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Review article

The Sylvia Lawry Centre for Multiple Sclerosis Research (SLCMSR)—Critical review facing the 20 anniversary

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ABSTRACT

The SLCMSR was formed as an international Multiple Sclerosis Trials, Research and Resource Center to identify clinical MRI and other predictors of the course of multiple sclerosis (MS) based on a large database of natural history and clinical trial data. Using an elaborate validation concept several key findings were published, challenging established outcome parameters and their assessment in MS such as disability ratings with Expanded Disability Status Scale (EDSS), relapses and MRI endpoints. Sustained increase of EDSS appeared to be an invalid outcome for 2–3 year clinical trials at least in patients with relapsing-remitting MS. The number of gadolinium-enhancing lesions and T2-lesion load on MRI were shown not to have a meaningful additional predictive value for the disease course. These issues risen some 15 years ago had triggered controversial discussions which have also been noticed by regulatory authorities and they all have not been resolved. In addition the SLCMSR contributed to the development of new outcomes such as real-world walking speed as an attractive, ecologically valid tool based on a wearable device. A so-called evidence-based-decision-support tool was constructed to provide individual prognostic estimates based on a matching algorithm to a given database. This paper condensates the findings of 20 years of critical MS research.

1. Introduction

The SLCMSR celebrated its 20th anniversary in 2021. Its vision was to create an "international Multiple Sclerosis Trials, Research and Resource Center" where "sophisticated statistical methods will be used to identify clinical and MRI predictors of the course of Multiple Sclerosis (MS)." As a key resource it was planned to build a large "database containing clinical and magnetic resonance imaging (MRI) data" (from the call for proposals advertisement in Nature, May 2000). The collaborative effort was focused on gathering data from pharmaceutical companies and from academic MS research centres in order to "to develop alternative approaches to clinical trials which will avoid the necessity for placebo control." The first main aim was thus the development of virtual placebo groups. The second aim was an attempt to validate short term outcomes based on MRI (number of lesions) or relapses (rate, severity, residual disability), as surrogate markers for meaningful responses to experimental therapies.

A full, transparent competing interest disclosure policy was installed and the center, established as not-for-profit organization according to German law, was able to gather data from 26.100 patients covering >100.000 patient-years, collected from 58 clinical trials and natural history datasets (http://www.slcmsr.net/en/partner/cooperations.html).

Mindful that many of the issues identified 20 years ago remain unresolved and still lack consensus in the field, this paper aims to review SLCMSR's achievements. It will cover topical areas, i.e. research

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methods – including a short overview of the management structure, assessing the predictive value of relapses and MRI on the long term progression and disability accumulation, exploring the potential use of "real-world walking speed" measured on mobile accelerometry as an outcome, discussing disease prognosis at an individual level and "virtual placebo groups" based on "robust prognostic matching" methodology.

1.1. Research methods

Published false-positive research findings are a major problem in the process of scientific discovery (Ioannidis, 2005). In general, there is a high rate of lack of results replication in clinical research and MS research is no exception. Without defining specific hypotheses or models first, analyses performed on datasets are at risk of generating hypotheses to fit the data through unwitting bias. Descriptive data analysis often drives the formulation of hypotheses thus undermining the validity of formal statistical interference by destroying the probabilistic basis of inferential statistics. Pre-publication validation here aims to reduce the number of false positive findings.

At the SLCMSR it was originally expected to provide access to a large fraction of the world-wide available data on MS disease evolution (placebo arm data from randomized controlled trials and data from natural history cohorts). Therefore, after successful negotiations with all major partners from pharma and academic centres, a special validation policy was developed and implemented. The policy, which is publicly available at (http://www.slcmsr.net/download/publikationen/Validation_Policy.pdf), prescribes a random split of any dataset into a hypothesis-generating/training ("open" dataset) and a validation cohort ("closed" dataset). In addition, the policy includes the establishment of a validation and publication committee and a group of "data trustees", who would have access to the "closed" part of the database and would be independent of the statisticians/researchers that are only allowed to explore the "open" dataset. A full validation following this approach was performed in five studies (Daumer et al., 2008), supervised by a validation committee according to the policy; in four studies the initial hypothesis was confirmed, while in one study (Young et al., 2006) the hypothesis could not be confirmed. Key results of SLCMSR studies will be summarized in the following and are displayed also in the table 1.

1.2. MRI as outcome in MS

MRI is a powerful tool to diagnose MS, but its predictive value for disability is a matter of ongoing discussion. The SLCMSR performed three studies from pooled MRI data from clinical trials to better understand the MRI evolution over time and its prognostic value. In a first study researchers showed that Gadolinium enhancement is dependent on the age at onset, on the disease duration and on the disease course, but also on the total number of T2 lesions (Barkhof et al., 2005). In a cross-sectional study of 1312 patients from 11 trials a weak to moderate correlations of T2 lesion load with the EDSS (Expanded-Disability-Status-Scale) score (Li et al., 2006) was confirmed. Among patients with EDSS higher than 4.5 the relationship decreased, indicating that MRI measures become insensitive as a correlate of disability evolution (Li et al., 2006). With data from $n = 223$ patients with relapsing-remitting MS (RRMS) observed over 2 years authors demonstrated that the change of the total lesion load is not predictive of disability at the trial end (Daumer et al., 2009). Introducing the number of gadolinium-enhancing lesions did not improve the prognostic accuracy of the model. This paper elicited a vivid discussion on whether relapses and disability progression measured by EDSS are more adequate measures of disease evolution than MRI (Barkhof and Filippi, 2009). Even today MRI is not accepted as a primary outcome for phase-3 trials by regulatory authorities. While little efforts have been done to establish multidimensional lesion mapping as study outcomes for multicenter work and different measures for neurodegeneration have been applied, there is no overall agreed set of radiological measures to monitor the degenerative component of the disease (Wattjes et al., 2021). In addition, the integration of spinal cord imaging follow-ups in studies and clinical care is largely missing.

The lack of standardization of MRI machines, protocols and the semi-automated process to extract parameters from the MRI images can account for these sobering results. To overcome these shortcomings, a grant proposal on "quantitative MRI" from the SLCMSR in collaboration with the main MRI manufacturers and academic MRI physicists did not get the necessary funding. One of the manufacturers had estimated the true costs for such a project to be around 50m€.

Table 1
Major project outcomes of SLCMSR studies.

	Number of patients and of included studies ()	Results	Reference
MRI as an outcome			
Correlations of GD+	1328 + 848 (17)	Relation to age at onset, disease duration, T2 lesions number	Barkhof 2005
T2 lesion load and EDSS correlation	1312 (11)	Weak to moderate, less beyond EDSS 4.5	Li 2005
T2 lesion load change and disability at trials end	223	No predictive value, Gd+ inclusion without effect	Daumer 2006
Relapses and progression as outcomes			
Predictive value of prestudy relapse rate	821 (22)	Could be validated for on study relapse rate	Held 2005
Relapse rate evolution in placebo cohorts	1465 + 505 (12)	Decline between 1988 and 2012	Stellmann 2012
Predictive value of relapse rate for progression	806 (1)	No overall association, possibly within the first 2 years but again with substantial heterogeneity	Scalfari 2010, Scalfari 2014
Predictive value of relapse rate for progression	576 (20)	Could not be validated for phase-2/3 trials	Young 2006
Predictive value of nadir EDSS for CDMS conversion	136 (2)	Did only show a trend in validation sample	Neuhaus 2008
Disability as an outcome	425 (31)	3 and 6 months confirmed EDSS worsening not consistent with EDSS at trials end	Ebers 2008
Predictors of conversion to SPMS	1023	Age as strongest predictor	Scalfari 2011
Predictors of progression in PPMS	597 (2)	Age, gender, first symptoms and early EDSS change not predictive	Stellmann 2014
Prognosis based on matching algorhythm			
Validation against neurologists estimate	717	Similar accuracy but high intra/interrater variability	Galea 2013
Evaluation by pwMS	110 + 90	Short-term and long-term tool appreciated	Heesen 2013 Kosch 2021
Accelerometry as an outcome			
Correlation with performance based measures	28	Low ecological validity of performance based measures	Stellmann 2015
Correlation with effect of fampridine on performance based measures	28	Performance based measures are not predictive for or related to the effect of the drug on everyday functioning	Stellmann 2016

1.3. Assessing relapses and progression in clinical trials and their predictive value

The use of relapse rate reduction, as a primary endpoint of MS phase-3 studies, is based on the assumption that the occurrence of inflammatory attacks mirrors the disease evolution and that the therapeutic prevention of relapse would result in halting the disability progression.

In 2005, Held et al. analyzed predictors of relapse rates based on data from 22 MS clinical trials, which had been undertaken until 1999. The relapse rate before entering one of these studies and the disease duration were predictors of on-study relapse rates (Held et al., 2005). A meta-analysis of the relapse evolution in placebo cohorts from phase-3 treatment trials was published in 2012 (Stellmann et al., 2012). In addition to the retrieved 12 cohorts, 505 patients from the open part of the SLCMSR database were included. There was a substantial decline of relapse rates in placebo cohorts during the 20 years of MS treatment trials and prestudy relapse rate remained the best predictor for on study relapses. New diagnostic criteria and availability of treatments are possible major contributing factors for the lower relapse rates today. These data are relevant to the design of clinical studies especially when resources are limited as in investigator-initiated work.

Although natural history data studies from the last century confirmed the predictive value of early relapses, they have also questioned the prognostic relevance of relapses later in the disease course for long-term disability (Confavreux et al., 2003; Scalfari et al., 2010; Tremlett et al., 2009, Leray et al., 2010, Krementchuzky et al., 1999). A larger number of relapses during the first 2–5 years from onset was found to be associated with a faster time to develop severe disability. However, the occurrence of inflammatory attacks during the later stage of the disease or overlapping the progressive course had little impact on the risk of accumulating disability. In addition, even among patients with a high frequency of early relapses (>/- 3 attacks during the first two years), there was a substantial heterogeneity and approximately 30% were found not to have been converted to secondary progressive MS (SPMS) despite being observed for a mean of 17 years (Scalfari et al., 2014). Emerging evidence also indicates that even during the early stage of RRMS the progression of disability mostly occurs independently of relapsing activity (PIRA) (Kappos et al., 2020). However, recent studies from large registry cohorts have argued that sustained disability in some extent is caused by individual relapses (Jokubaitis et al., 2016, Koch-Henriksen et al., 2019) which is questioned by other work (Cree et al., 2019).

The SLCMSR database of the placebo groups of clinical trials (20 trials, with a mean of 972 days of follow-up) was used to study the prognostic effect of relapses on short term disease evolution (Young et al., 2006). While the exploratory dataset analysis confirmed an association between the frequency of attacks and the disease progression, the validation study did not confirm that on study relapses yield higher disability scores at the end of the study. Interestingly, we found no newer study trying to unravel the interaction between relapses, temporary worsening and progression based on treatment study data following a rigorous validation approach.

Based on data from two trials including patients with clinically isolated syndrome (CIS) ($n = 136$), the number of T2 lesions and the degree of clinical recovery after the first event (nadir EDSS) were found to be predictive of the time to clinically definite MS (CDMS) in the exploratory dataset (Neuhaus et al., 2008). However, the validation dataset could only show a trend for nadir-EDSS to predict conversion to CDMS. As the dataset was small, further work is needed to unravel the predictive effect of nadir EDSS. In the Barcelona CIS cohort (Tintore et al., 2020) the number of T2 lesions at onset was found to be a relevant predictor of progression to EDSS 3.0, but we are not aware of any other studies to elucidate predictors of early disability progression based on an exploration and validation approach, or no study taking up the nadir EDSS as a possible predictor.

1.4. Disability as an outcome in MS trials

When the SLCMSR was founded, there was a vivid discussion on MS different disability trajectories, the occurrence of a more malignant and a more benign disease course and possible predictors based on controversial findings from different registries and short term data from RCTs (Daumer et al., 2010).

A dataset of placebo arms from 31 trials in relapsing-remitting and secondary-progressive MS was used to assess predictors for irreversible disability at trial end. Confirmed 0.5–1.0 point EDSS score worsening after 3 or 6 months was not consistently associated with progression at trial end (Ebers et al., 2008). Based on these results, the authors postulated that at least 1–2 points EDSS progression confirmed after one year of follow-up is needed to be definite and valid, but we are not aware of any MS treatment trial, that since then reported data on 1 year confirmed EDSS progression.

In addition to the work on the disease evolution based on clinical trials data, the SLCMSR tried to gather data from national registries in order to develop prognostic modeling. Initial work from three registry datasets presented at an ECTRIMS meeting in 2010 indicated substantial heterogeneity in these natural history cohorts (Daumer et al., 2010), showing large differences in the percentages of patients reaching EDSS 6 and 8 disability milestones. This observation is nowadays well documented, with selection and ascertainment bias being the most likely reasons (Bovis et al., 2018). However, we are not aware of any international effort to handle this problem by validating predictive models in different databases.

The London Ontario database could be analyzed by SLCMSR based on an agreement with the data donor. This is one of the most complete population-based cohort of patients, who were recruited during the non-treatment era (over the years 1950–1990), when the MS diagnosis was based on Schuhmacher and Poser criteria, and were followed up for 28 mean years. Age was found to be the strongest predictor of SPMS conversion independent of disease duration and relapse frequency (Scalfari et al., 2011). However, based on the older diagnostic criteria and the lack of any approved treatment together with overall improved general medical management, the London Ontario prognosis data can only be considered as a worst-case scenario for an actual MS cohort.

By aggregating data from eight primary progressive MS (PPMS) cohorts with data from London Ontario $n = 302$ and from the Hamburg MS Patient information database (HAPIMS) with $n = 295$ Stellmann et al. (2014) could not confirm age at onset, gender, type of first symptoms and early EDSS change as predictors of disability progression in PPMS.

Therefore, prediction in MS remains highly challenging. Especially with the new diagnostic criteria since 2017 and the increasing worldwide incidence, more efforts to better understand the change of the disease is of importance. Estimates on who will develop highly aggressive or a more benign MS disease course are of utmost need to tailor immunotherapies.

1.5. Prognosis based on matching algorithm

To enable evidence-based decision support in MS (EBDiMS) the SLCMSR developed an online analytical processing (OLAP) tool written in Java and R using an individual matching algorithm at its core (Daumer et al., 2007). The tool was aimed to be used by researchers, clinicians and at best also patients on their own. A given patient e.g. from an MS clinic is defined by a set of covariates which are potential prognostic factors: number of relapses in the last 12 months, disease duration from diagnosis, age at disease onset, disability level as measured by the EDSS, and the type of disease course. These data are put into the system and a matching algorithm then automatically selects from the database subgroups of patients presenting with similar covariates, whose disease course is ultimately analyzed to project a hypothesized outcome for the selected patient. Cohort evaluation work showed that the predictive accuracy of expert neurologists was similar

to the tool, but neurologists showed a significant intra-rater and inter-rater variability (Galea et al., 2013). Short-term matching (Heesen et al., 2013) as well as a the long-term prediction (Kosch et al., 2021) were highly appreciated by pwMS. Results were considered new, relevant, informative, not frightening and helpful for treatment decision making. The matching algorithm is now available for other well-defined cohorts to validate its predictive potential on data from the new diagnostic and treatment era.

1.6. Real-world walking speed measured by accelerometry as an outcome

The results from the analysis of disability outcomes and predictors show that MRI parameters and relapses are difficult surrogates for disability, and that EDSS is an imprecise and noisy measure of disability. It has been proposed 20 years ago that mean walking speed is a more stable parameter than walking distance, which is at the core of the EDSS score (Albrecht et al., 2001). The SLCMSR therefore decided to focus on alternative objective measures of disability (accelerometry based) rather than on the application of bio-statistical methods on conventional scores. The SLCMSR here has gradually expanded its scope beyond biostatistical analyses/methodology and has contributed to the development of a technology platform to assess real-world walking speed based on accelerometers that are worn by patients in their daily life. Mobile accelerometry offers the possibility to gain ecologic valid, objective and reliable mobility data that are linked to "feel and function" from pwMS in their daily life environment. Over a period of 7 days (to include weekends) it allows the assessment of real-world walking speed and other parameters as distance, steps or sequences of a defined walking period. The SLCMSR developed and validated "actibelt" based on motion sensing technology (Daumer et al., 2007; Schimpl et al., 2011). Early validation work in MS disclosed that correlations to performance-based measures as the 25 Foot-Walk-Test, 6 or 2 Min--Walking-Test is limited and that in their daily live pwMS with minor residual disability show very few uninterrupted walking periods of 2 min or more (Stellmann et al., 2015). Another study addressed the effect of fampridine, which is supposed to improve mobility measured by performance-based tests (Stellmann et al., 2016). While all of performance-based measure improve only 50% of patients showed changes in real life measures such as walking steps/day, distance/day or velocity questioning the effect of the drug. More work was performed in other clinical conditions and recently the SLC was involved in the development and presentation of an evidence dossier for FDA and EMA as a possible guideline for regulatory authorities to establish accelerometry as a primary outcome in clinical trials in all conditions which impact mobility (Walton et al., 2020, Daumer et al., 2017)

2. Discussion

The SLCMSR was funded to establish an independent database of MS natural history and clinical trial data in order to improve prognostic estimates and trial designs in MS and to speed-up and optimize treatments development. It established a highly transparent data hosting, protection and analysis concept with a strong validation strategy at its core. This kind of critical approach to prognostic markers is still highly relevant as for example the actual discussion on neurofilament light chain as a predictor shows (Barro et al., 2020).

Despite difficulties with obtaining sufficient funding several key findings were published, challenging outcome parameters and their assessment in MS such as disability ratings with EDSS, relapses and MRI, as disease surrogate markers. Sustained worsening of EDSS appeared to be an invalid outcome at least in patients with relapsing-remitting MS. MRI parameters such as the number of Gadolinium-enhancing lesions and T2-lesion load did not show to have a meaningful additional predictive value for the short-term disability evolution. The frequency of relapses was found to correlate weakly with the disease evolution and its predictive value is be limited to the early stage, yet it remains the primary outcome measure in RCTs. These issues highlighted some 10–15 years ago triggered a controversial discussion which has been noticed by regulatory authorities and has still not been resolved. However, concepts to develop automated MRI analysis, virtual placebo groups and more robust clinical outcomes have been proposed by the SLCMSR.

So-called evidence-based-decision-support-tools were constructed based on short term placebo data from RCTs and one of the population-based natural history MS cohorts from London Ontario, Canada. Aiming for individualized risk counselling validation steps confirmed the safety, robustness and strong interest in the approach from the patient's perspective. Real-world data and registries with all their limitations nowadays represent the major source of long-term patient data future and need to be used by these matching tools. The new "Darwin EU" initiative, the "Data Analysis and real world interrogation network" supported by the EMA with the coordination center being located at the Erasmus University Medical center Rotterdam, might be in the position to implement these methodologies for a wide range of diseases (https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu). The recently published NIH statement, called a "seismic mandate" (Kozlov, 2022) that NIH funding, starting January 2023, will need the commitment to make data publicly available may substantially help to share data publicly.

The aim to develop virtual placebo groups could not be reached largely due to limitations of currently used outcomes in MS and due to the fact that so-called "study effects" – differences between the distribution of outcomes among otherwise similar studies - are of a similar same order of magnitude as expected treatment effects (Daumer and Lederer, 2014).

A new generation of outcome measures based on wearables, such as real world walking speed, that allows objective assessment of disability in a real-world setting that is reflective of a patient's day-to-day activities (Daumer et al. 2017) may lead to more robust and meaningful long-term data that could be used for virtual placebo groups. This accounts not only for treatments addressing disease course modification but also for symptomatic treatments and lifestyle modifications (e.g. exercise, nutrition).

The questions, and the potential studies and methodologies that were proposed by SLCMSR are as relevant today as they were in 2001. Why then, after 20 years, is the MS community still seeking answers to these questions? International initiatives with strict conflict of interest rules and validation policies for any analysis approach are warranted. We strongly believe that only large multinational integrative efforts will help to overcome the mentioned barriers.

4. Funding

The current work has no funding source.

Conflict of interest

Martin Daumer serves on the editorial board of *MedNous*; is author on patents re: Apparatus for measuring activity (Trium Analysis Online GmbH), Method and device for detecting a movement pattern (Trium Analysis Online GmbH), Device and method to measure the activity of a person, Device and method to determine the fetal heart rate from ultrasound signals, Method and device for detecting drifts, jumps and/or outliers of measurement values, Device and method to determine the global alarm state of a patient monitoring system, Method of communication of units in a patient monitoring system, Method and device for detecting drifts, jumps and/or outliers of measurement values, System and method for patient monitoring, reducing leakage of face masks; serves as Managing Director of and holds stock/stock options in Trium Analysis Online GmbH (50% effort).

All other authors declare of having no conflicts of interest in relation to the submitted work.

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