

Network Metanalysis of Disease Modifying Treatments for MS

Health Outcome Descriptors

1. Disability or Dependency [modified from MS Database: Robby Nieuwlaat] (<https://ms.gradeapro.org/>)

Background: impairment or reliance on others.

Symptoms: You will not be able to function anymore as well as before your disease, or as most of your unaffected peers, and you are likely dependent on others to perform your daily routines. You may feel frustrated and depressed for not being able to function as before, or as expected, and to depend on others.

Time Horizon: Depending on the type of your disability you may be dependent on others ranging from days to years. Your disability may improve or worsen in time, depending on the course and stage of MS. You may feel frustrated for a long time due to your disability or dependency.

Testing and Treatment: Depending on the type of disability you might have to undergo testing to assess its cause, or to monitor its effects in the long term. You may need to take treatments to prevent or treat complications related to the disability. Your caregiver may need to administer tests or treatments at home.

Consequences: You might be at risk for complications related to your disability. You will need to adjust your personal life and possibly also your professional life. You might need to arrange ongoing involvement of a caregiver.

2. Relapse of Multiple Sclerosis

Background: 'Relapse' is defined as the appearance of one or more new symptoms due to MS, or the deterioration of pre-existing symptoms, persisting more than 24 hours in the absence of fever and preceded by a period of stability of at least one month (McDonald 2001). Amount of relapse recovery is based on the change between the peak deficit and the residual deficit at least 6 months after the relapse (Vollmer 2007).

Symptoms: you experience a sudden unpleasant sensation that you may have experienced before, for example weakness or tingling or numbness in one part of your body (such as an arm, leg or your face), loss of vision in one eye, dizziness, urgency in urinating or difficulty in initiating it. Symptoms may not recover, recover completely or incompletely.

Time horizon: symptoms may appear over a few hours or over a few days.

Testing and treatment: Your doctor will check you, seeing if you show a complete recovery or an incomplete recovery, compared to before your relapse. In some cases, you may undergo a brain and spine scan that are painless and harmless, although some people feeling uncomfortable when they are in cramped spaces may develop anxiety. You may have to go to the hospital or infusion centre every day for a few days to be treated with intravenous steroids and you may also have to take drugs orally.

Consequences: over a few days usually you experience an improvement and in a few weeks your symptoms may disappear. In some instances you may not feel as well as you felt before the relapse, since some symptoms may not disappear completely. After a relapse you may be offered a different drug by the doctor.

3. Cognitive decline in multiple sclerosis

Background: This outcome will be considered if assessed according to validated neurocognitive batteries for MS, among which the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Langdon 2012; Benedict 2020).

Symptoms: you may experience difficulty with memory including remembering names, learning new information and recalling that information later. You may also experience difficulties when thinking fast when making decisions or solving problems.

Time horizon: in many cases symptoms never occur, or they may appear in the early years after diagnosis of MS and become bothersome over years.

Testing and treatment: your doctor may offer you testing by means of questionnaires and scales, and sessions of training to improve your memory performance.

Consequences: your symptoms may impact your efficiency in your job and create problems in your personal life.

4. Quality of Life Impairment [MS Database: Holger Schunemann, Romina Brignardello-Petersen, Mikkael Sekeres, Mark Litzow] (<https://ms.gradeapro.org/>)

Background: Health-related quality of life (HRQoL) is a patient reported outcome that comprises a comprehensive subjective measure of the patient's health status. HRQoL is assessed by generic or MS-specific validated instruments. For example, the Multiple Sclerosis Quality of Life-54 (MSQOL-54) (Vickrey 1995) is a multidimensional health-related quality of life measure. The questionnaire includes the generic Short-Form 36-item QoL instrument, supplemented with 18 MS-specific items that were based on expert opinion and literature review. There is no single overall score for MSQOL-54. Two summary scores — physical health and mental health — can be derived from a weighted combination of scale scores (scale scores range from 0 to 100 and a higher scale score indicates improved quality of life).

Symptoms: Quality of life impairment indicates a reduced state of wellbeing related to a change in your health status. Many symptoms may cause a reduction in your quality of life. The more severe your symptoms, the more impaired will be your quality of life. Psychological impairment and symptoms will cause a reduction in quality of life, too.

Time horizon: Quality of life impairment will persist for the duration of symptoms, impairment or the condition.

Testing and treatment: Depending on the condition, testing and treatment will be administered. Many tests and treatments may affect your quality of life. Quality of life can be measured with questionnaires.

Consequences: Depending on your condition and treatment your quality of life may improve or worsen.

5. New or enlarging T2 weighted MRI lesions

Symptoms: you may experience no symptoms, and only be notified that your MRI is different from the previous one you undertook. Otherwise, your doctor may offer you an MRI scan after you experience the symptoms of a relapse.

Time horizon: the timing of modifications in your MRI will depend on how often the doctor suggests to perform it.

Testing and treatment: brain and spine MRI scans are painless and harmless, although some people feeling uncomfortable when they are in cramped spaces may develop anxiety. Keeping still for the duration of the scan (30-45 minutes) may cause discomfort. The MRI table will move back and forth during the scan: this may cause discomfort and dizziness.

Consequences: Basing on the results of a new MRI, your doctor may discuss with you the possibility of starting a drug treatment or – in case you are already on a drug treatment - of changing the type of drug you are taking.

6. New gadolinium-enhancing positive T1 weighted MRI lesions.

Symptoms: you may experience no symptoms, and only be notified that your MRI is different from the previous one you undertook. Otherwise, your doctor may offer you an MRI scan after you experience the symptoms of a relapse.

Time horizon: the modifications in your MRI are usually visible for about 4-8 weeks, therefore they will be reported depending on how often the doctor suggests performing it.

Testing and treatment: brain and spine MRI scans are painless and harmless, although some people feeling uncomfortable when they are in cramped spaces may develop anxiety. Keeping still for the duration of the scan (30-45 minutes) may cause discomfort. The MRI table will move back and forth during the scan: this may cause discomfort and dizziness. The doctor will put an IV line in your arm to inject during the scan a contrast medium called gadolinium, which may be harmless but in some case, particularly if repeated in time, may produce a damage in parts of your brain.

Consequences: Basing on the results of a new MRI, your doctor may discuss with you the possibility of starting a drug treatment or – in case you are already on a drug treatment - of changing the type of drug you are taking.

7. Discontinuation of treatment due to adverse events

Symptoms: you experience feeling sick and/or your laboratory tests show abnormalities so you have to stop taking a medication.

Time horizon: adverse events may result in symptoms that last for a few days, weeks or months after you started taking your medication.

Testing and treatment: you may be offered a different medication after experiencing an adverse event. The symptoms or laboratory test abnormalities that you had because of the medication you were taking usually improve and disappear after stopping it. You may need further tests and check-up by the doctor after stopping the medication that caused the adverse event.

Consequences: the different medication that you will be offered may make you feel better than the one you had to stop, without giving you adverse events. After starting the new medication you may be required laboratory tests and regular follow-up by doctors.

8. Serious adverse events (SAEs)

Background: Serious Adverse Events will be considered if defined either by means of the international classification (grade 3 and grade 4 SAE¹) or according to the definition by the authors of the study. If an insufficient number of studies will report the total number of SAEs and person-years, we plan to use the number of participants with at least one SAE as defined in the study.

Symptoms: you may have to stop taking a medication because the drugs make you feel sick or because your blood tests show abnormalities. Such symptoms and abnormalities might require specific treatments.

Time horizon: you may have to stop taking medications a few days, weeks or months after you started taking them.

Testing and treatment: you may be offered a different drug after experiencing a serious adverse event. The symptoms or blood test abnormalities that you had because of the drugs you were taking, may disappear after simply stopping it or after taking specific treatments. You may need blood tests and checking by the doctor after stopping the old drug.

Consequences: the different drug that you will be offered may make you feel better than the one you had to stop, without giving you adverse events. It may require blood tests and checking by doctors every few months.

¹ U.S. Department of Health and Human Services. Criteria for Adverse Events (CTCAE) v5.0, 2017
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

9. Mortality [MS Database: Holger Schunemann, Romina Brignardello-Petersen, Mikkael Sekeres] (<https://ms.gradepro.org/>).

Symptoms: You are dead and feel no pain. You may experience other symptoms prior to dying but you do not feel when you are dead.

Time horizon: Before you die, you experience other states of disease.

Testing and treatment: Tests and treatment will have ceased.

Consequences: You lose your vital bodily and mental functions, ending your life.