what are the most effective pharmacotherapeutic and non-pharmacotherapeutic treatments to alleviate cognitive impairment?
3.20	How effective is movement or exercise in reducing symptoms and complications, including urinary tract infections, body sores, respiratory infections, spasticity, and de-conditioning/muscle loss/weakening?

3.21	In patients with relapsing remitting multiple sclerosis and significant fatigue, compare pharmaceutical approaches to reduce the level of fatigue.
3.22	What are the comparative benefits and risks of individual and online individual format fatigue management education for persons with MS and fatigue?

Group 4 - Timing of therapy and study design

4.a	In patients with primary progressive multiple sclerosis, what are the harms and benefits of continuing compared to discontinuing DMTs on symptoms, disability, and mortality?
4.b	What are the harms and benefits of early vs. delayed (2-3 years) treatment with DMTs, in terms of symptoms and quality of life?
4.c	Study designs – What are the advantages and disadvantages of clinical trials that focus on a specific subset of populations, interventions, and outcomes vs. a larger, more comprehensive large observational study?

Original (refined) questions

4.1	What are the comparative benefits and harms, in terms of both clinically-assessed outcomes and patient-reported outcomes, of treatment with each of the currently-approved disease modifying therapies (DMTs), as well as the case where they opt for no DMT at all, for people with relapsing-remitting multiple sclerosis (RRMS)?
4.2	In patients with SPMS, compare continuation vs. stopping immunomodulatory medications on outcomes. In patients with SPMS, compare continuation vs. stopping immunomodulatory medications on outcomes.
4.3	What are the harms and benefits of long-term vs. short-term or stopping or no DMT in terms of symptoms, disability, and mortality in patients with PPMS?
4.4	In patients who transition from relapse remitting MS to secondary progressive MS, what are the long term benefits and harms of prolonged treatment (more than 3 years) with DMTs vs. discontinuing DMTs?
4.5	Compare the outcomes (clinical and health) of patients with MS who begin treatment on a DMD early versus patients who delay treatment for 2-3 years.
4.6	In stable MS patients over the age of 5, compare clinically relevant outcomes in those who discontinue DMTs vs. continue DMTs to compare the risk of recurrent inflammatory MS activity, the risk of disability progression, and quality of life and other patient-reported outcomes (PROs).

4.7	Perform a longitudinal study, including data on age at diagnosis, gender, ethnicity, number of relapses/year, number of lesions, location of lesions, medication exposure (which drugs, treatment duration, include all drugs in analysis, failures, switches, etc.), exercise habits, co-morbidities, changes in mobility at six month increments to determine associations with outcomes, including cognitive function, performance of ADL's, employment, etc.

Cross-cutting issues

C.1	How should the MS person's voice [e.g. Patient-reported outcome (PRO) measures] be used in a clinical trial aimed at slowing or stopping the progression of MS?
C.2	How should MS persons' input be leveraged to develop new clinician rated or performance based clinical outcome measures for MS?
C.3	What outcomes should be used to determine the effectiveness of disease modifying drugs in clinical practice, and how should the MS person's voice be weighted?
C.4	What are the best ways to inform patients with primary progressive MS about current research results and clinical trials?
C.5	In patients with MS, what are the best screening tools to evaluate the presence and severity of MS-related fatigue?
C.6	For MS patients experiencing a relapse, how do shared decision making aids impact patient satisfaction and patient reported outcomes?
C.7	What are performance based assessments that can be utilized to assess cognitive function in outpatient clinical setting of patients with MS?
C.8	What key patient reported outcomes could be used to support comparative effectiveness assessments for MS treatments and help MS patients making treatment decisions?
C.9	How do the most frequently used MS outcomes (e.g., annualized relapse rate, disease progression, and disability) correlate with symptom severity, health-related quality of life, and other patient-centered outcomes that are meaningful to patients?
C.10	What considerations are most important to patients and providers in deciding between various DMTs and/or other symptomatic treatment options?
C.11	How do patient preferences influence the trade-offs between symptom relief and other treatment goals in MS?
C.12	What factors impact decision making when it comes to motherhood and MS?
C.13	In patients with MS and visual impairment, what is the effect on medication compliance of use of alternative prescribing instructions suitably for the visually impaired?

C.14	In patients with MS with mobility challenges, what is the effect on use of preventive screening and patient experience by providing accessible exam equipment, such as exam table scales, compared to usual care?
C.15	Perform a longitudinal study, including data on age at diagnosis, gender, ethnicity, number of relapses/year, number of lesions, location of lesions, medication exposure (which drugs, treatment duration, include all drugs in analysis, failures, switches, etc.), exercise habits, co-morbidities, changes in mobility at six month increments to determine associations with outcomes, including cognitive function, performance of ADL's, employment, etc.