

Multidisciplinary data infrastructures in multiple sclerosis: Why they are needed and can be done!

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## MULTIDISCIPLINARY DATA INFRASTRUCTURES IN MULTIPLE SCLEROSIS: WHY THEY ARE NEEDED & CAN BE DONE!

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Abstract:	Personalized treatment is highly desirable in Multiple Sclerosis (MS). We believe that multidisciplinary measurements including clinical-, functional and patient reported outcome measures in combination with extensive patient profiling can enhance personalized treatment and rehabilitation strategies. We elaborate on four reasons behind this statement: 1° MS disease activity and progression are complex and multidimensional concepts in nature and thereby defy a one-size-fits-all description, 2° Functioning, progression, treatment and rehabilitation effects are interdependent and should be investigated together, 3° Personalized health care is based on the dynamics of system biology and on technology that confirms a patient's fundamental biology and 4° Inclusion of patient-reported outcome measures can facilitate patient relevant healthcare. We

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	discuss currently available multidisciplinary MS data initiatives and introduce joint actions to further increase the overall success. With this topical review, we hope to drive the MS community to invest in expanding towards more multidisciplinary and longitudinal data collection.

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4 **MULTIDISCIPLINARY DATA INFRASTRUCTURES IN MULTIPLE**  
5 **SCLEROSIS: *WHY THEY ARE NEEDED & CAN BE DONE!***  
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55 **multiple sclerosis**  
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## 1 **Introduction**

2 Management of Multiple Sclerosis (MS) comprises a wide range of drugs with different  
3 modes of action, a broad spectrum of proposed rehabilitation strategies and varying levels of  
4 efficacy that need meticulous monitoring. Diverse high quality data is needed for many  
5 different purposes. Regulators need data for life-cycle assessment, effectiveness and safety of  
6 medicines in clinical practice. Health technology assessment (HTA) bodies want to  
7 incorporate data from clinical practice into the drug development process. Researchers want  
8 to get a better understanding of the disease and neurologists wish to build decision support  
9 systems to support MS diagnosis, prognosis and treatment. We believe that multidisciplinary  
10 measurements (as summarized in figure 1) including clinical-, functional and patient reported  
11 outcome measures in combination with extensive patient profiling (including immunology,  
12 genetics, ...) can enhance personalized treatment (=medical and rehabilitation). In this paper,  
13 we elaborate on different reasons for this statement. We discuss currently available  
14 multidisciplinary MS data initiatives and propose future steps to jointly move forward.

### 15 **Four reasons why consistent longitudinal multidisciplinary screening is required.**

16 One could question whether multidisciplinary evaluation is truly superior, as it often requires  
17 a multidisciplinary team that is larger than the neurologist and nurse. Here, we elaborate on 4  
18 reasons why we believe the additional efforts are worth it.

19 *Reason 1: MS disease activity and progression are complex and multidimensional concepts in*  
20 *nature and thereby defy a one-size-fits-all description.*

21 “Progression” or “deterioration” can occur in the motor, visual, and sensory systems, but can  
22 also refer to cognitive changes, fatigue, bowel- and bladder function, sexual dysfunction,  
23 quality of life as well as work productivity and activity. Most measures focus primarily on  
24 physical disability. Indeed, a commonly used outcome measure is the expanded disability

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3 25 severity score (EDSS). However, the limitations of EDSS are well known.<sup>1</sup> Physical disability  
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5 26 in mobility and upper limb function is of great importance in MS. However, to encompass the  
6  
7 27 multi-dimensional aspects of MS, there is an urgent need to also define standard and  
8  
9 28 comprehensive packages of measures that capture cognitive, psychological, emotional life  
10  
11 29 function impacting quality of life.<sup>2</sup> A single measure of sustained disease progression may  
12  
13 30 remain elusive. Rather, an integration of current and new outcome measures may be most  
14  
15 31 appropriate and utilization of different measures depending on the MS population and stage of  
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17 32 the disease may be preferred. Composite measures including multiple accepted measures  
18  
19 33 could be superior to any of the single measurements in analysing progression. Several of these  
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21 34 measures have been introduced. A well know example is the multiple sclerosis functional  
22  
23 35 composite (MSFC).<sup>3</sup> Another example is the “EDSS plus”, adding the timed-25-foot walk and  
24  
25 36 the nine hole peg test to EDSS, as an improved endpoint to identify disability progression in  
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27 37 secondary progressive MS.<sup>4</sup> It is noted however that still components like fatigue and quality  
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29 38 of life are not integrated in these composite scores.

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34 39 *Reason 2: Functioning, progression, treatment and rehabilitation effects are interdependent*  
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36 40 *and should be investigated together*

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38 41 There is increasing evidence that an active lifestyle can impact on comorbidity, cognitive and  
39  
40 42 mobile function and quality of life. Next to this, cognitive and physical interventions have  
41  
42 43 been shown to impact structural and functional neuroplasticity.<sup>5</sup> It is suggested that there may  
43  
44 44 be a neuroprotective or even neuro-restorative effect of physical exercise<sup>6</sup>, while it is known  
45  
46 45 that exercise can reduce elements of cognitive impairment, fatigue and depression.<sup>7</sup> Fatigue  
47  
48 46 self-management programs were shown to be effective to reduce fatigue and likely the  
49  
50 47 participation to society of PwMS.<sup>8</sup> Other examples of effective rehabilitation treatment can be  
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52 48 provided in the domain of cognitive function.<sup>9</sup> In fact, it is believed that high activity in the  
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54 49 motor and cognitive domain is extremely important in order to enhance motor and cognitive

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3 50 neural reserve and delay progression, even in the early MS phase.<sup>10</sup> Overall, there is a need of  
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5 51 a large cohort sample with comprehensive data to demonstrate the interactions more clearly.  
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8 52 The international classification of functioning (ICF) distinguishes the levels of body function  
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10 53 and structures, activities and participation, influenced by environmental and personal factors.  
11  
12 54 All domains are considered to be potentially interlinked and might even impact on the disease  
13  
14 55 pathophysiology self.<sup>11</sup> A core set of the ICF has been developed for MS, and can be applied  
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16 56 to characterize the functional domains where limitations can occur in MS.<sup>12</sup>  
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19 57 *Reason 3: Personalized health care is based on the dynamics of system biology and on*  
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21 58 *technology that confirms a persons with MS (PwMS)' fundamental biology*  
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24 59 Considerable research effort is invested to understand the impact of the individual PwMS'  
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26 60 molecular profile on disease activity and progression. In the absence of single, highly  
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28 61 predictive markers, personalization will depend on clusters of markers in multiple models.  
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30 62 Sensitive markers of disease markers are emerging, for example monitoring cerebrospinal  
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32 63 fluid (CSF)- or serum neurofilament light chain (Nf-L) concentration.<sup>13</sup> Furthermore, the  
33  
34 64 prognostic value of CSF oligoclonal band (OCB) has been investigated and validated by  
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36 65 several researchers. More research is necessary for other less well validated but possibly  
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38 66 important candidate prognostic- and diagnostic markers in CSF and serum. Variations in  
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40 67 genes may play a role in MS susceptibility and disease progression; genome-wide association  
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42 68 studies (GWAS) uncovered more than 300 implicated genetic loci each which moderate to  
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44 69 low odds ratio's.<sup>14</sup> Finally, including data on immunological subset phenotyping in decision  
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46 70 support systems could be a valuable approach.<sup>13, 15</sup> Insights in the relative importance of these  
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48 71 different factors in combination with increase knowledge on how these factors interact will be  
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50 72 extremely valuable for tailoring the therapy of individual PwMS. It will also lead to better  
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52 73 understanding of the involved processes and pathways in MS.  
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3 74 *Reason 4: Inclusion of patient-reported outcome measures can facilitate patient relevant*  
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5 75 *healthcare*

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8 76 With a shift towards patient-relevant healthcare, patient- and person-reports of health-related  
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10 77 factors are seen as important determinants for evaluating and improving healthcare. Including  
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12 78 ‘hidden’ symptoms like fatigue, cognition, depression in data-driven (regulatory)-decision  
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14 79 making processes is an urgent unmet need for patients.<sup>16</sup> Patient reported outcome measures  
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16 80 (PROMs) are defined, as “any report of a patient’s health condition that comes directly from  
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18 81 the patient, without interpretation of the patient’s response by a clinician or anyone else”.<sup>17</sup> A  
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20 82 comprehensive, systematic categorization of patient- and person-reports is currently lacking in  
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22 83 literature, even though several methods are used to measure patient-reports. PROMS could  
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24 84 offer significant advantages over assessment by a physician: they better capture the impact of  
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26 85 disease on the person; they are often easier and cheaper to record; and they can often be  
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28 86 completed from the home environment, potentially enabling long-term, geographically  
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30 87 diverse, and large-scale observational and interventional studies with shorter intervals  
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32 88 between time-points as compared to only recording physician-based outcome measures.<sup>18</sup>

### 36 89 **Current observational multidisciplinary MS data initiatives**

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39 90 A growing number of MS databases and registries have started to produce long-term outcome  
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41 91 data from large cohorts of PwMS treated with disease-modifying therapies in real-world  
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43 92 settings. Multidimensional patient documentation systems are developed to support these data  
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45 93 collection. For example, the MS documentation system (MSDS) allows data collection and  
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47 94 communication between PwMS, MS nurses and neurologists.<sup>19</sup> Other examples of innovative  
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49 95 comprehensive MS specific electronic data capture systems are the Knowlegde Program<sup>20</sup>   
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51 96 Bioscreen For MS.<sup>21</sup>



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3 97 Many other efforts contributed to the development of better data infrastructures. In 2017,  
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5 98 Bebo et al. performed a landscape analysis of MS patient registries and cohorts and revealed a  
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7 99 significant number of independent parallel studies. Several cohorts collect both physician- as  
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9 100 well as patient reported outcomes (e.g. Cleveland Clinic Knowledge Program, Danish MS  
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11 101 Registry, North American Research Committee Research on MS (NARCRMS),   
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13 102 PROMOPROMS, MSBase, British Columbia MS Database ...) and some even additionally  
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15 103 collect biological samples, DNA and RNA and MRI imaging data (Accelerated Cure project,  
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17 104 Comprehensive Longitudinal Investigation of MS (CLIMB), the Norwegian MS Registry and  
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19 105 Biobank, the MS EPIC study (MS genetics, expression, proteomics, imaging clinical), NY  
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21 106 State MS Consortium, Serially Unified Multi-center MS Investigation (SUMMIT), the  
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23 107 Swedish MS registry).<sup>22</sup> Another promising and recently launched example of  
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25 108 multidimensional screening is the multicentre collaboration named “MS paths”, which is  
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27 109 extending the Cleveland Clinical Knowledge program as well as adding biobanking  
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29 110 ([www.mspaths.com](http://www.mspaths.com)).

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33 111 There is increasing international interest to collaborate and share data among different  
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35 112 stakeholders<sup>23, 24</sup>. There are several reasons to share (and not share) data and to use (or not  
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37 113 use) shared data which are illustrated in figure 2. Policies of data sharing should rest upon  
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39 114 knowledge of how data is shared and how end-users use data that have been shared to them.  
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41 115 To ensure that both sharing data and using shared data is encouraged, a community of trust  
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43 116 and transparency is required. Global collaborations to address, at low cost, additional  
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45 117 important questions about patient natural history, medicine efficacy and adverse events are  
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47 118 being pioneered by the MSBase consortium and similar organizations. MSBase is a web-  
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49 119 platform designed to collect prospective MS data. It enables participating neurologists to  
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51 120 contribute data on diagnosis, treatment and progress, to review anonymous aggregated data  
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53 121 and to benchmark their patient population against other patients subsets or the entire dataset.<sup>25</sup>  
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3 122 **Proposition of joint action steps to shape the future**  
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5 123 We propose in the following paragraphs several joint actions to further increase the success  
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7 124 rate of consistent longitudinal multidisciplinary screening:  
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10 125 *Joint action 1: Inclusion of multidisciplinary staff in the data collection process.*  
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13 126 Sorensen et al. describe the urgent need for the international implementation of  
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15 127 multidisciplinary care units for MS.(MS care unit position paper, European Charcot  
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17 128 Foundation, submitted in Multiple Sclerosis Journal). We propose to include data routinely  
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19 129 collected and shared by multidisciplinary teams including the neurologists, rehabilitation  
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21 130 physician, ophthalmologists, radiologists, clinical and research nurses, physiotherapists,  
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23 131 psychologists, occupational therapist, speech therapists, and PwMS or PwMS' relatives. In  
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25 132 table 1, we present variables that, among others, could be included in a multidisciplinary data  
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27 133 infrastructure categorized according to a potential primary data collector.  
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31 134 *Joint action 2: Agreement on minimal datasets meaningful to PwMS*  
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34 135 Community efforts are undertaken to harmonize and define a minimal dataset. Defining a  
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36 136 “minimal dataset” is challenging and requires discussions and consensus between all  
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38 137 stakeholders involved. The National Institute of Neurological Disorders and Stroke (NINDS)  
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40 138 developed a first set of Common Data Elements for MS in 2011  
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42 139 ([www.commondataelements.ninds.nih.gov](http://www.commondataelements.ninds.nih.gov)). In 2015, the European Medicines Agency  
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44 140 (EMA) set up an initiative to make better use of existing registries and facilitate the  
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46 141 establishment of high-quality new registries, providing an adequate source for post-  
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48 142 authorization data for regulatory decision making.<sup>26</sup> MS and cystic fibrosis were the selected  
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50 143 conditions chosen for the pilot phase of this initiative. During a workshop on MS registries in  
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52 144 July 2017, a first draft of a minimal dataset to support long-term longitudinal post-  
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54 145 authorization safety studies was proposed.<sup>27</sup> For now, limited emphasis is put on including  
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3 146 patient reported and functional outcome measures. Although a plentitude of outcome  
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5 147 measures has been developed and applied, there is increasing agreement on the dimensions of  
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7 148 functioning that should be measured and on appropriate and commonly accepted outcome  
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9 149 measures. Researchers are also increasingly labelling and selecting standard outcome  
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11 150 measures according to the ICF framework.<sup>28</sup> It may serve as a conceptual framework for on-  
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13 151 going initiatives of MSIF in collaboration with international partner associations to focus on  
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15 152 patient-relevant outcomes. The multiple sclerosis outcome assessment consortium (MSOAC)  
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17 153 has reconfirmed the T25FW and 9HPT as golden  dards for measuring walking speed and  
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19 154 manual dexterity as part of the multiple sclerosis functional composite score (MSFC).<sup>29, 30</sup>  
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21 155 Besides, MSOAC advocates the use of the symbol digit modality test (SDMT) instead of the  
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23 156 paced serial addition test (PASAT) for the domain of cognitive function, added with the low-  
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25 157 contrast letter acuity for visual function as part of a standard test battery.<sup>31</sup> Secondly, an  
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27 158 overview of commonly accepted multi-disciplinary tests was published based on a multi-  
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29 159 stakeholder pan-European meeting.<sup>32</sup>  
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33 160 Ideally, we could also come to a consensus concerning a minimal dataset for MRI outcome  
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35 161 measures, serum-and CSF biomarkers and/or genetic risk factors. However, before we get  
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37 162 there, much more research is necessary on the relative importance of these factors. Several  
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39 163 consortia, initiatives and projects focus on overcoming these challenges. Powerful examples  
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41 164 here are MAGNIMS (Magnetic Resonance Imaging in MS) and The International MS  
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43 165 Genetics Consortium (IMSGC). More research is necessary to investigate the relative  
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45 166 importance of these genetic risk factors and also to identify gene variants that influence  
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47 167 progression in MS. We anticipate steps forward concerning these major unmet needs because  
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49 168 of several synergistic and collaborative initiatives focusing on this topic. For example,  
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51 169 *MultipleMS* ([www.multipleMS.eu](http://www.multipleMS.eu)) aims to identify a combination of clinical, biological, and  
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53 170 lifestyle biomarkers that can predict the clinical course, stratify patients based on their risk  
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3 171 and the therapeutic response to the existing disease modifying treatments (DMTs), thus  
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5 172 spearheading the development of personalized medicine. (Ingrid Kockum, personal  
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7 173 communication).

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10 174 *Joint action 3: Implementation of standards and common data models (CDMs) in data*  
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12 175 *collection procedures*

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15 176 A first step to increase interoperability between databases is to define standard protocols to  
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17 177 measure outcomes. Especially for the functional- and PRO, no standards are available yet  
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19 178 and need to be defined. For adoption in research and clinical practice, it is required that  
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21 179 outcome measures are standardized, have demonstrated psychometric properties (test-retest  
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23 180 reliability, discriminant and content validity and sensitivity to change) and clinical utility. The  
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25 181 implementation of internationally approved standards could greatly increase the possibilities  
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27 182 to connect and pool datasets. More and more MS specific IT platforms are incorporating  
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29 183 standards to label variables. For example, data standards for MS were established by the  
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31 184 Clinical Data Interchange Standards Consortium (CDISC)  
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33 185 (<http://www.cdisc.org/standards/therapeutic-areas/multiple-sclerosis>). Next to this, the EMA  
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35 186 workshop highlighted the need to include Medical Dictionary for Regulatory Activities  
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37 187 (MedRa) dictionary when collecting post-marketing authorisation safety data.<sup>27</sup>

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41 188 Several American initiatives support the relevance the implementation of CDMs when  
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43 189 developing multi-purpose data networks: the Food and Drug Administration's Mini-Sentinel  
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45 190 program, the National Institutes of Health's Health Care Systems Research Collaboratory  
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47 191 Distributed Research Network, the Electronic Medical Record Support for Public Health  
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49 192 system<sup>33</sup> and the National Patient-Centered Clinical Research Network<sup>34</sup>.

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53 193 To the best of our knowledge, the relevance and implementation of two main CDMs in  
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55 194 Europe is investigated today: the Clinical Building Blocks (CBB) and the Observational

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3 195 Medical Outcomes Partnership (OMOP). The OMOP model is the central CDM behind the  
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5 196 Innovative Medicine Initiatives (IMI) European Medical Information Framework (EMIF) and  
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7 197 European Health Data and Evidence Network (EHDEN).<sup>35</sup> The Clinical Building Blocks are  
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9 198 an initiative of the 8 Dutch University Medical Centres (UMCs) to work together on the  
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11 199 standardization of healthcare data and are used by healthdata.be to integrate data from various  
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13 200 sources in a decentralised health care systems.<sup>36</sup>  
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15  
16 201 Especially for multidisciplinary datasets, where even local collaboration between physicians-,  
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18 202 researchers and PwMS is required, the need to move towards “ independent data  
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20 203 infrastructures” is timely and urgent. Figure 3 visualizes the difference between IT dependent  
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22 204 and IT independent data infrastructures. Integrating data from various sources is a particular  
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24 205 challenge in decentralised health care systems and can require substantial investment in  
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26 206 technical solutions and political will to overcome long-standing fragmentation. In order for IT  
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28 207 independent data infrastructures to succeed, the implementation of standards and CDMs is  
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30 208 required.

### 31 32 33 34 209 **Conclusion**

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37 210 If detailed clinical-, functional- and patient reported data are accompanied by both magnetic  
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39 211 resonance imaging of the central nervous system and biological samples, significant insight  
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41 212 into MS pathophysiology could be achieved. Still, data collection is extremely expensive and  
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43 213 time consuming. Important projects can happen by seeking out admirable partners and diverse  
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45 214 collaborators who are willing to share ideas, share work and share data. With improvements  
46  
47 215 in technology, tools and communication, it is becoming easier to collect, save, manage,  
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49 216 distribute and reuse data. However, the slow adaptation of tools and services such as data  
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51 217 repositories are indications that technology alone cannot change scientific practices; other  
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53 218 social and cultural factors must also encourage data sharing. It is important that technical  
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3 219 solutions as well as governance solutions are developed in order to enable an eco-system in  
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5 220 which all stakeholder are comfortable.  
6

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39  
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41  
42 237 capacity as Director External Affairs of the European MS Platform, he served in advisory  
43  
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242 committee member of Neurocompass, participated to advisory board meetings of BIOGEN  
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## 244 References

- 245 1. Cadavid D, Tang Y and O'Neill G. [Responsiveness of the Expanded Disability Status  
246 Scale (EDSS) to disease progression and therapeutic intervention in progressive forms of  
247 multiple sclerosis]. *Rev Neurol*. 2010; 51: 321-9.
- 248 2. Noble JG, Osborne LA, Jones KH, Middleton RM and Ford DV. Commentary on  
249 'disability outcome measures in multiple sclerosis clinical trials'. *Mult Scler*. 2012; 18: 1718-  
250 20.
- 251 3. Polman CH and Rudick RA. The multiple sclerosis functional composite: a clinically  
252 meaningful measure of disability. *Neurology*. 2010; 74 Suppl 3: S8-15.
- 253 4. Cadavid D, Cohen JA, Freedman MS, et al. The EDSS-Plus, an improved endpoint for  
254 disability progression in secondary progressive multiple sclerosis. *Mult Scler*. 2017; 23: 94-  
255 105.
- 256 5. Prosperini L, Piattella MC, Gianni C and Pantano P. Functional and Structural Brain  
257 Plasticity Enhanced by Motor and Cognitive Rehabilitation in Multiple Sclerosis. *Neural*  
258 *Plast*. 2015; 2015: 481574.
- 259 6. Feys P, Moumdjian L, Van Halewyck F, et al. Effects of an individual 12-week  
260 community-located "start-to-run" program on physical capacity, walking, fatigue, cognitive  
261 function, brain volumes, and structures in persons with multiple sclerosis. *Mult Scler*. 2017:  
262 1352458517740211.
- 263 7. Sandroff BM, Motl RW, Scudder MR and DeLuca J. Systematic, Evidence-Based  
264 Review of Exercise, Physical Activity, and Physical Fitness Effects on Cognition in Persons  
265 with Multiple Sclerosis. *Neuropsychol Rev*. 2016.
- 266 8. Khan F and Amatya B. Rehabilitation in Multiple Sclerosis: A Systematic Review of  
267 Systematic Reviews. *Arch Phys Med Rehabil*. 2017; 98: 353-67.
- 268 9. Goverover Y, Chiaravalloti ND, O'Brien A and DeLuca J. Evidenced Based Cognitive  
269 Rehabilitation for Persons with Multiple Sclerosis: An Updated Review of the Literature from  
270 2007-2016. *Arch Phys Med Rehabil*. 2017.
- 271 10. Riemenschneider M, Hvid LG, Stenager E and Dalgas U. Is there an overlooked  
272 "window of opportunity" in MS exercise therapy? Perspectives for early MS rehabilitation.  
273 *Mult Scler*. 2018; 24: 886-94.
- 274 11. Maritz R, Aronsky D and Prodinge B. The International Classification of  
275 Functioning, Disability and Health (ICF) in Electronic Health Records. A Systematic  
276 Literature Review. *Appl Clin Inform*. 2017; 8: 964-80.
- 277 12. Karhula ME, Kanelisto KJ, Ruutiainen J, Hamalainen PI and Salminen AL. The  
278 activities and participation categories of the ICF Core Sets for multiple sclerosis from the  
279 patient perspective. *Disabil Rehabil*. 2013; 35: 492-7.
- 280 13. Comabella M and Montalban X. Body fluid biomarkers in multiple sclerosis. *Lancet*  
281 *neurology*. 2014; 13: 113-26.
- 282 14. Sawcer S, Franklin RJ and Ban M. Multiple sclerosis genetics. *Lancet neurology*.  
283 2014; 13: 700-9.
- 284 15. Peeters LM, Vanheusden M, Somers V, et al. Cytotoxic CD4+ T Cells Drive Multiple  
285 Sclerosis Progression. *Front Immunol*. 2017; 8: 1160.
- 286 16. Members of the MSitsCSG, Rieckmann P, Centonze D, et al. Unmet needs, burden of  
287 treatment, and patient engagement in multiple sclerosis: A combined perspective from the MS

- 1  
2  
3 288 in the 21st Century Steering Group. *Multiple sclerosis and related disorders*. 2018; 19: 153-  
4 289 60.
- 5 290 17. Kallaur AP, Reiche EM, Oliveira SR, et al. Genetic, Immune-Inflammatory, and  
6 291 Oxidative Stress Biomarkers as Predictors for Disability and Disease Progression in Multiple  
7 292 Sclerosis. *Mol Neurobiol*. 2017; 54: 31-44.
- 8 293 18. Fayers P and Machin D. *Quality of life: the assessment, analysis and interpretation of*  
9 294 *patient-reported out-*  
10  
11 295 *comes*. Hoboken (New Jersey): John Wiley & Sons, 2013.
- 12 296 19. Ziemssen T, Kempcke R, Eulitz M, et al. Multiple sclerosis documentation system  
13 297 (MSDS): moving from documentation to management of MS patients. *J Neural Transm*  
14 298 *(Vienna)*. 2013; 120 Suppl 1: S61-6.
- 15 299 20. Katzan I, Speck M, Dopler C, et al. The Knowledge Program: an innovative,  
16 300 comprehensive electronic data capture system and warehouse. *AMIA Annu Symp Proc*. 2011;  
17 301 2011: 683-92.
- 18 302 21. Gourraud PA, Henry RG, Cree BA, et al. Precision medicine in chronic disease  
19 303 management: The multiple sclerosis BioScreen. *Annals of neurology*. 2014; 76: 633-42.
- 20 304 22. Bebo BF, Jr., Fox RJ, Lee K, Utz U and Thompson AJ. Landscape of MS patient  
21 305 cohorts and registries: Recommendations for maximizing impact. *Mult Scler*. 2017:  
22 306 1352458517698250.
- 23 307 23. Peeters LM. Fair data for next-generation management of multiple sclerosis. *Mult*  
24 308 *Scler*. 2017: 1352458517748475.
- 25 309 24. Held Bradford E, Baert I, Finlayson M, Feys P and Wagner J. Feasibility of an  
26 310 International Multiple Sclerosis Rehabilitation Data Repository: Perceived Challenges and  
27 311 Motivators for Sharing Data. *International Journal of MS Care*. 2017.
- 28 312 25. Butzkueven H, Chapman J, Cristiano E, et al. MSBase: an international, online  
29 313 registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler*.  
30 314 2006; 12: 769-74.
- 31 315 26. European Medicine Agency SMH. Initiative for patient registries: strategy and pilot  
32 316 phase. Inspections and Human Medicines Pharmacovigilance Division, 2015.
- 33 317 27. European Medicine Agency SMH. Report on Multiple Sclerosis Registries - workshop  
34 318 7 July 2017. Inspections, Human Medicines, Pharmacovigilance and committee Division,  
35 319 2017.
- 36 320 28. Engelhard MM, Patek SD, Lach JC and Goldman MD. Real-world walking in  
37 321 multiple sclerosis: Separating capacity from behavior. *Gait Posture*. 2018; 59: 211-6.
- 38 322 29. Feys P, Lamers I, Francis G, et al. The Nine-Hole Peg Test as a manual dexterity  
39 323 performance measure for multiple sclerosis. *Mult Scler*. 2017; 23: 711-20.
- 40 324 30. Motl RW, Cohen JA, Benedict R, et al. Validity of the timed 25-foot walk as an  
41 325 ambulatory performance outcome measure for multiple sclerosis. *Mult Scler*. 2017; 23: 704-  
42 326 10.
- 43 327 31. Balcer LJ, Raynowska J, Nolan R, et al. Validity of low-contrast letter acuity as a  
44 328 visual performance outcome measure for multiple sclerosis. *Mult Scler*. 2017; 23: 734-47.
- 45 329 32. Feys P, Giovannoni G, Dijsselbloem N, Centonze D, Eelen P and Lykke Andersen S.  
46 330 The importance of a multi-disciplinary perspective and patient activation programmes in MS  
47 331 management. *Mult Scler*. 2016; 22: 34-46.
- 48 332 33. Curtis LH, Brown J and Platt R. Four health data networks illustrate the potential for a  
49 333 shared national multipurpose big-data network. *Health Aff (Millwood)*. 2014; 33: 1178-86.
- 50 334 34. Fleurence RL, Curtis LH, Califf RM, Platt R, Selby JV and Brown JS. Launching  
51 335 PCORnet, a national patient-centered clinical research network. *J Am Med Inform Assoc*.  
52 336 2014; 21: 578-82.



1  
2  
3 337 35. Vaudano E, Vannieuwenhuysse B, Van Der Geyten S, et al. Boosting translational  
4 338 research on Alzheimer's disease in Europe: The Innovative Medicine Initiative AD research  
5 339 platform. *Alzheimers Dement.* 2015; 11: 1121-2.  
6 340 36. Healthdata. Healthdata. Collecte des données. . In: Healthdata, (ed.). Brussels: WIV-  
7 341 ISP, 2015.  
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For Peer Review

**Table 1: List of variables to be potentially included in a multidisciplinary data**

**infrastructure:** Variables are categorized according to a potential primary data collector. We highlighted the variables included in recommendations of the European Medicine Agency (EMA) patient registry initiative for multiple sclerosis (MS) and used an asterix (\*) for the minimal dataset and hashtag (#) for the wish list (=items that were regarded important, but for different reasons were not accepted by consensus). Abbreviations used: JCV: John Cunningham Virus; VZV: Varicella-Zoster Virus, EBV: Epstein-Barr Virus, PwMS: person with Multiple Sclerosis

Data collector	Category/ function	Examples
Neurologist	MS – characteristics	Year of onset*, year of diagnosis*, disease subtype* at diagnosis and during follow up
	MS – disease course – clinical activity	Relapses*, steroid treatments*
	MS – disease course – clinical progression	EDSS*
	MS – disease course – complications/ adverse events	Serious adverse events*, Co-morbidities*
	MS – treatment	DMT start and stop date*, and reason for switching*, symptomatic therapy*, clinical trial participation#
	Reproduction data	MS course during pregnancy*, pregnancy outcome*, delivery date*, live/still birth, birth weight, abortion, complications*
	Clinical neurophysiology	Evoked potentials (visual, somato-sensoric, motoric, ...)
Rehabilitation specialist	Rehabilitation strategy	Rehabilitation program details, start date rehabilitation program, end date rehabilitation program
	Spasticity measures	Tardieu scale
Urologist	Urological data	Urgency, retention, Urinary tract infections, examination and clinical tests
Ophthalmologist	Ophthalmological examination	Visual acuity, other ocular pathology, Optical Coherence Tomography

Radiologist	MRI – lesions	T2 lesion load, persistent black holes, localisation
	MRI – volumes	T2 lesion volume, whole brain volume, white/ grey matter volume, corpus callosum size, ventricular volumes
	MRI – other	Diffusion tensor imaging, functional MRI
Clinical nurse	Demographical data	Date of birth* and of death*, gender*, ethnicity#, country of residence*, Education level#, family history#
	General medical data*	Co-morbidities*, other medication/ treatment*, family history*
	Social data	Employment status, marital status, progeny, education level
	Other	Smoking, alcohol use, drugs, dietary habits
Study nurse	Trial participation	Yes/ no*, name trial
	Clinical measures	MS functional composite, symbol digit modalities test#, low contrast letter acuity#
Physiotherapist	Ambulatory function measures	Timed 25 foot walk#, 6 minute walking test
	Hand function measures	Nine-hole peg test#
	Balance measures	Trunk Control Test, MiniBest, Timed-up-and-go
Psychologist	Cognitive functioning	RAO, Paced Auditory Serial Addition Test#, Controlled Oral Word Association Test, Symbol Digit Modalities Test#
	Depression	Brief Depression Scale, Hospital Anxiety and Depression Scale – Depression
	Anxiety	Fatigue Scale for Motor and Cognitive Functions, Hospital Anxiety and Depression Scale – Anxiety
Occupational therapist	Strength and upper limb measurements	Max isometric handgrip and pinch strength, Action Research Arm Test, Manual Ability Measure-36
Speech therapist	Speech ability tests	Radboud Oral Test, Swallowing tests, Penetration Aspiration Scale
Automated data	Laboratory tests – blood	Blood count*, liver enzymes*, renal function, thyroid hormones, JCV status#, VZV serology#, vitamin D, Anti-EBV, Immuno-phenotype, genetic profile, Serum cytokine profile, ...
	Laboratory tests – CSF	Oligoclonal bands*, CSF biomarkers
PwMS and relatives	PROM #– quality of life	MS Quality of Life-54, The MS International Quality of Life Questionnaire, Functional Assessment of MS

PROM #- depression and anxiety	Beck Depression Inventory, Patient Health Questionnaire-9, Hospital Anxiety and Depression Scale
PROM #- fatigue	Modified Fatigue Impact Scale, Fatigue Impact Scale for Daily Use
PROM #- single functional domain	MS Walking Scale-12, Arm Function in MS Questionnaire, Visual Function Questionnaire-25
PROM #- multiple domains	Short Form-36, MS Impact Scale-29, Guy's Neurological Disability Scale, MS Impact Profile

For Peer Review

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3 **Figure 1: To solve the puzzle of multiple sclerosis (MS), multidisciplinary measurements**  
4 **are required:** to capture the complexity and heterogeneity of MS, consistent longitudinal  
5 multidisciplinary measurement are required. This figure illustrates what we mean with “a  
6 multidisciplinary data infrastructure” referring to datasets, registries and/or cohorts including  
7 clinical-, functional and patient reported outcome measures in combination with extensive  
8 patient profiling (immunology, genetics, ...)  
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16 **Figure 2: Data sharing requires a community of trust and transparency:** there are several  
17 reasons the share (and not share) data and to use (or not use) shared data. Policies of data  
18 sharing should rest upon knowledge of how data is shared and how end-users use data that  
19 have been shared to them. To ensure that both sharing data and using shared data is  
20 encouraged, a community of trust and transparency is required.  
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28 **Figure 3: The difference between IT dependent and IT independent data**

29 **infrastructures:** Simply put, when implementing an IT independent multidisciplinary data  
30 infrastructure, different data controllers can use their preferred software. Based on unique  
31 identifier, the data can be connected if necessary or desired.  
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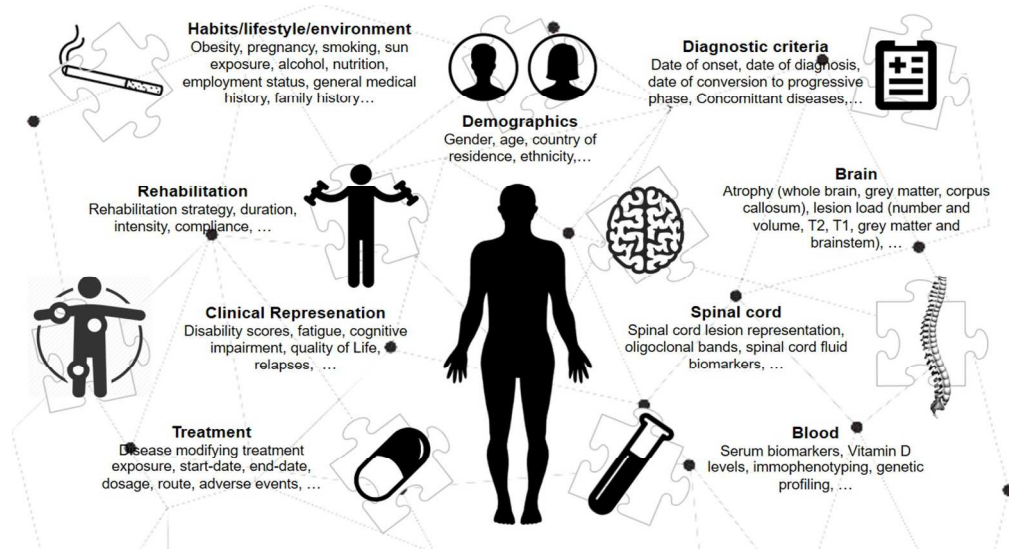


Figure 1: To solve the puzzle of multiple sclerosis (MS), multidisciplinary measurements are required

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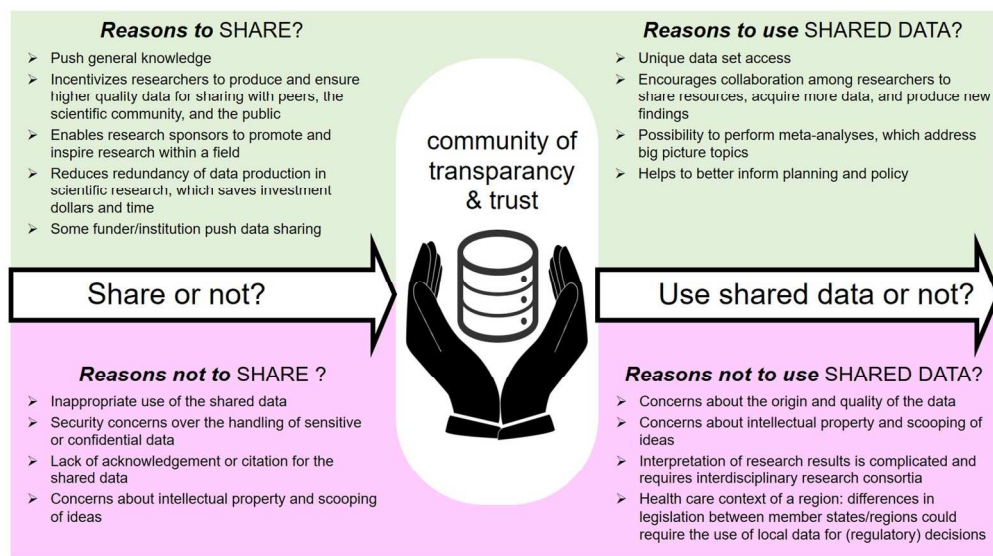


Figure 2: Data sharing requires a community of trust and transparency

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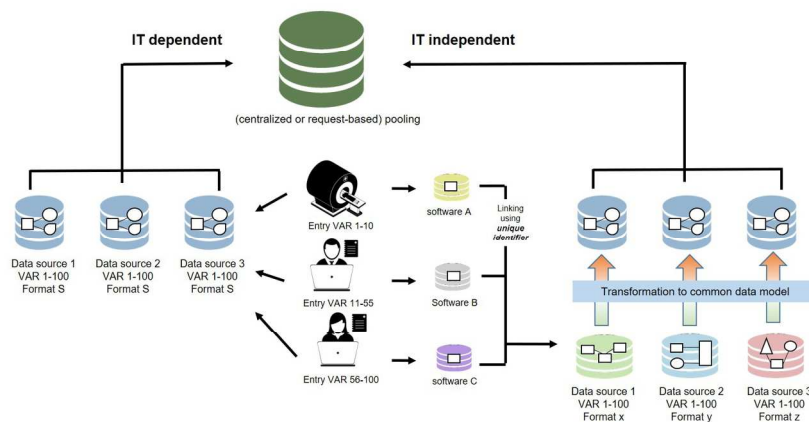


Figure 3: The difference between IT dependent and IT independent data infrastructures

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