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Facing the urgency of therapies for progressive MS - A Progressive MS Alliance proposal

Fernando Dangond[1]*, Alexis Donnelly[2], Reinhard Hohlfeld[3,4], Catherine Lubetzki[5], Susan Kohlhass[6], Letizia Leocani[7,8], Olga Ciccarelli[9,10], Bruno Stankoff[11], Maria Pia Sormani[12], Jeremy Chataway[13,14], Federico Bozzoli[15], Francesco Cucca[16,17], Lisa Melton[18], Timothy Coetzee[19], Marco Salvetti[20,21]

[1]EMD Serono, Inc., Billerica, MA, USA.

[2]Department of Computer Science, O'Reilly Institute, Trinity College, Dublin, Ireland.

[3]Institute of Clinical Neuroimmunology, Biomedical Center and Hospital of the Ludwig Maximilians Universität München, Munich, Germany.

[4]Munich Cluster for Systems Neurology (Synergy), Munich, Germany.

[5]Neurology Department, Sorbonne University, Pitié-Salpêtrière hospital, Paris, France.

[6]Multiple Sclerosis Society, UK.

[7]Vita-Salute San Raffaele University, Milan, Italy.

[8]Neurorehabilitation Department and Experimental Neurophysiology Unit, INSPE, Scientific Institute Hospital San Raffaele, Milan, Italy.

[9]Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, Faculty of Brain Sciences, University College London (UCL), London, UK.

[10]National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, UK.

[11]Sorbonne University, Brain and Spine Institute, ICM, Pitié-Salpêtrière hospital, Paris, France.

[12]Department of Health Sciences (DISSAL), University of Genova, Genova, Italy/IRCCS Ospedale Policlinico San Martino, Genova, Italy.

[13]Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK.

[14]National Institute for Health Research, University College London Hospitals, Biomedical Research Centre, London, UK

[15]Italian Multiple Sclerosis Society, Genoa, Italy.

[16]Dipartimento di Scienze Biomediche, Università di Sassari, Sassari, Italy.

[17]Dipartimento di Scienze Biomediche, Università di Sassari, Sassari, Italy.

[18]MS Research Australia.

[19]National Multiple Sclerosis Society, New York, NY, USA.

[20]Department of Neurosciences, Mental Health and Sensory Organs, Centre for Experimental Neurological Therapies (CENTERS), Faculty of Medicine and Psychology, Sapienza University, Rome, Italy.
[21]IRCCS Istituto Neurologico Mediterraneo (INM) Neuromed, Pozzilli, Italy.

*on behalf of Industry Forum members of the international Progressive Multiple Sclerosis Alliance

Corresponding author:
Marco Salvetti, e-mail: marco.salvetti@uniroma1.it

Abstract

While therapies for infiltrative inflammation in multiple sclerosis (MS) have advanced, neurodegeneration and compartmentalized inflammation remain virtually untargeted, as in other diseases of the nervous system. The consequences of this dichotomy are that the relapsing-remitting form of the disease has benefited from new therapies while the progressive forms remain essentially untreated. The objective of the International Progressive MS Alliance is to expedite the development of effective therapies for progressive MS. A key strategy in this task is to avoid duplicating research that the national MS societies (and other funding agencies) already support, thereby developing new complementary initiatives that may foster innovative thinking and concrete advancements. Based on these principles, the Alliance is developing a new funding program that will focus on Experimental Medicine Trials (ExMT). Here we discuss the reasons behind this choice, potential strengths and weaknesses of the program and why we hope to achieve the twofold objective of advancing therapies while at the same time improving understanding of progression in MS and of neurodegeneration in general. We are soliciting public and academic feedback which will contribute to a better shaping of the program and of future strategies of the Alliance.

Key points

- As in other neurological diseases, available therapies do not satisfactorily target the neurodegenerative component of progressive multiple sclerosis (PMS).
- The continuing negative results in therapeutic development, demand new strategies to steer research in new directions, in the hope of expediting the development of effective therapies.
- Experimental Medicine Trials (ExMTs), defined in the main text, may constitute one such strategy.
- The key issues that will be addressed in the ExMTs funding program(s) are: polytherapies, prioritization and harmonization of outcome measures, balance between innovation in trial design and comparability among trials.
- The participation of people with MS both in the conception of the program and in the review process will be a key asset of the initiative.

In recent years, translational research in neurological diseases has been repeatedly described as unpromising[1-3]. Very recent results reinforce this negative view[4,5], for a field that epidemiological projections indicate as a most pressing need for addressing in the years ahead. Among neurological diseases, progressive MS (PMS) represents a major challenge. In the relapsing-remitting (RR) form of the condition, the pathophysiology is dominated by the inflammatory response, and a range of effective immune-modulating therapies have been successfully developed. In PMS, different pathophysiologic mechanisms seem to interact, resulting in myelin damage and neurodegeneration through incompletely understood mechanisms. As a consequence, while targeting inflammatory pathways has advanced the efficacy of treatments in RRMS, progressive forms lag behind, with clinical trial failures or cancellations of development plans that are particularly disappointing when they occur in phase 3. Furthermore, it is fundamental to consider that neuropathological, imaging and biomarker studies suggest a continuous destructive process across all forms of MS[6-10], from clinically isolated syndromes to primary progressive disease. And in fact, progression of disability develops in MS independently of disease phase: disability can accrue insidiously also during the RR phase of the disease[11,12] and in this case the term worsening is used instead of progression, which is reserved to patients in the progressive phase of the disease[13]. Furthermore, a significant percentage of people with RRMS, even though treated with the most effective therapies, still develop SPMS[14]. However, the pathological correlate of disease progression in MS remains, to some extent, elusive with studies suggesting a different pathophysiology for slowly expanding lesions in relapsing-remitting disease as compared to PP and SPMS[15,16]. On the other hand, on a genetic basis, variants that are enriched in the progressive disease compared to the relapsing-remitting form have been described. However, clear difference between SP and PPMS did not emerge so far[17].

Some phase 3 trials in PMS, which have tested immunomodulatory therapies, have reported positive results, thereby bringing hope[18,19]. Nevertheless, it remains to be determined how baseline demographics and disease characteristics (in particular the relatively high percentage of patients with active inflammation) influenced the positive results of these trials.

However, not everything is going wrong. It is important to enable those actions that have the potential to convert emerging opportunities into tangible benefits. This is the mission of the International Progressive Multiple Sclerosis Alliance (Alliance) - a collaboration between people

with MS, clinicians and academicians, industry and regulators, convened by MS societies of several countries - “to expedite the development of effective disease-modifying and symptom management therapies for progressive forms of MS”[20]. Over the years, the Alliance has been refining and adapting its strategy to support and fund research efforts that may provide significant impact. Besides the focus on treatment development, fundamental to the Alliance’s mission is to prevent the duplication of research that the national societies (and other funding agencies) already support locally.

Driven by these principles, the Alliance has identified experimental medicine trials (ExMT) – defined, for this particular purpose, as “phase 2a clinical trials, that explore treatments and targets while generating hypotheses about disease mechanisms, through a coherent pool of biological and clinical measures; and that should be informative even in the event of a negative outcome” - as an area that may provide advances in a relatively short period of time. Furthermore, it may cover a territory that is quite uncharted and represents a natural continuation of or complement to another research area (drug screening) that has provided important contributions in recent years. In fact, various high-throughput screenings have identified molecules with promising effects on remyelination and neuroprotection, including compounds already registered for other indications[21-25]. Interestingly, some of these compounds may promote oligodendrocyte maturation through a common pathway, suggesting a unified mechanism for oligodendrocyte maturation enhancers (these and other aspects about remyelination and neuroprotection mechanisms and strategies have been recently discussed[26]). Thanks to such advances (which, incidentally, have also sparked an increasing interest in repurposing drugs for other uses) there is, for the first time, a substantial number of molecules accompanied by robust preclinical data, that deserve to be tested in neurodegenerative diseases, including PMS. Furthermore, the Alliance is already supporting two extensive drug screening projects, one primarily aimed at targeting the aberrant activation of microglia and astrocytes and the other aimed at identifying protective or regenerative drugs for oligodendrocytes and neurons (https://www.progressivemsalliance.org/research/collaborative-network-awards/). Taken together, these results and projects reinforce the general need to develop more productive discovery programs[27].

In this paper, we describe the reasons behind the strategy, and why they may be important for PMS and for other neurodegenerative diseases. We are outlining our approach now, in advance

of formalizing programs to be developed by the Alliance and other stakeholders in the MS community, in order to solicit feedback and reflections that may be used to further refine the strategy.

Importance of ExMTs

There is a rich literature on how to tackle the obstacles to translational research in neuroscience. In addition to the obvious need for better understanding of basic disease mechanisms, emphasis has been placed on the poor reliability and reproducibility of preclinical research data - which undermine the very foundations of the drug development pipeline[28,29], despite the detailed preparatory work which pharmaceutical companies must carry out in compliance with regulations (a factor with a key impact on the drug development process, to which we draw the reader's attention in Appendix). Also for animal models of MS, there have been repeated calls for the adoption of rigorous standards in preclinical studies, similar to those in clinical trials[30,31]. On the contrary, the need for a deep and rigorous biological assessment in early phase clinical trials (similar to what may occur in preclinical studies) has been less emphasized and seldom put into practice[32-36]. This is surprising since a major leap in the entire drug development pipeline (the transition from animal to human biology) takes place when early phase trials are initiated[37] (interestingly, to help cope with these difficulties, interspecies translation models are under development in autoimmune diseases[38]).

The case of recent trial failures of beta secretase β-site amyloid precursor protein–cleaving enzyme (BACE) inhibitors in Alzheimer's disease may illustrate the difficulties in translating from animal biology to human mechanisms. Preclinical work showed that these compounds inhibit BACE and decrease the processing of amyloid precursor protein, with positive effects on the accumulation of β-amyloid, strongly suggesting potential as therapeutic agents[39]. Nevertheless, such agents failed in phase 3 clinical trials[4,5]. More recent preclinical data[40] now suggest that Verubecestat and other BACE inhibitors repress long-term potentiation, hence offering an explanation for the impaired memory and cognition that had been observed in the failed phase 3 trials. It is possible that a more thorough assessment of these mechanisms (e.g. long-term potentiation) - for example in the context of early phase clinical trials - might have generated some caution regarding the effects of these drugs.

Furthermore, in the absence of a deeper understanding of the effects of a drug on the biology of the disease in humans, it is difficult to tell if and why any given therapeutic attempt has failed. This is particularly true in conditions with a complex pathophysiology, and with a diseased tissue that it is difficult to access, such as in central nervous system disorders in general and PMS in particular. Here, positive biological effects on a given type of insult may be masked by other mechanisms of damage, not targeted by a single treatment. Finally, a comprehensive understanding of the effects of a therapy on human pathophysiology may help qualify new biomarkers[41] [a recent phase 1-2 trial on idebenone in PPMS provides a first example of such an opportunity: in spite of the negative result, this study suggested Growth/Differentiation factor 15 (GDF15) as a new biomarker of mitochondrial damage[33]] . It may also enable new preclinical studies to be designed around questions emerging from the clinical trials, in a fruitful "bench-to-bedside-to bench-again" approach[42,43] that may advance treatments while generating new knowledge about the biology of the disease. Indeed, administering a therapy in the context of a clinical trial compares to evoking a phenotypic response under well-controlled conditions, thus facilitating inferences about causal biology[44].

Considering these premises, it seems contradictory that substantial resources are devoted to studies that investigate mechanisms of action in the post-marketing phase. Though, in some cases, these investigations provide highly relevant data[45], it is undisputable that the impact of the same or similar results is greater in the earlier phases of the drug development process. To our knowledge, in the neuroscience field there have been few initiatives aimed at refocusing early phase trials from tests of efficacy to studies of disease mechanisms: in 2014, the National Institutes of Mental Health (NIH) released funding announcements focused on experimental therapeutics, in which interventions had to be used as tests of efficacy as well as probes of disease mechanisms[46].

Based on the growing impact of causal biology on drug discovery[47,48], and on recent developments in trial design and execution[49-51], we think that it is now possible to revive this challenge by facilitating ExMTs through funding programs that balance openness to innovation with the need for coordination[52,53]. The latter would be important to ensure good quality standards and comparability of the results. Following a reference trial protocol would be ideal in this respect. However, as we aim at collecting new concepts for a new field, being too prescriptive may shut the door to unexpected ideas that may spark progress where innovation

is much needed, i.e. trial design in neurological disease. Furthermore, in a disease with a complex pathophysiology, with myriads of potential therapeutic targets, it is difficult to imagine a master protocol to be followed in all instances.

Balancing innovation with comparability (FIG. 1)

Based on these premises, we call on investigators to embrace the above definition of ExMT and incorporate additional features that will be strongly encouraged to increase comparability and are briefly addressed below:

Polytherapies

It is possible that the prevailing strategy of targeting the numerous pathophysiologic mechanisms of PMS (and of other neurodegenerative diseases) with one therapy at a time, has been one of the issues responsible for some of the failures of therapies targeting neurodegeneration. This strategy did not result from underestimating the complexity of neurodegeneration. Rather, pragmatic considerations about tolerability, costs and clarity of the results (i.e. being sure that the effects are attributable to the drug under investigation) prevailed. However, given the negative results obtained so far, these concerns should be re-prioritised.

In the context of advanced trial designs, for example, the factorial approach is one method to test multiple drugs simultaneously and efficiently. Factorial trial designs have treatment groups with all possible combinations of treatments. They can therefore assess the effects attributable to each drug and their interactions in combination[54-55]. Moreover, in factorial design trials, each individual experimental drug is given only to a proportion of the subjects. Therefore, each patient's data contributes to many data comparisons. Finally, the factorial design provides the opportunity to simultaneously assess more than one drug per trial. In MS, examples of factorial or "partial" factorial clinical trials can be found in the relapsing-remitting disease[56-59].

Other aspects that may be deepened for the design of innovative polytherapy trials include the temporal dynamics underpinning the biological effects of each therapy. For some treatments, the biological impact may gradually diminish due to the homeostatic response of the organism. In such cases, treatment regimens including cyclic withdrawals may be envisaged, facilitating for example combination therapy regimens where treatments are alternated rather than administered simultaneously[60]. While we encourage trials exploring polytherapies, we should

not exclude trials of single treatments when supported by a consistent rationale (e.g. therapies that may be better suited for elderly or particularly fragile patients).

Trials on background of immunosuppression

To reduce the heterogeneity that polytherapy trials might bring about (different trials testing different therapies in various combinations), and to counteract a clinically ascertained driver of damage during progression (i.e. inflammation), we encourage evaluation of new drug(s) in combination with a licensed modern immunosuppressive therapy, chosen because of its clinical indication in the study population and taking into account other considerations such as potential synergies with the "neuroprotective" therapy, patients' quality of life, and costs.

Prioritizing and harmonizing measures

The heterogeneity of disease mechanisms in PMS and, consequently, of therapeutic targets, makes it very difficult to recommend a unique architecture of outcome measures that will fit all purposes. We encourage investigators to follow the scheme depicted in FIG. 2, which integrates several measures of biological and paraclinical efficacy according to target mechanism(s). Examples in the figure are rather straightforward. However, investigators may devise new and more subtle relationships between measures. For example, miR-142-3p has been recently shown to promote an IL1beta-dependent glutamate dysfunction by targeting glutamate-aspartate transporter[61]. It would be interesting, in case of therapeutic attempts targeting these mechanisms, to match miR-142-3p measurements with specific MR spectroscopy measurements of glutamate. More information about each biological and clinical efficacy marker can be found in Supplementary Tables 1, 2 and 3 and in Supplementary information on candidate PET outcomes.

Apart from this scheme, a stricter, though not absolute, recommendation is the inclusion of measures listed in FIG. 3. These represent: a core set of markers to evaluate the biological efficacy of the immunosuppressive therapy in case of anti-CD20 treatments [already applied in an ExMT with intrathecal rituximab[36]]; clinical measures (with special attention to measures of. upper limb function); peripheral transcriptomics; a core set of paraclinical measures such as MRI (brain atrophy), neurophysiology (VEP and/or OCT) and fluid (serum neurofilaments (NfL)) markers of tissue damage.

We also suggest considering peripheral blood transcriptomics. A high-throughput, non-hypothesis driven measurement of the biological effects of a treatment is certainly desirable when evaluating its effects. This may be particularly relevant with repurposed therapies that typically carry uncertainties about their exact mechanism of action (we expect that a substantial proportion of the applications will deal with repurposed drugs with multiple potential targets). In this respect, exploration of peripheral blood mononuclear cells of patients undergoing experimental therapies for CNS diseases has been deemed poorly informative. Alternatives, such as the use of neural cells derived from induced pluripotent stem cells[62], are still in a very exploratory phase[35]. However, very recently, it has been shown that peripheral blood mononuclear cells, that express many central nervous system receptors and signaling proteins involved in neuropsychiatric disorders, may provide important information also in the case of primary neurological targets[63]. In this context, and with particular reference to the monitoring of the immunosuppressive therapies, it may be relevant to refer to workflows recently developed for the immune monitoring of immunotherapies in cancer but deemed appropriate also for immunophenotyping in autoimmunity[64].

Advances in genetics now allow the detection of coincident associations between disease risk and quantitative trait levels that mark disease-related intermediate phenotypes. Such phenotypes may be particularly attractive as therapeutic targets. In fact, it has been shown that drug targets having genetic associations with the disease significantly increase the probability of success in drug development[65]. Hence, particular relevance during the evaluation of the proposals will be given to projects that will test compounds whose candidate targets are intermediate phenotypes bearing coincident associations with the disease[66]. Furthermore, even if a potential target is not druggable, upstream or downstream molecules in a pathway involving a protein associated with the disease will be considered as significant (see for example Fang et al. 2019[48] for recent methods for target prioritization).

As the Alliance and others engage in this work, we encourage openness to new strategies that may improve the understanding of a treatment's efficacy (e.g. blood-based biomarkers[67]; neural-derived extracellular vesicles as accessible indicators of signals within the CNS, also in response to treatments[68]; induced pluripotent stem cells as a personalized disease model in clinical trials[62]). It is also important, for industry and for academicians, to design studies where informed consent allows for future use of biosamples (or to devise new ways to investigate

previous studies' cohorts and biosamples); this will facilitate the exploration and identification of biomarkers. Industry could also contribute by uploading raw imaging data to electronic repositories; this would allow to perform retrospective analysis of pooled data from progressive MS patient trials. Along with the knowledge developed in industry about conditions necessary for repurposing certain drugs, these action items would also prove invaluable in industry/academic collaborations.

Inclusion criteria and SOPs

The homogeneity of inclusion criteria among trials is a key pre-requisite to achieve comparability. Interindividual differences in pharmacokinetics and pharmacodynamics have a genetic basis but also differ by sex[69]. Furthermore, most disease phenotypes exhibit some degree of sex differences and MS is no exception. It is therefore important that inclusion criteria foresee a female/male ratio that does not deviate too much from the ratio in the population. Disease duration, ageing and non-continuous trajectories of progression, especially at different disability stages, are three other drivers of variability in clinical trial populations. It is important to note that patients with late-onset MS tend to progress to Expanded Disability Status Scale (EDSS) 6.0 (i.e. requiring unilateral assistance to walk) faster than patients with onset at younger ages[70]. In addition, as patients progress in disability during the trials, the speed of progression may vary according to the EDSS range at baseline[71]. Therefore, the commonly used trial eligibility requirement of having experienced progression within the past year may inadvertently ignore other factors impacting prospectively-planned outcomes. Finally, comorbidities are more frequent in MS compared with the general population[72]. Comorbidities (and related treatments) may interfere with MS pathophysiology and therapies and, therefore, influence outcomes. All in all, we think that there are good reasons for not being restrictive: all people with PMS should have the opportunity of seeing their condition therapeutically explored and we cannot exclude that specific mechanisms of action of drugs under scrutiny, or specific hypotheses about disease pathophysiology (e.g. asynchronous manifestations of different neurodegenerative components of the disease[73]) will dictate the need for studying specific disease courses or age ranges. The interactive review process (see immediately below) may possibly reduce unnecessary heterogeneities among trials. For the same reasons, the programs in development by the Alliance will welcome trials in SPMS and PPMS.

Stringent standard operating procedures (SOPs) will be required for MRI quantification of brain atrophy, VEP, OCT, PET, serum NfL, peripheral blood transcriptomics and sampling procedures in general. Importantly, biobanking of samples for future, unforeseen, analyses will be strongly recommended.

Considerations on clinical trial design

For good reasons, clinical trial design is quite an unadventurous field. This contrasts with, and limits the exploitation of, the dynamism of basic research[74]. In PMS it will be difficult to transform the many potentially effective compounds into therapies if our means to evaluate them in the clinical phase does not change drastically, as it happened years ago with RRMS[75-77]. We hope that our drive towards refocusing on biological effects, in conjunction with clinical and paraclinical measures, will inspire new solutions and enable stakeholders to experiment with the design of clinical trials. New designs may possibly lead to shorter trials and, at the same time, limit the risk of false negative results due to too short study durations in combination with relatively insensitive outcome measures. In this context, adaptive trial designs[78,79] (including those based on Bayesian methods) are encouraged, to help advance the field and fulfill the requirement for more informative phase 2 PMS studies. Re-estimating the sample size, using the appropriate statistical techniques as the trial advances, can help decide whether it is worth continuing the study as planned or whether an increased sample size is necessary (with all the attendant delays implied by longer recruitment times), and whether (re)-randomization schemes may be varied. Similarly, enrichment or futility designs can be considered. Importantly, these trials are compatible with factorial designs[50] and, therefore, also with the previously emphasized need for evaluating polytherapies. Recently the MS-SMART trial[80] effectively demonstrated how three well–powered phase 2 trials could take place under one protocol and be completed within a single trial time-frame. The MS-SMART trial was negative, but it somehow pioneered the development of master protocols[81] in the MS field. In future efforts, it will be important to exploit biological knowledge also to increase patients' homogeneity at baseline and to identify appropriate biomarker-drug pairs[49]. Other designs, such as cross-over, cohort comparison database studies (including propensity score matching techniques) may be considered but must be properly justified with the appropriate number of patients and power calculations. However, for phase 2 PMS studies, it is recommended to pursue active comparator-based, double-blind, randomized, controlled studies. If responder analysis is selected, it must be pre-specified. Similarly, time-to-event outcome measures may

be helpful in evaluating results of small studies with an expected large number of events (as provided by some composite measures). In addition to these general reflections, more specific considerations are listed in Box 1. More detailed recommendations for study design and conduct can be found in Supplementary information.

Interactive review process

Similarly to other funding programs (e.g. the Immune Tolerance Network), we anticipate that trials considered by the Alliance and others should incorporate interactive and iterative review processes to ensure strategic fit with stakeholder priorities and ambitions, if needed. This approach will also allow to identify key design components and operational aspects that may be introduced across the funded trials in order to achieve better coordination[49]. We envisage a two-tier process where an outline is submitted first. At this stage, proposals are reviewed for technical merit and alignment with strategic goals and for targeting the objectives of the call. Applicants whose proposals are deemed of interest, possibly showing synergies with other proposals, will be asked to submit a full application. For the best projects we foresee interactions with individual applicants to ensure precise targeting of the core objectives, to maximize the information yield, to improve complementarity and comparability as far as possible and to apply appropriate late-breaking results/techniques which may have been published after the call was finalized. Monitoring of trial execution by *ad-hoc* oversight committees will ensure that trials maintain necessary conditions to be informative[82].

Participation of People with MS (PwMS)

The participation of people with MS in trials – beyond their inclusion as subjects – is of critical importance. Special attention will also be paid to the outcomes that matter to people with MS - an increasingly important priority of which enabling initiatives including the Patient Centered Outcomes Research Institute in the United States, EUPATHI in Europe and the priority-setting exercise between researchers and the UK MS Society with the facilitation of the James Lind Alliance are notable examples. More recent work has identified eight key actions to improve the engagement of PwMS in the health-related initiatives[83]. These actions are designed to improve outcomes and optimise care by bridging knowledge gaps, removing communication barriers and ultimately building trust - so that PwMS become informed, skilled managers of their own care. Furthermore, the economic value of this involvement of and partnership with

PwMS in clinical trials is becoming evident[84] - mostly in reduced delays, more rapid enrollment, increased adherence and wider dissemination of the results. The immediate (and ready) availability of their informed perspectives during critical discussions has steered us away from flawed decisions (e.g. overly restrictive inclusion criteria that might limit learning opportunities and away from where a weak signal of success is masked or drowned out by negative results in performance tests that are unnecessarily onerous and exhaust patients). The word "informed" in the previous sentence is important - it has two meanings. Clearly, we have been informed (even educated) by the lived experience of PwMS – by guides who are intimately familiar with a territory for which a full map does not yet exist. Furthermore, as PwMS become more familiar with the methods of scientific research and with the MS research landscape in particular, they ask insightful questions and inform our priorities and research questions. If our own experience within the international Alliance is any guide, having people with MS themselves sharing the helm as we have developed our initiatives has been immensely valuable. We would strongly advocate the fullest participation of people with MS as first rank co-pilots in the design of future clinical trials.

Conclusions

There is little dispute that breakthroughs are sorely needed not only in PMS but in related neurological diseases. In this paper we have described our reflections to date as to possible reasons for this lack of success. It is intended that the ExMTs funded according to the principles outlined here will advance our knowledge of disease pathophysiology and bring us closer to developing treatments that slow or even stop progression. We look forward to expanding these and other (e.g. the creation of trial-ready cohorts) ideas and identifying ways ahead for the field to move forward and even make breakthroughs.

At present the Alliance is exploring different approaches to enable ExMTs (e.g. having a program for trials on protective or regenerative drugs for oligodendrocytes and neurons and another one for trials targeting the aberrant activation of microglia and astrocytes). Much will depend on the state of the art of scientific knowledge at the time of the final framing of the funding program, on the level of resources available, and on the public and academic feedback we will receive about our plans. Critical to this will be engagement of stakeholders in a feedback process on the concepts outlined here. We envision soliciting input through various

means including, but not limited to, conduct of DELPHI surveys among key stakeholders, and convening experts in focused workshops under the auspices of the Alliance focused workshops.

We must always be cautious of two factors that may limit fuller exploitation of this initiative. Firstly, we expect that the majority of the proposals to the Alliance will test drugs already registered for different indications, with well-known difficulties as far as the industrial development of the treatment is concerned; secondly, most of the trials with first-in-human drugs will continue to be conducted in a traditional context, with objective difficulties in maximizing the information that could be extracted, collected and disseminated during the early stages of clinical research. The Alliance is currently evaluating policies to balance the return for all the stakeholders involved with the rapid achievement of research goals. In this context, initiatives are being developed that try to implement new models of "collective-sustainability" of biomedical research[85], through the identification of common metrics that take into account the diverse claims of different stakeholders (https://www.multiact.eu/). These, together with the use of scientific approaches to share data under fair principles (e.g. http://sagebionetworks.org/) may represent ideal counterparts to foster the full exploitation of this funding program.

References

1. Stovall S. R&D cuts curb brain-drug pipeline. The Wall Street Journal. http://www.wsj.com/articles/SB10001424052748704474804576222463927753954 (2011).
2. Pankevich, D. E., Altevogt B. M., Dunlop, J., Gage, F. H. & Hyman FE. Improving and accelerating drug development for nervous system disorders. *Neuron* **84**, 546-553 (2014).
3. Giovannoni, G., Baker, D. & Schmierer, K. The problem with repurposing: is there really an alternative to Big Pharma for developing new drugs for multiple sclerosis? *Mult. Scler. Rel. Disord.* **4**, 3-5 (2015).
4. Egan, M. F. et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. *N. Engl. J. Med.* **380**, 1408-1420 (2019).
5. Henley, D. et al. Preliminary results of a trial of atabecestat in pre-clinical Alzheimer's disease. *N. Engl. J. Med.* **380**, 1483-1485 (2019).
6. Pfeifenbring, S. et al. Remyelination after cuprizone-induced demyelination is accelerated in juvenile mice. *J. Neuropathol. Exp. Neurol.* **74**, 756–766 (2015).
7. Trapp, B. D., Peterson, J., Ransohoff, R. M., Rudick, R., Mörk, S., & Bö, L. Axonal transection in the lesions of multiple sclerosis. *N. Engl. J. Med*. **338**, 278–285 (1998).
8. De Stefano, N. et al. Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes. *Neurology* **74**, 1868–1876 (2010).
9. Disanto, G. et al. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. *Ann. Neurol.* **81**, 857–870 (2017).
10. Barro, C. et al. Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. *Brain* **141**, 2382-2391 (2018).
11. University of California, San Francisco MS-EPIC Team, et al. Silent progression in disease activity-free relapsing multiple sclerosis. *Ann. Neurol.* **85**, 653-666 (2019).
12. Kappos, L. et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol.* e201568. Advance online publication. https://doi.org/10.1001/jamaneurol.2020.1568.
13. Lublin, F. D. et al. Defining the clinical course of multiple sclerosis. The 2013 revisions. *Neurology* **83**, 278-286 (2014).

14. Green, A. J. Potential benefits of early aggressive treatment of multiple sclerosis. *JAMA Neurol*. **76**, 254-256 (2019).
15. Frischer, J. M. et al. Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque. *Ann Neurol*. **78**, 710-721 (2015).
16. Jäckle, K. et al. Molecular signature of slowly expanding lesions in progressive multiple sclerosis. *Brain* **143**, 2073-2088 (2020).
17. Jia, X. et al. Genome sequencing uncovers phenocopies in primary progressive multiple sclerosis. *Ann. Neurol* **84**, 51-63 (2018).
18. Montalban, X. et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N. Engl. J. Med.* **376**, 209-220 (2017).
19. Kappos, L et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 study. *Lancet* **391**, 1263-1273 (2018).
20. Fox, R. J. et al. Setting a research agenda for progressive multiple sclerosis. The International Collaborative on Progressive MS. *Mult. Scler*. **18**, 1534-1540 (2012).
21. Deshmukh , V. A. et al. A regenerative approach to the treatment of multiple sclerosis. *Nature* **502**, 327-332 (2013).
22. Mei, F. et al. Micropillar arrays as high-throughput screening platform for therapeutics in multiple sclerosis. *Nat. Med.* **20**, 954-960 (2014).
23. Najm, F.J. et al. Drug-based modulation of endogenous stem cells promotes functional remyelination in vivo. *Nature* **522**, 216-220 (2015).
24. Eleuteri, C. et al. A staged screening of registered drugs highlights remyelinating drug candidates for clinical trials. *Sci Rep*. **7**, 45780. doi: 10.1038/srep45780 (2017).
25. Rankin, K. A. et al. Selective estrogen receptor modulators enhance CNS remyelination independent of estrogen receptors. *J. Neurosci*. **39**, 2184-2194 (2019).
26. Lubetzki, C., Zalc, B., Williams, A., Stankoff, B. Remyelination in multiple sclerosis: from basic science to clinical translation. *Lancet Neurol* **19**, 678-688 (2020).
27. DiMasi, J. A. The value of improving the productivity of the drug development process. *Pharmacoeconomics* **20,** Suppl 3, 1-10 (2002).
28. Baker, D., Lidster, K., Sottomayor, A. & Amor, S. Two years later: journals are not yet enforcing the ARRIVE guidelines on reporting standards for pre-clinical animal studies. *PLoS Biol*. **12**, e1001756. doi: 10.1371/journal.pbio.1001756 (2014).

29. Kilkenny, C., Browne, W. J., Cuthill, I. C., Emerson, M., Altmann, D. G. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol*. **8**, e1000412 doi: 10.1371/journal.pbio.10004122010 (2010).
30. Baker, D. & Amor, S. Publication guidelines for refereeing and reporting on animal use in experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* **242**, 78-83 (2012).
31. Baker, D. & Amor, S. Checklist for reporting and reviewing studies of experimental animal models of multiple sclerosis and related disorders. *Mult. Scler. Relat. Disord.* **1**, 111-115 (2012).
32. Bergman, J. et al. Intrathecal treatment of rituximab in progressive MS. *Neurology* **91**, 1893-1901 (2018).
33. Kosa, P. et al. Idebenone does not inhibit disability progression in primary progressive MS. *Mult. Scler. Relat. Disord.* https://doi.org/10.1016/j.msard.2020.102434 (2020).
34. Gnanapavan, S. et al. Biomarker report from the phase II lamotrigine trial in secondary progressive MS – Neurofilament as a surrogate of disease progression. *PLoS One* **8**, e70019. doi: 10.1371/journal/pone.0070019 (2013).
35. Green, A. J. et al. Clemastine and fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomized, controlled, double-blind, crossover trial. *Lancet* **390**, 2481-2489 (2017).
36. Komori, M. et al. Insufficient disease inhibition by intrathecal rituximab in progressive multiple sclerosis. *Ann. Clin. Transl. Neurol.* **3**, 166-179 (2016).
37. Brubaker, D. K., & Lauffenburger D. A. Translating preclinical models to humans. *Science* **367**, 742-743 (2020).
38. Brubaker, D. K. et al. An interspecies translation model implicates integrin signaling in infliximab-resistant inflammatory bowel disease. Sci. Signal. 13, eaay3258. doi:10.1126/scisignal.aay3258.
39. Kennedy, M. E. et al. The BACE1 Inhibitor Verubecestat (MK-8931) Reduces CNS β-Amyloid in Animal Models and in Alzheimer's Disease Patients. *Sci. Transl. Med.* **8,** 363ra150-363ra150 (2016).
40. Li, S., Liu ,L. & Selkoe D. Verubecestat for prodromal Alzheimer's disease. *N. Engl. J. Med.* **381,** 388-389 (2019).
41. Dubuisson, N., Puentes, F., Giovannoni, G., Gnanapavan, S. Science is 1% inspiration and 99% biomarkers. *Mult. Scler. J*. **23**, 1442-1452 (2017).

42. Franklin, R. J. M. & ffrench-Constant, C. Regenerating CNS myelin -from mechanisms to experimental medicines. *Nat. Rev. Neurosci.* **18**, 753-769 (2017).
43. Hauser, S. L. Progress in multiple sclerosis research: an example of bedside to bench. *JAMA* doi:10.1001/Jama.2020.1522 (2020).
44. FitzGerald, G. et al. The future of humans as model organisms. *Science* **361**, 552-553 (2018).
45. Klotz, L. et al. Teriflunomide treatment for multiple sclerosis modulates T cell mitochondrial respiration with affinity-dependent effects. *Sci. Trasl. Med.* **11**, eaao5563 (2019).
46. Insel, T. R. The NIMH experimental medicine initiative. *World Psychiatry* **15**, 151-153 (2015).
47. Plenge, R. M. Disciplined approach to drug discovery and early development. *Sci. Trasl. Med.* **8,** 349ps15 (2016).
48. Fang, H. et al. A genetics-led approach defines the drug target landscape of 30 immune-related traits. *Nat. Genet.* **51**, 1082-1091 (2019).
49. Woodcock, J. & LaVange , L.M. Master protocols to study multiple therapies, multiple diseases, or both. *N. Engl. J. Med.* **377,** 62-74 (2017).
50. Pardini, M., Cutter, G. & Sormani, M. P. Multiple sclerosis: clinical trial design 2019. *Curr. Opin. Neurol.* ***32***: 358-364 (2019).
51. Dickson, D. et al. The master observational trial: A new class of master protocol to advance precision medicine. *Cell* **180**, 9-14 (2020).
52. Granovetter, M. The strength of weak ties. *Am. J. Sociol.* **78**, 1360-1380 (1973).
53. Bodin, O. Collaborative environmental governance: Achieving collective action in social-ecological systems. *Science*; **357**, pii: eaan1114. doi: 10.1126/science.aan1114 (2017).
54. Cipriani, A & Barbui, C. What is a factorial trial. *Epidemiol. Psychiatr. Sci*. **22,** 213-215 (2013).
55. FDA Guidance for Industry: Co-development of two or more new investigational drugs for use in combination, June 2013.
56. Conway, D., Cohen, J,A. Combination therapy in multiple sclerosis. *Lancet Neurol*. **9**, 299-308 (2010).
57. Cohen, J. A. et al. Avonex Combination Trial in relapsing--remitting MS: rationale, design and baseline data. *Mult. Scler*. **14**, 370-382 (2008).

58. Cohen, J. A, et al. Results of the Avonex Combination Trial (ACT) in relapsing-remitting MS. *Neurology* **72**, 535-541 (2009).
59. Lublin, F. D. et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann. Neurol*. **73**, 327-340 (2013).
60. Romano, S. et al. Drug holiday of interferon beta 1b in multiple sclerosis: a pilot, randomized, single-blind study of non-inferiority. *Front. Neurol.* 10:95. doi: 10.3389/fneur.2019.00095 (2019).
61. Mandolesi, G. et al. miR-142-3p is a key regulator of IL-1beta-dependent synaptopathy in neuroinflammation. *J. Neurosci.* **37,** 546-561 (2017).
62. Inoue, H., Nagata, N., Kurokawa, H. & Yamanaka, S. iPS cells: a game changer for future medicine. *EMBO Journal* **33**, 409-417 (2014).
63. Lago, S. G. et al. Drug discovery for psychiatric disorders using high-content single-cell screening of signaling network responses ex vivo. *Sci. Adv*. **5**, eaau9093. doi: 10.1126/sciadv.aau9093 (2019).
64. Hartmann, F. J. et al. Comprehensive immune monitoring of clinical trials to advance human immunotherapy. *Cell Reports* **28**, 819-831 (2019).
65. Nelson, M.R. et al. The support of human genetic evidence for approved drug indications. *Nat. Genet*. **47**, 856-860 (2015).
66. Floris, M., Olla, S., Schlessinger, D. & Cucca, F. Genetic-driven druggable target identification and validation. *Trends Genet.* **34**, 558-570 (2018).
67. Ashton, N. J. et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. *Nat. Rev. Neurol.* **16**, 265-284 (2020).
68. Dubal, D.B., Pleasure, S.J. Neural-derived extracellular vesicles in clinical trials: message in a bottle. *JAMA Neurol*. **76**, 402-404 (2019).
69. Khramtsova, E.A., Davis, L. K. & Stranger, B. E. The role of sex in the genomics of human complex traits. *Nat. Rev. Genet.* **20**, 173-190 (2019).
70. Alroughani, R. et al. Is time to reach EDSS 6.0 faster in patients with late-inset vs young-onset multiple sclerosis? *PLoS One* **11**(11):e0165846 (2016).
71. Cinar, B. P., Yorgun, Y. G. What we learned from the history of multiple sclerosis measurement: expanded disability status scale. *Noro Psikiyatr. Ars*. **55**(Suppl 1): S69-S75 (2018).

72. Smith, K. A. et al. Comorbid disease burden among MS patients 1968-2012: a Swedish register-based cohort study. *Mult. Scler. J.* 1352458520910497. doi:10.1177/1352458520910497 (2020).
73. Giovannoni, G.et al. Is multiple sclerosis a length-dependent central axonopathy? The case for therapeutic lag and the asynchronous progressive MS hypotheses. *Mult. Scler. Relat. Disord*. **12**, 70-78 (2017).
74. Berry, D. A. The brave new world of clinical cancer research: adaptive biomarker-driven trials integrating clinical practice with clinical research. *Mol. Oncol*. **9**, 951-959 (2015).
75. McFarland, H. F. et al. Using gadolinium-enhanced magnetic resonance imaging lesions to monitor disease activity in multiple sclerosis. *Ann. Neurol*. **32**, 758-766 (1992).
76. Frank, J. A. et al. Serial contrast-enhanced magnetic resonance imaging in patients with early relapsing-remitting multiple sclerosis: implications for treatment trials. *Ann. Neurol.* **36**, Suppl: S86-90 (1994).
77. Nauta, J. J., Thompson, A. J., Barkhof, F., Miller, D.H. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis patients: statistical power of parallel-groups and crossover designs. *J. Neurol. Sci*. **122**, 6-14 (1994).
78. Pallmann, P. et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Medicine* https://doi: 10.1186/s12916-018-1017-7 (2018).
79. The Adaptive Platform Trial Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat. Rev. Drug Discov.* https://doi.org/10.1038/s41573-019-0034-3 (2019).
80. Chataway, J. et al. Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial. *Lancet Neurol*. **19**, 214-225 (2020).
81. Renfro, L. A., Sargent, D. J. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. *Ann. Oncol*. **28**, 34-43 (2017).
82. Zarin, D.A., Goodman, S.N. & Kimmelman, J. Harms from uninformative clinical trials. JAMA https://doi:10.1001/jama.2019.9892 (2019).
83. Rieckmann, P. 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. *Mult. Scler. Rel. Disord.* **19**, 153-160 (2018).

84. Levitan, B. et al. Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project. *Therapeutic Innovation & Regulatory Science* doi:10.1177/2168479017716715201 7.
85. Salvetti, M. et al. Steps towards collective sustainability in biomedical research. *Trends Mol. Med.* **24**, 429-432 (2018).
86. Solaro, C, et al. Box and block test, hand grip strength and nine-hole peg test: correlations between three upper limb objective measures in multiple sclerosis. *Eur. J. Neurol*. 10.1111/ene.14427. doi:10.1111/ene.14427 (2020).
87. Newsome, S. D.et al. Longitudinal assessment of hand function in individuals with multiple sclerosis. *Mult. Scler. Relat. Disord*. **32**, 107-113 (2019).
88. Kapoor, R. et al. Serum neurofilament light as a biomarker in progressive multiple sclerosis. *Neurology* **95**, 1-9. doi:10.1212/WNL.0000000000010346 (2020).
89. Williams, T., Zetterberg, H., Chataway, J. Neurofilaments in multiple sclerosis. A systematic review. *J. Neurol.* doi: 10.1007/s00415-020-09917-x (2020).
90. Amiri, H. et al. Urgent challenger in quantification and interpretation of brain grey matter atrophy in individual MS patients using MRI. *Neuroimage Clin.* **19**, 466-475 (2020).
91. Leocani, L., Guerrieri, S., Comi, G. Visual evoked potentials as a biomarker in multiple sclerosis and associated optic neuritis. *J. Neuroophtalmol.* **38**, 350-357 (2018).
92. Cruz-Herranz, A. et al. The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. *Neurology* **86**, 2303-2309 (2016).

Box 1. Considerations for study design

General:

- Use biological rationale and clinical outcomes to seek proof of concept in Phase 2
- Document pharmacology and toxicology testing even for repurposed drugs
- Follow good clinical practices and ethical principles
- Justify prohibited and permitted medications
- Describe preparation, handling and accountability of investigational product
- Explain dose selection rationale, emergency unblinding scenarios, discontinuation of study drug, contraception measures, plans for drug re-challenge and AE reporting
- Clarify randomization measures and avoid stratification by too many variables
- Pre-specify statistical handling of intercurrent events, and covariate adjustments
- Collect and store samples for later analyses under standardized methods
- Describe use of data registries or historical cohorts for comparison

Specific for PMS:

- Use eligibility criteria seeking homogeneity
- Aim to reflect clinical characteristics of a real-world PMS population
- Provide proper justification when selecting a restricted population range
- Consider combination with an immunosuppressant, or longer study duration, when evaluating presumed neuroprotective compounds
- Expect that shorter-duration Phase 2 PMS designs will provide statistical trends
- For designs that combine anti-inflammatory with neuroprotective agents, include biologic measures relevant to each mechanism
- Factor in the impact of ageing, disease duration and stage of disease on motor strength, gait, hand coordination, and cognition, when selecting quality of life measures
- Consider specific measures for patients with advanced disability, such as cognition and hand function outcomes
- Besides agents that directly target axonal injury, drugs that target residential compartmentalized inflammation in lymphoid follicles can be studied

- The use of proper composite clinical outcome measures may help to increase power. Consider ancillary testing with electrophysiologic methods, technology-assisted measures for mobility or vision
- Assays of serum neurofilaments and estimates of brain atrophy are encouraged, with the understanding that much remains to be learned about their predictive and prognostic value
- Seek progressive MS patient feedback in the study design elements
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Figure legends

Fig. 1 **Balancing innovation with comparability.** Innovation often implies breaking with conventional thinking and established norms. This may be detrimental for the comparability of the results among different trials. To preserve both, we suggest some key common features and an interactive-iterative review process to identify key design components and operational aspects that may be introduced across the funded trials in order to achieve better coordination.

Fig. 2 **Markers of biological and paraclinical efficacy.** Measures of treatment effects are listed according to putative target. 11C-PIB, 11C Pittsburgh compound B; 14-3-3, 14-3-3 proteins; NOGO, neurite outgrowth inhibitor-A; BDNF, brain-derived neurotrophic factor; CHI3L1, chitinase-3-like protein 1; CHI3L2, chitinase-3-like protein 2; CHIT1, chitinase 1; FABP3, fatty acid binding protein 3; GAP-43, growth associated protein 43; GFAP, glial fibrillary acid protein; IL-1b, interleukin-1b; IL-1ra, interleukin-1 receptor antagonist; MBP, myelin basic protein; MEP, motor evoked potentials; MRI, magnetic resonance imaging; NAA, N-acetylaspartate; NfH, neurofilament heavy chain; NfL, neurofilament light chain; NGF, nerve growth factor; Nox, nitric oxide; OCT, optical coherence tomography; PET, positron emission tomography; SEP, somatosensory evoked potentials; sNCAM, soluble neural cell adhesion molecule; Tau, tau protein; TNFa, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; VEP, visual evoked potentials.

Fig. 3 **Proposed set of core measures.** Recommended measures to obtain information on clinical, paraclinical and immunological effects. Immune treatment response markers are presented for trials that include anti-CD20 therapies and are suggested based on their use in previous exploratory trials with such treatments[36]. Therapies targeting other arms of the immune response should use different markers. Concerning the suggested clinical measures, besides EDSS it is important to consider specific functions (i.e. arm/hand function), particularly in severely disabled patients[86,87]. Peripheral transcriptomics is also recommended for non-hypothesis driven measurements of the biological effects. With respect to paraclinical measures, serum NfL is a plausible marker of neurodegeneration. Its limitations, including the difficulty of teasing apart the effects of disease activity from those of disease progression, are discussed in references 88 and 89. More details on the rationale and challenges in the use of brain atrophy, VEP. and OCT can be found in references 90-92. More technical information is in Supplementary tables 2 and 3. BAFF,

B-cell activating factor; CXCL13, C-X-C Motif Chemokine Ligand 13; EDSS, Expanded Disability Status Scale; NfL, neurofilament light chain; OCT, optical coherence tomography; sCD14, soluble CD14; sCD21, soluble CD21; sCD27, soluble CD27; VEP, visual evoked potentials.

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Competing interests
The authors declare no competing interests.