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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

	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.

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

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Introduction

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

Four reasons why consistent longitudinal multidisciplinary screening is required.

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

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

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

severity score (EDSS). However, the limitations of EDSS are well known.[1] Physical disability in mobility and upper limb function is of great importance in MS. However, to encompass the multi-dimensional aspects of MS, there is an urgent need to also define standard and comprehensive packages of measures that capture cognitive, psychological, emotional life function impacting quality of life.[2] A single measure of sustained disease progression may remain elusive. Rather, an integration of current and new outcome measures may be most appropriate and utilization of different measures depending on the MS population and stage of the disease may be preferred. Composite measures including multiple accepted measures could be superior to any of the single measurements in analysing progression. Several of these measures have been introduced. A well know example is the multiple sclerosis functional composite (MSFC).[3] Another example is the "EDSS plus", adding the timed-25-foot walk and the nine hole peg test to EDSS, as an improved endpoint to identify disability progression in secondary progressive MS.[4] It is noted however that still components like fatigue and quality of life are not integrated in these composite scores.

Reason 2: Functioning, progression, treatment and rehabilitation effects are interdependent and should be investigated together

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

neural reserve and delay progression, even in the early MS phase.[10] Overall, there is a need of a large cohort sample with comprehensive data to demonstrate the interactions more clearly.

The international classification of functioning (ICF) distinguishes the levels of body function and structures, activities and participation, influenced by environmental and personal factors. All domains are considered to be potentially interlinked and might even impact on the disease pathophysiology self.[11] A core set of the ICF has been developed for MS, and can be applied to characterize the functional domains where limitations can occur in MS.[12]

Reason 3: Personalized health care is based on the dynamics of system biology and on technology that confirms a persons with MS (PwMS)' fundamental biology

Considerable research effort is invested to understand the impact of the individual PwMS' molecular profile on disease activity and progression. In the absence of single, highly predictive markers, personalization will depend on clusters of markers in multiple models. Sensitive markers of disease markers are emerging, for example monitoring cerebrospinal fluid (CSF)- or serum neurofilament light chain (Nf-L) concentration.[13] Furthermore, the prognostic value of CSF oligoclonal band (OCB) has been investigated and validated by several researchers. More research is necessary for other less well validated but possibly important candidate prognostic- and diagnostic markers in CSF and serum. Variations in genes may play a role in MS susceptibility and disease progression; genome-wide association studies (GWAS) uncovered more than 300 implicated genetic loci each which moderate to low odds ratio's.[14] Finally, including data on immunological subset phenotyping in decision support systems could be a valuable approach.[13, 15] Insights in the relative importance of these different factors in combination with increase knowledge on how these factors interact will be extremely valuable for tailoring the therapy of individual PwMS. It will also lead to better understanding of the involved processes and pathways in MS.

Reason 4: Inclusion of patient-reported outcome measures can facilitate patient relevant healthcare

With a shift towards patient-relevant healthcare, patient- and person-reports of health-related factors are seen as important determinants for evaluating and improving healthcare. Including 'hidden' symptoms like fatigue, cognition, depression in data-driven (regulatory)-decision making processes is an urgent unmet need for patients.[16] Patient reported outcome measures (PROMs) are defined, as ''any report of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else''.[17] A comprehensive, systematic categorization of patient- and person-reports is currently lacking in literature, even though several methods are used to measure patient-reports. PROMS could offer significant advantages over assessment by a physician: they better capture the impact of disease on the person; they are often easier and cheaper to record; and they can often be completed from the home environment, potentially enabling long-term, geographically diverse, and large-scale observational and interventional studies with shorter intervals between time-points as compared to only recording physician-based outcome measures.[18]

Current observational multidisciplinary MS data initiatives

A growing number of MS databases and registries have started to produce long-term outcome data from large cohorts of PwMS treated with disease-modifying therapies in real-world settings. Multidimensional patient documentation systems are developed to support these data collection. For example, the MS documentation system (MSDS) allows data collection and communication between PwMS, MS nurses and neurologists.[19] Other examples of innovative comprehensive MS specific electronic data capture systems are the Knowlegde Program[20] and Bioscreen For MS.[21]

Many other efforts contributed to the development of better data infrastructures. In 2017, Bebo et al. performed a landscape analysis of MS patient registries and cohorts and revealed a significant number of independent parallel studies. Several cohorts collect both physician- as well as patient reported outcomes (e.g. Cleveland Clinic Knowledge Program, Danish MS Registry, North American Research Committee Research on MS (NARCRMS), PROMOPROMS, MSBase, British Columbia MS Database …) and some even additionally collect biological samples, DNA and RNA and MRI imaging data (Accelerated Cure project, Comprehensive Longitudinal Investigation of MS (CLIMB), the Norwegian MS Registry and Biobank, the MS EPIC study (MS genetics, expression, proteomics, imaging clinical), NY State MS Consortium, Serially Unified Multi-center MS Investigation (SUMMIT), the Swedish MS registry).[22] Another promising and recently launched example of multidimensional screening is the multicentre collaboration named "MS paths", which is extending the Cleveland Clinical Knowledge program as well as adding biobanking (www.mspaths.com).

There is increasing international interest to collaborate and share data among different stakeholders [23, 24]. There are several reasons to share (and not share) data and to use (or not use) shared data which are illustrated in figure 2. Policies of data sharing should rest upon knowledge of how data is shared and how end-users use data that have been shared to them. To ensure that both sharing data and using shared data is encouraged, a community of trust and transparency is required. Global collaborations to address, at low cost, additional important questions about patient natural history, medicine efficacy and adverse events are being pioneered by the MSBase consortium and similar organizations. MSBase is a web-platform designed to collect prospective MS data. It enables participating neurologists to contribute data on diagnosis, treatment and progress, to review anonymous aggregated data and to benchmark their patient population against other patients subsets or the entire dataset.[25]

Proposition of joint action steps to shape the future

We propose in the following paragraphs several joint actions to further increase the success rate of consistent longitudinal multidisciplinary screening:

Joint action 1: Inclusion of multidisciplinary staff in the data collection process.

Sorensen et al. describe the urgent need for the international implementation of multidisciplinary care units for MS.(MS care unit position paper, European Charcot Foundation, submitted in Multiple Sclerosis Journal). We propose to include data routinely collected and shared by multidisciplinary teams including the neurologists, rehabilitation physician, ophthalmologists, radiologists, clinical and research nurses, physiotherapists, psychologists, occupational therapist, speech therapists, and PwMS or PwMS' relatives. In table 1, we present variables that, among others, could be included in a multidisciplinary data infrastructure categorized according to a potential primary data collector.

Joint action 2: Agreement on minimal datasets meaningful to PwMS

Community efforts are undertaken to harmonize and define a minimal dataset. Defining a "minimal dataset" is challenging and requires discussions and consensus between all stakeholders involved. The National Institute of Neurological Disorders and Stroke (NINDS) developed a first set of Common Data Elements for MS in 2011 (www.commondataelements.ninds.nih.gov). In 2015, the European Medicines Agency (EMA) set up an initiative to make better use of existing registries and facilitate the establishment of high-quality new registries, providing an adequate source for post-authorization data for regulatory decision making.[26] MS and cystic fibrosis were the selected conditions chosen for the pilot phase of this initiative. During a workshop on MS registries in July 2017, a first draft of a minimal dataset to support long-term longitudinal post-authorization safety studies was proposed.[27]. For now, limited emphasis is put on including

patient reported and functional outcome measures. Although a plentitude of outcome measures has been developed and applied, there is increasing agreement on the dimensions of functioning that should be measured and on appropriate and commonly accepted outcome measures. Researchers are also increasingly labelling and selecting standard outcome measures according to the ICF framework.[28] It may serve as a conceptual framework for on-going initiatives of MSIF in collaboration with international partner associations to focus on patient-relevant outcomes. The multiple sclerosis outcome assessment consortium (MSOAC) has reconfirmed the T25FW and 9HPT as golden standards for measuring walking speed and manual dexterity as part of the multiple sclerosis functional composite score (MSFC).[29, 30] Besides, MSOAC advocates the use of the symbol digit modality test (SDMT) instead of the paced serial addition test (PASAT) for the domain of cognitive function, added with the low-contrast letter acuity for visual function as part of a standard test battery.[31] Secondly, an overview of commonly accepted multi-disciplinary tests was published based on a multi-stakeholder pan-European meeting.[32]

Ideally, we could also come to a consensus concerning a minimal dataset for MRI outcome measures, serum-and CSF biomarkers and/or genetic risk factors. However, before we get there, much more research is necessary on the relative importance of these factors. Several consortia, initiatives and projects focus on overcoming these challenges. Powerful examples here are MAGNIMS (Magnetic Resonance Imaging in MS) and The International MS Genetics Consortium (IMSGC). More research is necessary to investigate the relative importance of these genetic risk factors and also to identify gene variants that influence progression in MS. We anticipate steps forward concerning these major unmet needs because of several synergistic and collaborative initiatives focusing on this topic. For example, *MultipleMS* (www.multipleMS.eu) aims to identify a combination of clinical, biological, and lifestyle biomarkers that can predict the clinical course, stratify patients based on their risk

and the therapeutic response to the existing disease modifying treatments (DMTs), thus spearheading the development of personalized medicine. (Ingrid Kockum, personal communication).

Joint action 3: Implementation of standards and common data models (CDMs) in data collection procedures

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

Several American initiatives support the relevance the implementation of CDMs when developing multi-purpose data networks: the Food and Drug Administration's Mini-Sentinel program, the National Institutes of Health's Health Care Systems Research Collaboratory Distributed Research Network, the Electronic Medical Record Support for Public Health system[33] and the National Patient-Centered Clinical Research Network[34].

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

Medical Outcomes Partnership (OMOP). The OMOP model is the central CDM behind the Innovative Medicine Initiatives (IMI) European Medical Information Framework (EMIF) and European Health Data and Evidence Network (EHDEN).[35] The Clinical Building Blocks are an initiative of the 8 Dutch University Medical Centres (UMCs) to work together on the standardization of healthcare data and are used by healthdata.be to integrate data from various sources in a decentralised health care systems.[36]

Especially for multidisciplinary datasets, where even local collaboration between physicians-, researchers and PwMS is required, the need to move towards " independent data infrastructures" is timely and urgent. Figure 3 visualizes the difference between IT dependent and IT independent data infrastructures. Integrating data from various sources is a particular challenge in decentralised health care systems and can require substantial investment in technical solutions and political will to overcome long-standing fragmentation. In order for IT independent data infrastructures to succeed, the implementation of standards and CDMs is required.

Conclusion

If detailed clinical-, functional- and patient reported data are accompanied by both magnetic resonance imaging of the central nervous system and biological samples, significant insight into MS pathophysiology could be achieved. Still, data collection is extremely expensive and time consuming. Important projects can happen by seeking out admirable partners and diverse collaborators who are willing to share ideas, share work and share data. With improvements in technology, tools and communication, it is becoming easier to collect, save, manage, distribute and reuse data. However, the slow adaptation of tools and services such as data repositories are indications that technology alone cannot change scientific practices; other social and cultural factors must also encourage data sharing. It is important that technical

solutions as well as governance solutions are developed in order to enable an eco-system in which all stakeholder are comfortable.

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References

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

in the 21st Century Steering Group. *Multiple sclerosis and related disorders*. 2018; 19: 153-60.

17. Kallaur AP, Reiche EM, Oliveira SR, et al. Genetic, Immune-Inflammatory, and Oxidative Stress Biomarkers as Predictors for Disability and Disease Progression in Multiple Sclerosis. *Mol Neurobiol*. 2017; 54: 31-44.

18. Fayers P and Machin D. *Quality of life: the assessment, analysis and interpretation of patient-reported out-comes*. Hoboken (New Jersey): John Wiley & Sons, 2013.

19. Ziemssen T, Kempcke R, Eulitz M, et al. Multiple sclerosis documentation system (MSDS): moving from documentation to management of MS patients. *J Neural Transm (Vienna)*. 2013; 120 Suppl 1: S61-6.

20. Katzan I, Speck M, Dopler C, et al. The Knowledge Program: an innovative, comprehensive electronic data capture system and warehouse. *AMIA Annu Symp Proc*. 2011; 2011: 683-92.

21. Gourraud PA, Henry RG, Cree BA, et al. Precision medicine in chronic disease management: The multiple sclerosis BioScreen. *Annals of neurology*. 2014; 76: 633-42.

22. Bebo BF, Jr., Fox RJ, Lee K, Utz U and Thompson AJ. Landscape of MS patient cohorts and registries: Recommendations for maximizing impact. *Mult Scler*. 2017: 1352458517698250.

23. Peeters LM. Fair data for next-generation management of multiple sclerosis. *Mult Scler*. 2017: 1352458517748475.

24. Held Bradford E, Baert I, Finlayson M, Feys P and Wagner J. Feasibility of an International Multiple Sclerosis Rehabilitation Data Repository: Perceived Challenges and Motivators for Sharing Data. *International Journal of MS Care*. 2017.

25. Butzkueven H, Chapman J, Cristiano E, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler*. 2006; 12: 769-74.

26. European Medicine Agency SMH. Initiative for patient registries: strategy and pilot phase. Inspections and Human Medicines Pharmacovigilance Division, 2015.

27. European Medicine Agency SMH. Report on Multiple Sclerosis Registries - workshop 7 July 2017. Inspections, Human Medicines, Pharmacovigilance and committee Division, 2017.

28. Engelhard MM, Patek SD, Lach JC and Goldman MD. Real-world walking in multiple sclerosis: Separating capacity from behavior. *Gait Posture*. 2018; 59: 211-6.

29. Feys P, Lamers I, Francis G, et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Mult Scler*. 2017; 23: 711-20.

30. Motl RW, Cohen JA, Benedict R, et al. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. *Mult Scler*. 2017; 23: 704-10.

31. Balcer LJ, Raynowska J, Nolan R, et al. Validity of low-contrast letter acuity as a visual performance outcome measure for multiple sclerosis. *Mult Scler*. 2017; 23: 734-47.

32. Feys P, Giovannoni G, Dijsselbloem N, Centonze D, Eelen P and Lykke Andersen S. The importance of a multi-disciplinary perspective and patient activation programmes in MS management. *Mult Scler*. 2016; 22: 34-46.

33. Curtis LH, Brown J and Platt R. Four health data networks illustrate the potential for a shared national multipurpose big-data network. *Health Aff (Millwood)*. 2014; 33: 1178-86.

34. Fleurence RL, Curtis LH, Califf RM, Platt R, Selby JV and Brown JS. Launching PCORnet, a national patient-centered clinical research network. *J Am Med Inform Assoc*. 2014; 21: 578-82.

35. Vaudano E, Vannieuwenhuyse B, Van Der Geyten S, et al. Boosting translational research on Alzheimer's disease in Europe: The Innovative Medicine Initiative AD research platform. *Alzheimers Dement*. 2015; 11: 1121-2.
36. Healthdata. Healthdata. Collecte des données. . In: Healthdata, (ed.). Brussels: WIV-ISP, 2015.

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

Figure 1: To solve the puzzle of multiple sclerosis (MS), multidisciplinary measurements are required: to capture the complexity and heterogeneity of MS, consistent longitudinal multidisciplinary measurement are required. This figure illustrates what we mean with "a multidisciplinary data infrastructure" referring to datasets, registries and/or cohorts including clinical-, functional and patient reported outcome measures in combination with extensive patient profiling (immunology, genetics, …)

Figure 2: Data sharing requires a community of trust and transparency: there are several reasons the share (and not share) data and to use (or not use) shared data. Policies of data sharing should rest upon knowledge of how data is shared and how end-users use data that have been shared to them. To ensure that both sharing data and using shared data is encouraged, a community of trust and transparency is required.

Figure 3: The difference between IT dependent and IT independent data infrastructures: Simply put, when implementing an IT independent multidisciplinary data infrastructure, different data controllers can use their preferred software. Based on unique identifier, the data can be connected if necessary or desired.

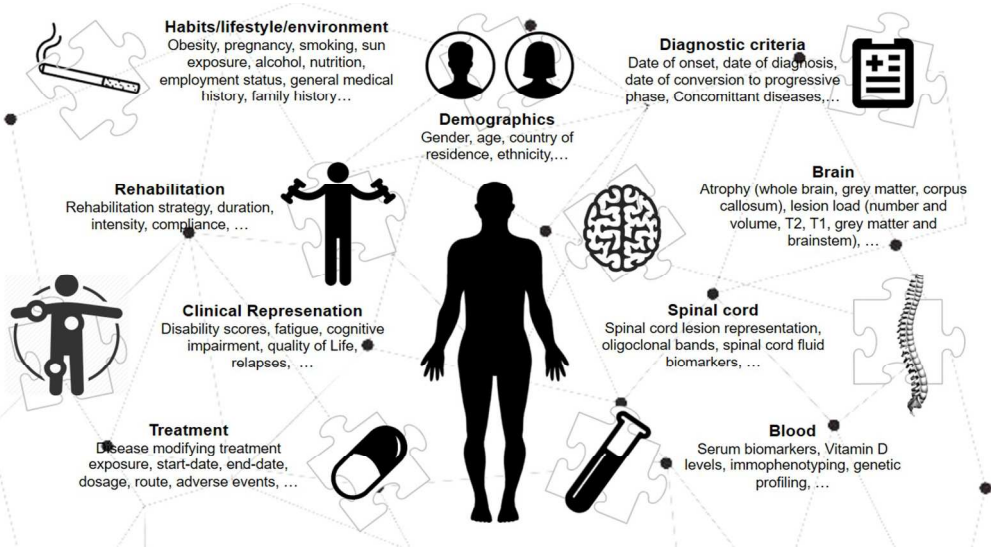

Figure 1: To solve the puzzle of multiple sclerosis (MS), multidisciplinary measurements are required

337x189mm (150 x 145 DPI)

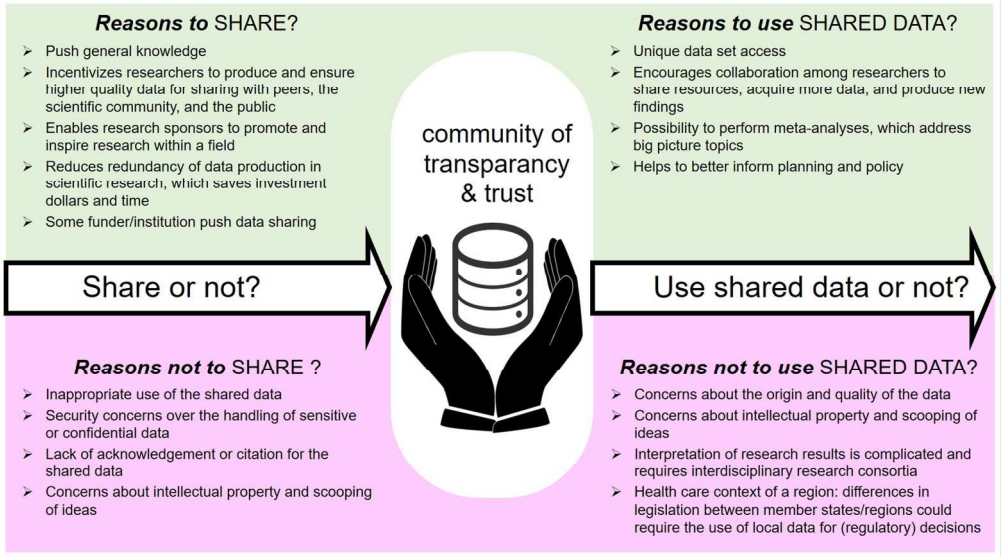

Figure 2: Data sharing requires a community of trust and transparency

314x178mm (150 x 150 DPI)

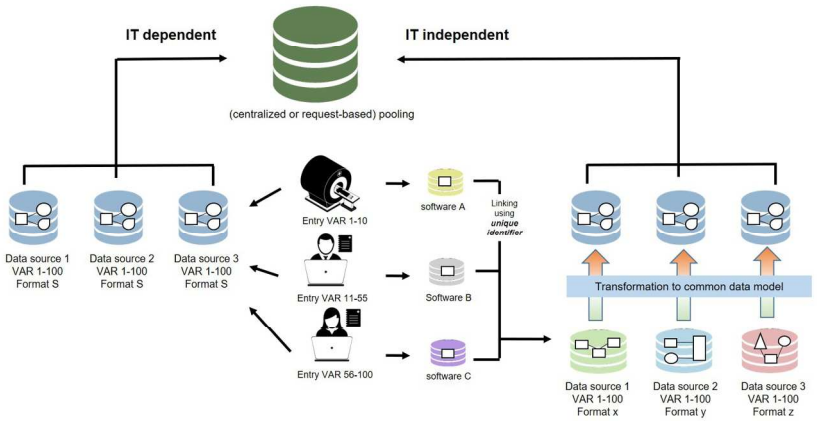

Figure 3: The difference between IT dependent and IT independent data infrastructures

406x228mm (120 x 120 DPI)