**Appendix 1.** Questionnaire used in this study and its rating considering the agreement, recommendation and applicability scales.

| Questions/statements | Agree (%) | Recommend (%) | Medium/long term applicability (%) | Short term applicability (%) | Not applied in clinical practice, but useful (%) | Already applied in clinical practice (%) |
|---|---|---|---|---|---|---|
| **Functional assessment** | | | | | | |
| 1. In patients with clinical and radiological **stability** receiving disease modifying therapies, clinical monitoring: | | | | | | |
| 1.1. Is recommended every 3 months | 18.2% | 18.2% | 6.4% | 9.1% | 45.5% | 9.1% |
| 1.2. Is recommended every 6 months | **100%** | 100% | 0 | 0 | 0 | 100% |
| 1.3. Will be determined by the physician on a case-by-case basis | **100%** | 90.9% | 0 | 0 | 18.2% | 81.8% |
| 2. In patients with clinical and radiological **instability** receiving disease modifying therapies, clinical monitoring: | | | | | | |
| 2.1. Is recommended every 3 months | **90.9%** | 90.9% | 9.1% | 0 | 36.4% | 54.5% |
| 2.2. Is recommended every 6 months | 27.3% | 36.4% | 18.2% | 27.3% | 18.2% | 36.4% |
| 2.3. Will be determined by the physician on a case-by-case basis | **100%** | 100% | 0 | 0 | 27.3% | 72.7% |
| 3. The EDSS score is the best measure available in clinical practice to define progression | **81.8%** | 90.9% | 0 | 18.2% | 0 | 81.8% |
| 4. Progression can be defined: | | | | | | |
| 4.1. By a minimal value of 4 in the EDSS score, a pyramidal function system of ≥ 2 and confirmation of progression for a minimum of 3 months, an increase of 1 point in the EDSS score if the initial score was ≤ 5.5 or an increase of 0.5 points if the initial score was ≥ 6. | 63.6% | 72.7% | 0 | 45.5% | 18.2% | 36.4% |
| 4.2. As an increase in confirmed disability (at 3, 6 or 12 months), measured by EDSS, regardless of the existence of relapses. | **90.9%** | 90.9% | 0 | 18.2% | 18.2% | 63.6% |
| 5. If progression is **suspected**, the patient should be evaluated: | | | | | | |
| 5.1. Every 3 months | 54.5% | 54.5% | 27.3% | 18.2% | 36.4% | 18.2% |

| | | | | | | |
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| 5.2. Every 6 months | 54.5% | 54.5% | 18.2% | 9.1% | 18.2% | 54.5% |
| 5.3. Will be determined by the physician on a case-by-case basis | **100%** | 100% | 0 | 9.1% | 18.2% | 72.7% |
| 6. A confirmed worsening of 2-points in any functional system (except the visual system), even without changes in EDSS, allows the **suspicion** of a progression diagnosis: | | | | | | |
| 6.1. Regardless of disease duration | 54.5% | 54.5% | 27.3% | 0 | 54.5% | 18.2% |
| 6.2. If disease duration < 10 years | 63.6% | 72.7% | 18.2% | 9.1% | 45.5% | 27.3% |
| 6.3. If disease duration between 10 and 20 years | **81.8%** | 72.7% | 18.2% | 9.1% | 36.4% | 36.4% |
| 6.4. If disease duration > 20 years | 63.6% | 63.6% | 27.3% | 0 | 45.5% | 27.3% |
| 6.5. If the patient is <35 years old | 72.7% | 72.7% | 18.2% | 9.1% | 36.4% | 36.4% |
| 6.6. If the patient is between 25 and 45 years old | 72.7% | 72.7% | 18.2% | 0 | 45.5% | 36.4% |
| 6.7. If the patient is > 45 years old | **81.8%** | 81.8% | 18.2% | 9.1% | 36.4% | 36.4% |
| 7. The physician should **suspect** of progression diagnosis when there is a confirmed 20% increase in: | | | | | | |
| 7.1. Only on the 25FTW | 45.5% | 45.5% | 18.2% | 36.4% | 27.3% | 18.2% |
| 7.2. Only on the 9HPT | 45.5% | 45.5% | 18.2% | 36.4% | 27.3% | 18.2% |
| 7.3. In 25FTW and in 9HPT | **90.9%** | 90.9% | 18.2% | 18.2% | 45.5% | 18.2% |
| 7.4. In EDSS Plus (25FTW, 9HPT and EDSS) | **90.9%** | 90.9% | 0 | 18.2% | 45.5% | 36.4% |
| 8. If a patient experiences repeated falls, reflecting a clear loss of physical endurance, even without changes in the EDSS score or other evaluation tools, disability progression should be **suspected**, after excluding other causes. | **81.8%** | 81.8% | 18.2% | 9.1% | 36.4% | 36.4% |
| 9. In a patient capable of walking 500 meters or more, without help or rest, a confirmed reduction from 500 to 300 meters indicates that more accurate progression diagnostic tools should be used. | **100%** | 100% | 9.1% | 18.2% | 27.3% | 45.5% |
| | **100%** | 100% | 9.1% | 9.1% | 18.2% | 63.6% |

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| 10. Transition from walking independently to needing any kind of support or help to walk, indicates that more precise progression diagnosis tools should be used. | | | | | | |
| 11. Regardless of the variable used, the minimum time to **confirm** the diagnosis of disability progression not associated with relapses is: | | | | | | |
| 11.1. 3 months | 45.5% | 45.5% | 18.2% | 18.2% | 45.5% | 18.2% |
| 11.2. 6 months | 72.7% | 72.7% | 0 | 27.3% | 36.4% | 36.4% |
| 11.3. 12 months | **81.8%** | 90.9% | 9.1% | 0 | 27.3% | 63.6% |
| 11.4. 18 months | 45.5% | 45.5% | 27.3% | 9.1% | 9.1% | 54.5% |
| 11.5. Will be determined by the physician on a case-by-case basis | 45.5% | 45.5% | 18.2% | 0 | 18.2% | 63.6% |
| 12. The progression diagnosis can be **confirmed** when there is a 20% increase in: | | | | | | |
| 12.1. Only on the 25FTW | 36.4% | 36.4% | 27.3% | 27.3% | 18.2% | 27.3% |
| 12.2. Only on the 9HPT | 36.4% | 36.4% | 27.3% | 27.3% | 18.2% | 27.3% |
| 12.3. In 25FTW and in 9HPT | **81.8%** | 81.8% | 27.3% | 0 | 27.3% | 45.5% |
| 12.4. In EDSS Plus (25FTW, 9HPT and EDSS) | **90.9%** | 90.9% | 9.1% | 9.1% | 54.5% | 27.3% |
| 13. A confirmed worsening of 2-points in any functional system (except the visual system), even without changes in EDSS, allows the **confirmation** of the progression diagnosis: | | | | | | |
| 13.1. Regardless of disease duration | 54.5% | 54.5% | 9.1% | 18.2% | 54.5% | 18.2% |
| 13.2. If disease duration < 10 years | 63.6% | 63.6% | 18.2% | 0 | 54.5% | 27.3% |
| 13.3. If disease duration between 10 and 20 years | **81.8%** | 81.8% | 18.2% | 9.1% | 45.5% | 27.3% |
| 13.4. If disease duration > 20 years | 72.7% | 72.7% | 18.2% | 0 | 63.6% | 18.2% |
| 13.5. If the patient is <35 years old | 63.6% | 63.6% | 18.2% | 9.1% | 54.5% | 18.2% |
| 13.6. If the patient is between 25 and 45 years old | 72.7% | 72.7% | 18.2% | 0 | 63.6% | 18.2% |
| 13.7. If the patient is > 45 years old | **81.8%** | 81.8% | 18.2% | 9.1% | 45.5% | 27.3% |
| 14. If a patient experiences repeated falls, reflecting a clear loss of physical endurance, even without changes in the EDSS score or other | 54.5% | 54.5% | 18.2% | 0 | 45.5% | 36.4% |

evaluation tools, disability progression can be **confirmed**, after excluding other causes.

| | | | | | | |
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| **Cognitive assessment** | | | | | | |
| 15. Since the diagnosis of the disease, a patient should have at least one cognitive assessment: | | | | | | |
| 15.1. Semiannually | 36.4% | 36.4% | 45.5% | 9.1% | 36.4% | 9.1% |
| 15.2. Annually | **90.9%** | 90.9% | 9.1% | 27.3% | 45.5% | 18.2% |
| 16. The cognitive assessment frequency may vary depending on the clinical situation of the patient and on the recommendation of the neurologist. | **81.8%** | 90.9% | 0 | 18.2% | 45.5% | 36.4% |
| 17. The cognitive assessment should include the largest number of domains possible, so it is recommended to apply at least one intermediate duration battery of tests such as BRB-N. | **81.8%** | 90.9% | 18.2% | 9.1% | 54.5% | 18.2% |
| 18. If it is not possible to apply an intermediate duration battery of tests, a short battery such as BICAMS should be applied. | **100%** | 100% | 18.2% | 18.2% | 45.5% | 18.2% |
| 19. To obtain a reliable cognitive assessment using a battery of tests, such as BICAMS, this battery needs to be applied by a neuropsychologist. | 63.6% | 63.6% | 27.3% | 27.3% | 27.3% | 18.2% |
| 20. If it is not possible to apply a short duration battery of tests, a test such as the SDMT should be applied. | **100%** | 100% | 0 | 0 | 45.5% | 54.5% |
| 21. If, after applying a short or intermediate battery of tests, progression of cognitive decline is suspected, a comprehensive neuropsychological study by a neuropsychologist is recommended. | **90.9%** | 90.9% | 0 | 9.1% | 45.5% | 45.5% |
| 22. A confirmed worsening of 20% in at least two subtests of the BRB-N or BICAMS battery of tests, after excluding other factors, allows the **suspicion** of progression diagnosis. | **90.9%** | 81.8% | 27.3% | 9.1% | 63.6% | 0 |
| 23. A confirmed reduction of 20% in SDMT allows the **suspicion** of progression diagnosis. | **81.8%** | 81.8% | 9.1% | 18.2% | 45.5% | 27.3% |

| | | | | | | |
|---|---|---|---|---|---|---|
| 24. An isolated worsening of cognitive function allows the **suspicion** of progression diagnosis. | 72.7% | 72.7% | 27.3% | 18.2% | 36.4% | 18.2% |
| 25. An isolated worsening of cognitive function is not enough to diagnose progression; it is also necessary that other functional systems worsen. | 45.5% | 54.5% | 27.3% | 27.3% | 18.2% | 27.3% |
| 26. A confirmed worsening of 20% in at least two subtests of the BRB-N or BICAMS battery of tests, after excluding other factors, is enough to **confirm** the progression diagnosis. | **81.8%** | 81.8% | 9.1% | 45.5% | 27.3% | 18.2% |
| 27. A confirmed reduction of 20% in SDMT is enough to **confirm** the progression diagnosis. | 36.4% | 36.4% | 9.1% | 36.4% | 27.3% | 27.3% |
| **Imagiological assessment** | | | | | | |
| 28. A change in the degree of brain atrophy, that is maintained and/or confirmed over time, should lead to the **suspicion** of disease progression. | **90.9%** | 90.9% | 27.3% | 0 | 63.6% | 9.1% |
| 29. A change in the degree of spinal cord atrophy, that is maintained and/or confirmed over time, should lead to the **suspicion** of disease progression. | **90.9%** | 90.9% | 27.3% | 9.1% | 54.5% | 9.1% |
| 30. The presence of diffuse hyperintensity in the brain white matter or confluence of lesions that are maintained and/or confirmed over time, should lead to the **suspicion** of disease progression. | 72.7% | 72.7% | 27.3% | 18.2% | 27.3% | 27.3% |
| **Biomarkers** | | | | | | |
| 31. The presence of increased levels of serum neurofilament light chain (sNfL) can be an important biomarker to detect disease progression. | **90.9%** | 90.9% | 27.3% | 27.3% | 45.5% | 0 |
| 32. Changes in OCT measurements could be an important biomarker to detect disease progression. | **90.9%** | 81.8% | 36.4% | 18.2% | 36.4% | 9.1% |
| 33. Digital devices, could be relevant tools for the early identification of disease progression. | **90.9%** | 90.9% | 27.3% | 36.4% | 36.4% | 0 |
| **Additional assessments** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 34. Since the diagnosis of the disease, patients must complete, at least once per year, a scale/questionnaire that assesses: | | | | | | |
| 34.1. Only fatigue | 18.2% | 18.2% | 18.2% | 0 | 63.6% | 18.2% |
| 34.2. Only depression | 18.2% | 18.2% | 18.2% | 0 | 54.5% | 27.3% |
| 34.3. Only quality of life | 36.4% | 36.4% | 27.3% | 9.1% | 54.5% | 9.1% |
| 34.4. Depression and fatigue | 54.5% | 45.5% | 27.3% | 0 | 63.6% | 9.1% |
| 34.5. Depression, fatigue and quality of life | **100%** | 100% | 9.1% | 27.3% | 54.5% | 9.1% |
| 35. Since the diagnosis of the disease, in case of alterations in the pyramidal functional system, patients must complete a scale that assesses spasticity, at least once per year. | **90.9%** | 90.9% | 9.1% | 9.1% | 63.6% | 18.2% |
| 36. Changes in scales that measure fatigue and depression hardly **confirm** the diagnosis of progression | **100%** | 72.7% | 9.1% | 9.1% | 45.5% | 36.4% |
| 37. Changes in questionnaires that measure quality of life should indicate that more accurate diagnostic tools for progression should be used. | **81.8%** | 81.8% | 27.3% | 18.2% | 54.5% | 0 |
| 38. A worsening of spasticity should indicate that more accurate diagnostic tools for progression should be used. | **90.9%** | 90.9% | 9.1% | 9.1% | 63.6% | 18.2% |
| 39. The patients should be asked proactively and in a structured manner if they are experiencing any deterioration or changes in their symptoms that may be considered **suspicion** of disease progression. | **90.9%** | 90.9% | 9.1% | 9.1% | 45.5% | 36.4% |

25FTW: 25-foot walk test; 9HPT: 9-Hole Peg Test; BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; BRB-N: Brief Repeatable Battery of Neuropsychological tests; EDSS: Extended Disability Status Scale; OCT: Optical Coherence Tomography; SDMT: Symbol Digit Modalities Test; sNfL: serum neurofilament light chain.