Aus dem Neurowissenschaftlichen Forschungszentrum
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

# Change Drivers within the Translational Ecosystem for the Benefit of Society

zur Erlangung des akademischen Grades
Doctor rerum medicinalium (Dr. rer. medic.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von
Sinje Gehr
aus Berlin

Datum der Promotion: 17.09.2021

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# 1 SYNOPSIS

## 1.1 Abstract

The translation of biomedical research into innovations that positively impact patient care is fundamentally important for the wellbeing of society. First and foremost, academic institutions are powerhouses of biomedical research, but insufficient when it comes to exploiting research results into clinical solutions. This raises questions regarding the underlying causes of this inefficacy and the inevitable need for a cultural change within the translational ecosystem. The goal of this doctoral thesis is to better understand the opportunities and obstacles of biomedical innovation notably within academic institutions and to identify concepts to enhance the translation of transformative ideas to benefit society. Hence, three relevant enablers of the translational ecosystem are explored: the institutions, the users and the actors. First, translational initiatives that change culture towards a translational mindset within the institutions were analyzed and described. Second, with regard to the users, a review of clinical phase III trials in Multiple Sclerosis revealed that patient needs are widely disregarded including deficits in Patient Reported Outcome Measures, reasonable primary endpoints, trial durations and comparators. Third, the actors, namely the academic offspring as future innovators, were in focus. A survey on academic career development programs demonstrated that the impact of universities in helping to create robust, translational career paths remains low and extensively neglects job opportunities outside academia. Finally, this thesis provides recommendations for cultural changes within the translational ecosystem by creating translational change drivers in order to improve biomedical innovations for the benefit of society.

## 1.2 Zusammenfassung

Die Translation biomedizinischer Forschung in Innovationen, die sich positiv auf die Patientenversorgung auswirken, ist für das Wohl der Gesellschaft von grundlegender Bedeutung. Akademische Einrichtungen sind zwar Zentren biomedizinischer Forschung, es gelingt ihnen jedoch nur unzureichend, die Forschungsergebnisse in klinische Lösungen zu translatieren. Dies wirft die Frage nach den Ursachen dieser Ineffizienz und der zwangsläufigen Notwendigkeit eines kulturellen Wandels innerhalb des translationalen Ökosystems auf. Ziel dieser Doktorarbeit ist es daher, die Chancen und Hindernisse biomedizinischer Innovationen insbesondere in akademischen Einrichtungen besser zu verstehen und Konzepte zu identifizieren, die die Translation transformativer Ideen zum Nutzen der Gesellschaft verbessern. Hierfür wurden drei aktive Gruppen innerhalb des translationalen Ökosystems untersucht: die Institutionen, die Nutzer und die Akteure. Zunächst wurden translationale Initiativen, die einen Kulturwandel hin zu einem translationalen Denken innerhalb der Institutionen anstoßen, untersucht. Zweitens ergab eine Untersuchung klinischer Phase-III-Studien in der Multiplen Sklerose, dass die Bedürfnisse der Nutzer, hier: der Patienten, weitgehend außer Acht gelassen wurden. Beispiel hierfür waren Defizite bei patientenberichteten oder angemessenen primären Endpunkten, Studiendauer und Komparatoren. Drittens standen die Akteure im Mittelpunkt, insbesondere der akademische Nachwuchs als künftige Innovatoren. Eine Umfrage zu akademischen Karriereentwicklungsprogrammen hat gezeigt, dass Universitäten nicht auf die Gestaltung robuster, translationaler Karrierewege fokussieren und Karrierepfade außerhalb der akademischen Welt weitgehend vernachlässigen.

Schlussendlich münden die Ergebnisse dieser Dissertation in konkreten Empfehlungen, wie kultureller Wandel im translationalen Ökosystem vorangetrieben werden kann, um die Translation biomedizinischer Forschung zum Nutzen der Gesellschaft zu fördern.

## 1.3 Introduction

Society is currently experiencing a medical renaissance as scientific innovation opens tremendous opportunities towards the creation of novel treatments and diagnostics of a broad range of diseases. Many of these are emerging from advances in molecular medicine, gene therapy, CRISPR/Cas9 genome editing, Advanced Therapy Medicinal Products, artificial intelligence and digitalization of medical data, leading to impactful and long-term changes in the quality of life of patients. Unfortunately, the expenses associated with the development of many of these new treatments and tools are enormous, limiting their broad implementation.

Many of these expenses are driven by the high cost of investments in research and development (R&D) as well as clinical trials of such new technologies. For example, Prasad and Mailankody analyzed 10 recently approved cancer drugs and found that the median time for drug development is ~7.3 years with the total revenue from sales reaching 9.3 times the amount of the overall R&D spending (1) (2). These figures from the oncological field illustrate, that while drug development as one area of biomedical innovation is risky, it can be highly profitable for pharmaceutical industries.

Sticking to the example of drug development, for “one hundred golden years” (3) pharmaceutical companies have been reliably responsible for the discovery and development of many new medical entities. However, these golden years are coming to an end as patents expire and the pharmaceutical industry fears a decline in revenues. For instance, 59% (N 34) of the 2018 U.S. Food and Drug Administration approvals are orphan drugs (4) with low predicted annual sales by their very nature. In the course of this trend, pharmaceutical industries in the more recent past have shifted financial resources from incalculable drug discovery to predictable late clinical development (3). Thus, much of pharma has decreased its venturesome investments in R&D and offloaded its expenses to less profitable rare diseases (5). An important question is if pharma is restricting its R&D efforts, who is driving forward the core research on all of these new innovative therapies? A big part of the answer is academia, as the pharmaceutical industry as well as society has passed over the responsibility, burden and risk of drug discovery to academic institutions (6), a

solution that is designed to place the cost of R&D on governments, thus solving industry`s pipeline problem.

Fortunately, academic institutions are powerhouses of biomedical research. Since the Bayh-Dole act in 1980[1] (7), public funded discoveries (8) can and should be patented. Although this led to a transformation that encouraged institutions to find applications for their research, outside of engineering few academic ideas ever reach the market (9). The hurdles associated with technology transfer are especially applicable to the complex biomedical research (10) as well as the tricky approval process of drug development. There is broad consensus that universities should capitalize on their tremendous Intellectual Property (IP), which is a function not only of significant federal funding, but a mandate by the National Institute of Health (NIH) who makes translational research a priority in the USA (11). Patient Organizations are also incredible drivers of this change in mindset. Academics and clinicians worldwide have embraced the opportunity to take on the social responsibility of biomedical translation (9), especially at the front end, and have been experimenting with different formats such as industry-academic partnerships (12), academic incubators or translational initiatives (13) to create effective pipelines for their innovative solutions. This new mindset has placed academia at the center of translational efforts to move basic biomedical research discoveries into fundamental changes in clinical practice, while harnessing clinical observations to enhance patients` quality of life in the long run.

### 1.3.1 Problem Formulation

"Culture strangles innovation in the crib" (14). Why are some institutions more innovative than others? What conditions are necessary to foster and sustain the development of innovative solutions that ultimately go to market and make a positive

[1] The Bayh Dole Act became a model for further countries such as Germany, where the „Hochschullehrerprivileg" guaranteed the full exploitation of an invention to the researcher of an university till this practice was replaced by the „Arbeitnehmererfindungsgesetz" in 2002.

impact on society? Which roles are played by different stakeholders, such as patients and scientists, in translational circles? Arguably, the culture and mindset of academic institutions plays a big role in how effectively they are able to translate innovations. It takes a dedicated commitment by the academic leadership of each institution as well as incentives that encourage faculty and students to apply their knowledge. Too often, these features are lacking and the translational output remains low. Thus it will take high academic aspiration to meet future unmet medical needs (15). Yet too often, the desire to translate is offset by the complex requirements and knowledge necessary to develop innovative solutions. Moreover, the culture within academia is largely not oriented towards translation, creating a high path-dependence (16), in which faculty are more interested in knowledge for knowledge's sake, honors associated with their research and the impact factor of their publications, than they are in finding application for that knowledge or embracing and fostering an entrepreneurial mindset. This melange slows the translation of basic research into commercialization. Thus, a major challenge for many of our academic institutions is how to change both the culture within these communities and the mindset of individuals to see the opportunities, while accepting the associated risks. There is also a dire need for academic institutions and their faculty to better understand each step in the translational cycle, how industry functions, and appropriate strategies for commercialization. Ultimately, such knowledge will transform ideas into products that can positively impact patient care (17).

### 1.3.2 Research Goal

The goal of this doctoral thesis is to better understand the opportunities and obstacles of biomedical innovation notably within academic institutions and to identify concepts to enhance the translation of transformative ideas to benefit patients.

### 1.3.3 Conceptional considerations

For the purpose of this thesis the following terms are defined below:

The term **"Innovation"** is described in multiple ways (16), but when it comes to innovation in life sciences, Roberts (17) defines it like that: invention + exploitation = innovation, yet simpler: *"turning a good idea into a practical solution"* (18). In the context of this doctoral thesis these definitions of innovation shall be amended by adding: … *that is fundamentally important for the wellbeing of society.*

The term "**Translational Research**" emerged in biomedicine at the turn of the millennium and describes the bridging from bench to bedside and vice versa to translate *"the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease* (19)." According to the NIH Roadmap, the stages of translation include four major steps from bench to society: translating basic research in early phase clinical trials to humans (T1), to patients in clinical trials (T2), to actual clinical practice (T3), and finally to society for public health (T4) by carrying scientific insights into people's everyday lives (20).

### 1.3.4 Concept, objectives and hypotheses of the doctoral thesis

Innovation within Biomedicine alongside the translational steps from T1 to T4 is a fusion between stakeholders in a complex translational medicines ecosystem (21). This thesis is designed to explore different areas that drive the translation of ideas to solutions. This includes efforts to better understand the status quo of biomedical translation, the associated problems, and possible solutions. Conceptually, this should help academic institutions translate basic research into clinical practice for the benefit of society. The main enablers of biomedical translation are the institutions, the users and the actors (fig. 1) within a complex regulatory and legislative environment.

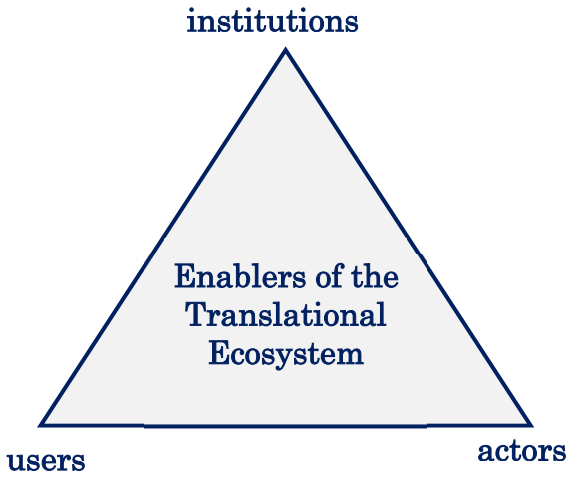


Figure 1: Enablers of the Translational Ecosystem (compiled by the author)

First, the **institutions** are complex and include academic institutions, research facilities, industries from Big Pharma to the lively startup community and authorities like the U.S. Food and Drug Administration or the European Medicines Agency, just to name a few. Understanding these institutions helps us to understand the interaction of participants as well as chances and hurdles of translation. Several open questions include: What is the idea of translation? Why is it so difficult? How are institutions operating? What is the role of academia? Do initiatives already exist, that successfully bridge the valley(s) of death? How do they succeed? What can be learned from them? The author explores the hypothesis that the failure to translate academic innovation into new clinical practice is due to a variety of challenges in academia and industry, including a non-translational mindset, albeit with geographical and cultural differences, within academia.

Second, the **users**, which are patients and their relatives, patient organizations as well as customers, prescribing physicians and healthcare workers have become strong enablers for translation as the need for innovative therapies, devices and medical guidelines is pressing. One facet of this thesis is to understand the role of patient centricity in this complex endeavor. Key questions are: How are patient populations involved? Do clinical trials benefit them, not only medically, but also from their own point of view? Do patients have a relevant voice, especially when it comes to clinical trials? Are Patient Reported Outcomes considered in drug development? This leads to the hypothesis that patient centricity in Multiple Sclerosis phase-III clinical trials as an example is low, reducing its usefulness to inform patient care.

Third, the **actors** such as scientists, clinicians, politicians and manufacturers make huge efforts in fostering translation every day. Hence, do academic institutions have the academic biomedical offspring in focus for these translational endeavors? Do young scientists consider the idea of translation as important to their careers? How well prepared are they for translation? And, bridging back to the institutions: do academic institutions take on the responsibility to prepare their young scientists for translation associated careers? These reflections directly led to the hypothesis that

most academic offspring lack sufficient career development opportunities that would ultimately benefit translation within the life sciences.

To drive translation, we need the three main enablers of the translational ecosystem to come together: the institutions, the users and the actors. This systemic approach aims to look at translation from different angles and therefore find systemic solutions. Conceptually this should notably help academic institutions to more effectively translate basic research into clinical practice. The research areas compiled in this doctoral thesis emerge from 3 associated academic working groups (table 1).

| | Publication | Associated Academic Working Group |
|---|---|---|
| Institutions | Gehr S, Garner CC. Rescuing the Lost in Translation. Cell. 2016;165(4):765-70. | SPARK Berlin, Berlin Institute of Health (BIH) |
| Users | **Chosen TOP Journal Publication**<br>Gehr S, Kaiser T, Kreutz R, Ludwig WD, Paul F. Suggestions for improving the design of clinical trials in multiple sclerosis-results of a systematic analysis of completed phase III trials. EPMA J. 2019;10(4):425-36. | The Charité Initiative for MS Patients, Charité Universitätsmedizin Berlin |
| Actors | Gehr S, Garner CC, Kleinhans KN. Translating academic careers into industry healthcare professions. Nature Biotechnology. 2020;38(6):758-63. | The Career Development Initiative, Einstein Center for Neurosciences |

Table 1: Publications and associated academic working groups

Above all, the central hypothesis of this doctoral thesis is that the main enablers of the translational ecosystem, namely the institutions, the users and the actors have to activate a cultural shift towards translation in order to foster biomedical innovations for the benefit of society.

## 1.4 Materials and methods

In order to explore the translational ecosystem the biomedical translational literature was carefully reviewed in the PubMed-database (22) at an international level.

For the purpose of exploring the **institutions,** the features of successful academic translational programs as well as the inherent obstacles in phase T1 (translation to humans), specifically, the translation of basic research into early phase human clinical trials, were evaluated (13). Based on the white paper by Duda et. al: "Changing the Mindset in Life Science Toward Translation: A Consensus" (23), the author focused her initial efforts towards understanding the process of translation, as well as on finding answers to the question of how to bridge the gap between industry and academia. In order to find answers to overcome the hurdles of translation, a review of academic translational programs was set up and evaluated for features that were either enabling or limiting. In addition to translational programs mentioned in different publications, the author conducted a desktop search using the keywords *translational program; translational initiative; academic + translational; industry + translational (*with most recent access on 23.09.2015) to detect further translational programs. The following characteristics of the translational programs were analyzed and described: mission, education (project-oriented vs. translational university courses), project-oriented mentoring, project-oriented advice, entrepreneurial effort, aim for cultural change, industry involvement, project- oriented funding, access to facilities, success rate and organizer (University, Government, Biopharma Company, Interface Company) (13).

Complementarily, the author explored the role of patients as a key **user** group within the translational ecosystem (24). Therefore, together with the Independent Institute for Quality and Efficiency in Health Care and the Drug Commission of the German Medical Association, a research project was set up within the "Charité Initiative for MS Patients" (25). Primarily focusing on phase T2 (translation to patients), the study paid attention to the quality of clinical trials in Multiple Sclerosis (MS) with the goal to answer the following question: how can the perspectives of patients be given more

consideration in clinical trials? Therefore, the primary and secondary endpoints of pivotal phase III trials in MS were explored. The following characteristics were investigated: duration of phase III trials, sample size, comparator drugs, patient reported as well as magnetic resonance imaging outcome measures. The literature search was based on a review published by Torkildsen et al. (26). This search was complemented by the author's own search mainly using the PubMed-database for published and completed phase III trials in MS (inclusion criteria) (24)[2].

Finally, it was crucial to explore the role of the **actors**, namely the academic offspring, in creating a new generation of bio-innovators who would work within different phases of the translational pipeline, e.g. T1 (translation to humans), T2 (translation to patients), T3 (translation to practice) and finally to T4 (translation to population health). There are major challenges in identifying and recruiting biomedical talent into the translational process. For example, how can we ensure talented graduate students, postdoctoral fellows and medical students enter translational fields? Within the context of this thesis, the endeavor focused on the translational mindset of life science students and the role of universities in helping create robust career paths in the life sciences. This was designed to understand how biomedical students identify and choose high impact jobs, which career they plan in the future and how prepared they feel for their future careers. Therefore, an online questionnaire was developed and underwent pretesting with members of the Einstein Career Development Initiative (34). The mixed methods–questionnaire contained 26 questions in English with several answer opportunities in alphabetical order. Due to reasons of data privacy the questionnaire was created on the academic portal www.questionpro.com and sent out by E-Mail to highly innovative communities such as Berlin, Stockholm, Oslo, Silicon Valley and Tel Aviv. Participating biomedical students could submit their responses over a nine-month period (January 25th to October, 25th 2018). To explore career opportunities within the Biotech Sector, the research project was mentored by a medtech investment expert (34).

[2] See supplement Chapter 3: Printed Copy of the Top Journal Publication

## 1.5 Results

In order to understand the challenges of translation and to develop solutions to improve translation within the life sciences, the complex translational ecosystem was explored by first analyzing the translational literature. The main goal here was to understand the iterative translational process itself and the underlying associated chances and obstacles. Looking at the **institutions,** it was ascertained that the culture in academia has changed from focusing on acquiring basic knowledge towards a more applied approach over the last 20 years. A main research finding was that academia is under immense pressure to translate research findings. However, the academic culture itself, as well as cultural differences (23) between translational ecosystems, negatively contribute to the low success rate of translation, commonly described as the "valley of death". In truth, there are multiple valleys of death along the translational pipeline. Two prominent examples include a gap between scientific discovery and out-licensing and a second one between in-licensing and the trials phase (27). Below, the main change drivers that could bridge these deadly valleys within the translational ecosystem are discussed from the perspective of the institutions, the users and the actors.

The research on translational programs resulted in a review of 27 such programs (13). These could be divided into 2 major groups: a) project–oriented educational programs (n=11) and b) translational local networks / translational institutes with a technology transfer office in the center (n=16).

The author detected joint characteristics for project-oriented programs, such as Harvard Catalyst, US (28); the German Accelerator in Boston, US (29) and several SPARK programs, summed up under the roof of SPARK Global (30). Most of these programs emerged from small academic grassroots initiatives and therefore access to university facilities is taken for granted. Programs in this group focused on cultural change within academia. These programs also supported a young, entrepreneurial start-up-like approach and offered individual project-oriented mentoring. In general, the success parameters were not well delineated.

Translational programs in the second group included local networks or translational institutes with technology transfer offices. Most of these programs were comprised of large regional or national networks, mainly driven by Universities and some by Government on a higher, broader level like SciLifeLab, Sweden (31), Max-Planck-Innovation, Germany (32) or TIAP, Canada (33). Most of these networks are centered on a technology-transfer office offering access to facilities and regional industry partners and focus on cultural change. Here, individual project mentoring and entrepreneurial education were largely missing. These networks primarily offered university courses on biomedical translation, such as bioinformatics, but no project–oriented education, nor entrepreneurship course work. In general, both groups were supported by government programs. The biggest outside player for these programs was industry, who naturally benefits from university-based innovations (13).

Complementary to the institutions, it was relevant to understand the role of the most important **user** group of translation: the patients. Here, a review of 29 pivotal phase III – trials in Multiple Sclerosis showed a deficit on patient needs, as no MS trials investigated patient-reported outcomes systemically, although patients do value subjective restrictions such as fatigue, visual function or depression over somatic functions. In general, the trial design focused mainly on relapse rate and disability progression as primary endpoints. In addition, technical endpoints (MRI) were also used in many of the trials. Furthermore, the trial duration lasted approximately 24 months. It could be shown that the number of recruited participants increased significantly over the course of the last 20 years e.g. from 372 patients (Interferon Beta 1b, MSSG trial) to 1841 patients (Daclizumab, DECIDE trial) (24)[3].

Besides focusing on the institutions and the users of translation, it is relevant to get an understanding of the career readiness of future **actors** of the translational ecosystem: the academic offspring in biomedicine. This talented pool is anticipated to become future innovators, turning biomedical findings into practice as well as translating patient needs back to laboratories. Three-Hundred-Fourteen national

[3] See supplement Chapter 3: Printed Copy of the Top Journal Publication

and international biomedical students participated in a questionnaire on career development in the life sciences (34). 66% of those surveyed were female, 33% male with life science backgrounds e.g. biologists (n=160), neuroscientists (n=136), biochemists (n=124).

The data collected revealed that in addition to education (93%), the academic offspring anticipated that training at their academic institutions would prepare them for their careers (82%). Forty-six percent took the idea of translation into their job considerations. Thirteen percent also received teaching of entrepreneurial skills. Intriguingly, while 74% received advice on academic careers, only 18% received advice on a career in industry or in the medical sector (14%). Of note, only 37% planned an academic career. It could be demonstrated that the impact of universities` career development offices is quite low with half of the survey group (52%) being unaware of the existence of a career development office at their institution or of any offered career development programs at their university (34).

## 1.6 Discussion

The central goal of this doctoral thesis was to gain insights into the opportunities and obstacles for biomedical innovation, and notably how academic institutions can most effectively foster the development of transformative ideas that ultimately benefit patients. This was accomplished by examining the main enablers within the translational ecosystem and their interactions.

With regard to the **institutions,** the hypothesis was that the failure to translate academic innovation into new clinical practice is due to a variety of challenges in academia and industry, including a non-translational mindset, albeit with geographical and cultural differences, within academia (13).

It could be demonstrated that there are major hurdles along T1 to T4 (20). The data also revealed that translational initiatives popped up worldwide to overcome the described hurdles over the last decade and are mainly driven by academic

institutions. Many of these endeavors identified similar needs within their ecosystems, such as finding solutions that promote cultural changes within each academic institution that supports translation. Although universities are hotspots of biomedical research, they are often not experienced in developing ideas into solutions or products that ultimately change clinical practice. Moreover, most academic cultures do not incentivize translation enough, nor enable idea development or their patenting. The research on translational programs revealed that the future success of translational programs within academia will depend on targeted project funding, educational entrepreneurial programs, mentoring, and advice from industry as well as access to infrastructure and support mechanisms in order to bridge the two main valleys of death to overcome the hurdles of translation and create an entrepreneurial mindset. Here it could be seen that key performance indicators that measure successful translation alongside T1 to T4 are widely missing. It is thus highly recommended that more academic institutions work towards the development of future transparent and comparable programs that change path-dependent academic organizational cultures towards ones that truly benefit society (13).

Thinking about society, one of the most important **user** groups within the translational ecosystem is patients. Patient organizations and especially their inherent influence on government have become important drivers of translation. Despite the vital role of patients, it could be shown by the example of Multiple Sclerosis that patient needs are widely disregarded in the conduct of clinical phase III trials (24). This leads to deficits in Patient Reported Outcome Measures (PROMs), as well as ignorance of reasonable primary endpoints, trial durations and comparators. Therefore, the hypothesis that patient centricity in Multiple Sclerosis phase-III clinical trials as an example is low, reducing its usefulness to inform patient care, was verified.

This is frustrating, especially as the European Medicines Agency emphasizes PROMs and the meaning of considering quality of life–aspects in clinical trials (35). This recommendation is supported by similar studies such as (36) (37) (38) and summed up by the Berlin Institute of Health showing the request by patient groups to have a

bigger say (39). The initial review on phase III trials in Multiple Sclerosis should be consequently updated as well as followed by comparable reviews in other fields (24).

**Actors** within the translational ecosystem, namely the academic offspring, are seldom in focus with regard to their contribution to translation. Here, academic culture is often misaligned with translation, due to inherent directives towards academic career paths, which lack entrepreneurial culture. A cultural clash could be demonstrated between traditional career expectations and much needed translational, entrepreneurial skills as a requirement for future innovations. One reason could be a strong path dependence as academics still emphasize academic careers, something they are most familiar with. It could be also shown that industry is becoming highly aware of the importance of supporting young talent as a key for future pipeline stability (40). The hypothesis that most academic offspring lack sufficient career development opportunities that would ultimately benefit translation within the life sciences could be demonstrated. The initial study on career development in life sciences should be followed by a more comprehensive international investigation to help identify new strategies to promote career development programs for this amazing talent pool (34).

Accordingly, the central hypothesis that the main enablers of the translational ecosystem, namely the institutions, the users and the actors, have to activate a cultural shift towards translation in order to foster biomedical innovations for the benefit of society could be confirmed. It became evident that a translational mindset within the institutions, particularly academia, would drive innovation enormously. These findings support the following key message of Duda et. al.: *"improved translation of basic research to clinical benefit can happen only with widespread changes in mindset* (23)*"*. Moreover, a shift towards patient centricity, placing the users in the focus of attention, is desperately needed. Finally, the actors of the translational ecosystem themselves deserve deliberate career development programs that will ensure that this talent pool remains focused on translation even after they leave their academic institutions. As discussed by Barnett, innovation can foster cultural change (41). Within the described studies, it became equally obvious that

society needs a collection of integrated drivers to create dynamic and effective translational ecosystems that include: a) an institutional mindset that fosters translation, b) a culture that pays attention to end-users, i.e. patients, when developing specific therapies and c) a recognition that future biomedical innovations are in the hands of our young talented scientists and clinicians, who need support as they transition into future biomedical careers. Taken together, the data collected within this thesis is aligned with the following recommendations that should further enhance biomedical innovation for the benefit of society:

## TRANSLATIONAL CHANGE DRIVERS

**First, foster a cultural change within the academic institutions:**

(01) Activate a cultural shift within academia towards innovation by making translation an institutional goal. Encourage industry to do more.
(02) Establish strong public- private partnerships to overcome intra-organizational gaps.
(03) Develop objectives and key results that measure successful translation alongside T1 to T4.
(04) Find tailored solutions for each community as there is no royal road.

**Second, involve the Users:**

(05) Listen to patient recommendations and take their perspectives seriously, especially when it comes to clinical trials. Measure reasonable primary endpoints, trial durations and comparators.
(06) Focus on PROMs, as they have the potential to enhance cultural change towards patient - centered therapies.

**Third, empower the Actors:**

(07) Train graduate students about translation and teach entrepreneurship from the first semester on.
(08) Learn from industry and government and develop bilateral internship programs.
(09) Create active, tailored career development programs for biomedical students based on future employee's needs.
(10) Take advantage of individual career development plans. Incentivize translation and support non-traditional Career Paths.
(11) Foster a diverse community.
(12) Enrich the general curriculum with job skills such as business skills, IP, communication skills.

Table 2: Translational Change Drivers (compiled by the author)

## 1.7 Index

### 1.7.1 References


1. Prasad V, Mailankody S. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. JAMA Intern Med. 2017;177(11):1569-75.
2. Goozner M. A Much-Needed Corrective on Drug Development Costs. JAMA Intern Med. 2017;177(11):1575-6.
3. Munos BH, Chin WW. How to revive breakthrough innovation in the pharmaceutical industry. Science translational medicine. 2011;3(89):89cm16.
4. Mullard A. 2018 FDA drug approvals. Nature reviews Drug discovery. 2019;18(2):85-9.
5. Parrish MC, Tan YJ, Grimes KV, Mochly-Rosen D. Surviving in the Valley of Death: Opportunities and Challenges in Translating Academic Drug Discoveries. Annual review of pharmacology and toxicology. 2019;59:405-21.
6. Zerhouni EA. Translational and clinical science--time for a new vision. N Engl J Med. 2005;353(15):1621-3.
7. Tahmooresnejad L, Beaudry C. Do patents of academic funded researchers enjoy a longer life? A study of patent renewal decisions. PLoS One. 2018;13(8):e0202643.
8. Fang FC, Casadevall A. Lost in translation--basic science in the era of translational research. Infection and immunity. 2010;78(2):563-6.
9. Mochly-Rosen DG, Kevin A Practical Guide to Drug Development in Academia. The SPARK Approach. 2014.
10. Perry CJ, Lawrence AJ. Hurdles in Basic Science Translation. Frontiers in pharmacology. 2017;8:478.
11. Woolf SH. The meaning of translational research and why it matters. Jama. 2008;299(2):211-3.
12. Chakravarthy R, Cotter K, DiMasi J, Milne CP, Wendel N. Public- and Private-Sector Contributions to the Research and Development of the Most Transformational Drugs in the Past 25 Years: From Theory to Therapy. Therapeutic innovation & regulatory science. 2016;50(6):759-68.
13. Gehr S, Garner CC. Rescuing the Lost in Translation. Cell. 2016;165(4):765-70.
14. Borgstrom E. Being Mortal: Illness, Medicine, and What Matters in the End, by Atul Gawande. Anthropol Med. 2015;22(3):333-5.
15. Vennemann M, Ruland V, Kruse JP, Harloff C, Trubel H, Gielen-Haertwig H. Future unmet medical need as a guiding principle for pharmaceutical R&D. Drug discovery today. 2019.
16. Goswami S, Mathew M. Definition of Innovation Revisited: an empirical study on indian information technology industry. International Journal of Innovation Management. 2005;09(03):371-83.
17. Roberts EB. Managing Invention and Innovation. Research-Technology Management. 2007;50(1):35-54.
18. Belloso WH. On Innovation. Therapeutic innovation & regulatory science. 2020.

19. Fontanarosa PB, DeAngelis CD. Basic science and translational research in JAMA. Jama. 2002;287(13):1728.
20. Kon AA. The Clinical and Translational Science Award (CTSA) Consortium and the translational research model. Am J Bioeth. 2008;8(3):58-60; discussion W1-3.
21. Mahant V. Translational medicines "Ecosystem". J Transl Med. 2020;18(1):158.
22. https://pubmed.ncbi.nlm.nih.gov/ (Retrieved: May 16, 2020).
23. Duda GN, Grainger DW, Frisk ML, Bruckner-Tuderman L, Carr A, Dirnagl U, et al. Changing the mindset in life sciences toward translation: a consensus. Science translational medicine. 2014;6(264):264cm12.
24. Gehr S, Kaiser T, Kreutz R, Ludwig WD, Paul F. Suggestions for improving the design of clinical trials in multiple sclerosis-results of a systematic analysis of completed phase III trials. Epma j. 2019;10(4):425-36.
25. https://www.bihealth.org/en/research/quest-center/mission-approaches/stakeholder-engagement/stakeholder-engagement-in-the-bih-research-area/the-charite-ms-initiative/ (Retrieved: May 05, 2020).
26. Torkildsen O, Myhr KM, Bo L. Disease-modifying treatments for multiple sclerosis - a review of approved medications. Eur J Neurol. 2016;23 Suppl 1:18-27.
27. Fernandez-Moure JS. Lost in Translation: The Gap in Scientific Advancements and Clinical Application. Front Bioeng Biotechnol. 2016;4:43.
28. https://catalyst.harvard.edu/about/ (Retrieved: May 03, 2020).
29. https://www.germanaccelerator.com/our-programs/life-sciences/ (Retrieved: May 20, 2020).
30. https://sparkglobal.io/ (Retrieved: May 22, 2020).
31. https://www.scilifelab.se/ (Retrieved: May 05, 2020).
32. https://www.max-planck-innovation.com/ (Retrieved: June 06, 2020).
33. https://tiap.ca/ (Retrieved: May 16, 2020).
34. Gehr S, Garner CC, Kleinhans KN. Translating academic careers into industry healthcare professions. Nature Biotechnology. 2020;38(6):758-63.
35. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-multiple-sclerosis_en-0.pdf (Retrieved: June 7, 2020).
36. Sacristán JA, Aguarón A, Avendaño-Solá C, Garrido P, Carrión J, Gutiérrez A, et al. Patient involvement in clinical research: why, when, and how. Patient Prefer Adherence. 2016;10:631-40.
37. Radecki B, Keen A, Miller J, McClure JK, Kara A. Innovating Fall Safety: Engaging Patients as Experts. J Nurs Care Qual. 2020;35(3):220-6.
38. Guan M, Han JY, Shah DV, Gustafson DH. Exploring the Role of Social Support in Promoting Patient Participation in Health Care among Women with Breast Cancer. Health Commun. 2020:1-9.
39. https://www.bihealth.org/en/research/quest-center/mission-approaches/stakeholder-engagement/resources-and-links-patient-stakeholder-engagement/ (Retrieved: May 10, 2020).
40. https://assets.kpmg/content/dam/kpmg/nl/pdf/2019/sector/unlocking-the-life-sciences-potential.pdf (Retrieved: May 20, 2020).

41. Barnett HG. Innovation: the basis of cultural change. New York, NY, US: McGraw-Hill; 1953. ix, 462-ix, p.

### 1.7.2 List of Abbreviations

CRISPR/Cas9……
…….. ..... Clustered Regularly Interspaced Short Palindromic Repeats/associated9
IP..... Intellectual Property
MRI ..... Magnetic Resonance Imaging
MS..... Multiple Sclerosis
NIH ..... National Institute of Health
PROMs..... Patient Reported Outcome Measures
R&D ..... Research & Development

# 2 DECLARATIONS

## 2.1 Statutory Declaration

"I, Sinje Gehr, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic **Change Drivers within the Translational Ecosystem for the Benefit of Society - Veränderungstreiber im translationalen Ökosystem zum Wohle der Gesellschaft**, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The section s on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date Signature

## 2.2 Declaration of Contribution

Gehr S, Kaiser T, Kreutz R, Ludwig WD, Paul F. Suggestions for improving the design of clinical trials in multiple sclerosis-results of a systematic analysis of completed phase III trials. EPMA J. 2019;10(4):425-36.

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"MEDICINE, RESEARCH and EXPERIMENTAL"**
Selected Category Scheme: WoS
**Gesamtanzahl: 136 Journale**

| Rank | Full Journal Title | Total Cites | Journal Impact Factor | Eigenfactor Score |
|---|---|---|---|---|
| 1 | NATURE MEDICINE | 79,243 | 30.641 | 0.162840 |
| 2 | Science Translational Medicine | 30,485 | 17.161 | 0.121980 |
| 3 | JOURNAL OF CLINICAL INVESTIGATION | 108,879 | 12.282 | 0.139970 |
| 4 | TRENDS IN MOLECULAR MEDICINE | 9,946 | 11.028 | 0.018900 |
| 5 | JOURNAL OF EXPERIMENTAL MEDICINE | 63,983 | 10.892 | 0.071790 |
| 6 | EMBO Molecular Medicine | 7,507 | 10.624 | 0.025980 |
| 7 | Annual Review of Medicine | 6,068 | 10.091 | 0.009030 |
| 8 | MOLECULAR THERAPY | 16,991 | 8.402 | 0.030050 |
| 9 | MOLECULAR ASPECTS OF MEDICINE | 5,568 | 8.313 | 0.009020 |
| 10 | Theranostics | 8,769 | 8.063 | 0.020270 |
| 11 | EBioMedicine | 5,401 | 6.680 | 0.022310 |
| 12 | ALTEX-Alternatives to Animal Experimentation | 1,361 | 6.183 | 0.001920 |
| 13 | Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology | 2,345 | 6.140 | 0.004130 |
| 14 | JCI Insight | 4,351 | 6.014 | 0.020440 |
| 15 | Molecular Therapy-Nucleic Acids | 3,189 | 5.919 | 0.010410 |
| 16 | Molecular Therapy-Oncolytics | 486 | 5.710 | 0.001990 |
| 17 | Nanomedicine-Nanotechnology Biology and Medicine | 10,131 | 5.570 | 0.014480 |
| 18 | Cold Spring Harbor Perspectives in Medicine | 6,223 | 5.564 | 0.016730 |
| 19 | CLINICAL SCIENCE | 10,951 | 5.237 | 0.014190 |
| 20 | JOURNAL OF BIOMEDICAL SCIENCE | 4,083 | 5.203 | 0.006300 |

| Rank | Full Journal Title | Total Cites | Journal Impact Factor | Eigenfactor Score |
|---|---|---|---|---|
| 21 | npj Vaccines | 282 | 5.020 | 0.001120 |
| 22 | AMYLOID-JOURNAL OF PROTEIN FOLDING DISORDERS | 1,335 | 4.919 | 0.003270 |
| 23 | Translational Research | 3,669 | 4.915 | 0.008530 |
| 24 | Molecular Therapy-Methods & Clinical Development | 1,078 | 4.875 | 0.004020 |
| 25 | Vaccines | 1,077 | 4.760 | 0.003910 |
| 26 | JOURNAL OF MOLECULAR MEDICINE-JMM | 7,195 | 4.746 | 0.010880 |
| 27 | EXPERIMENTAL AND MOLECULAR MEDICINE | 4,046 | 4.743 | 0.007380 |
| 28 | Stem Cell Reviews and Reports | 2,436 | 4.697 | 0.004690 |
| 29 | CANCER GENE THERAPY | 2,842 | 4.681 | 0.003200 |
| 30 | EPMA Journal | 815 | 4.661 | 0.001320 |
| 31 | JOURNAL OF CELLULAR AND MOLECULAR MEDICINE | 12,391 | 4.658 | 0.015760 |
| 32 | Stem Cell Research & Therapy | 6,132 | 4.627 | 0.015810 |
| 33 | Cancer Biology & Medicine | 1,043 | 4.467 | 0.003040 |
| 34 | EXPERT REVIEWS IN MOLECULAR MEDICINE | 1,758 | 4.407 | 0.001450 |
| 35 | mAbs | 4,415 | 4.405 | 0.011150 |
| 36 | MOLECULAR PHARMACEUTICS | 16,792 | 4.396 | 0.028020 |
| 37 | CYTOTHERAPY | 5,969 | 4.297 | 0.009690 |
| 38 | JOURNAL OF INHERITED METABOLIC DISEASE | 5,868 | 4.287 | 0.008410 |
| 39 | PPAR Research | 1,434 | 4.186 | 0.001600 |
| 40 | ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE | 10,039 | 4.151 | 0.012620 |
| 41 | Journal of Translational Medicine | 10,831 | 4.098 | 0.022910 |
| 42 | CTS-Clinical and Translational Science | 1,351 | 3.989 | 0.003190 |

**Contribution**

Gehr S, Kaiser T, Kreutz R, Ludwig WD, Paul F. Suggestions for improving the design of clinical trials in multiple sclerosis-results of a systematic analysis of completed phase III trials. EPMA J. 2019;10(4):425-36.

Sinje Gehr contributed to the publication as follows:

(01) Complete literature search on pivotal clinical phase III trials in Multiple Sclerosis as well as on outcomes, measurements instruments.

(02) Full description of materials and methods, p. 436.

(03) Full data collection as listed in table 1, p. 427.

(04) Full data analysis as listed in chapter results, p. 426 – 429.

(05) Composing the manuscript equally with co-authors.

(06) Corresponding author.

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Signature, date and stamp of supervising university professor / lecturer

_____

Signature of doctoral candidate

# 3 PRINTED COPY OF THE TOP JOURNAL PUBLICATION

EPMA Journal (2019) 10:425–436
https://doi.org/10.1007/s13167-019-00192-z

REVIEW


## Suggestions for improving the design of clinical trials in multiple sclerosis—results of a systematic analysis of completed phase III trials

Sinje Gehr[1] · Thomas Kaiser[2] · Reinhold Kreutz[1] · Wolf-Dieter Ludwig[3] · Friedemann Paul[1]

Received: 8 August 2019 / Accepted: 18 October 2019 / Published online: 22 November 2019


**Abstract**
This manuscript reviews the primary and secondary endpoints of pivotal phase III trials with immunomodulatory drugs in multiple sclerosis (MS). Considering the limitations of previous trial designs, we propose new standards for the planning of clinical trials, taking into account latest insights into MS pathophysiology and patient-relevant aspects. Using a systematic overview of published phase III (pivotal) trials performed as part of application for drug market approval, we evaluate the following characteristics: trial duration, number of trial participants, comparators, and endpoints (primary, secondary, magnetic resonance imaging outcome, and patient-reported outcomes). From a patient perspective, the primary and secondary endpoints of clinical trials are only partially relevant. High-quality trial data pertaining to efficacy and safety that stretch beyond the time frame of pivotal trials are almost non-existent. Understanding of long-term benefits and risks of disease-modifying MS therapy is largely lacking. Concrete proposals for the trial designs of relapsing (remitting) multiple sclerosis/clinically isolated syndrome, primary progressive multiple sclerosis, and secondary progressive multiple sclerosis (e.g., study duration, mechanism of action, and choice of endpoints) are presented based on the results of the systematic overview. Given the increasing number of available immunotherapies, the therapeutic strategy in MS has shifted from a mere "relapse-prevention" approach to a personalized provision of medical care as to the choice of the appropriate drugs and their sequential application over the course of the disease. This personalized provision takes patient preferences as well as disease-related factors into consideration such as objective clinical and radiographic findings but also very burdensome symptoms such as fatigue, depression, and cognitive impairment. Future trial designs in MS will have to assign higher relevance to these patient-reported outcomes and will also have to implement surrogate measures that can serve as predictive markers for individual treatment response to new and investigational immunotherapies. This is an indispensable prerequisite to maximize the benefit of individual patients when participating in clinical trials. Moreover, such appropriate trial designs and suitable enrolment criteria that correspond to the mode of action of the study drug will facilitate targeted prevention of adverse events, thus mitigating risks for individual study participants.

**Keywords** Multiple sclerosis · Clinical trial · Phase III · Patient-reported outcome measures (PROM) · Comparator · Patient preferences · Personalized provision of medical care · Predictive surrogate measures · Targeted prevention · Predictive preventive personalised medicine · Immunotherapy · Immunomodulatory drugs · Patient stratification · Patient benefits · Risk analysis · Mitigation · Relapse-prevention approach · Fatigue · Depression · Cognitive impairment · Criteria

✉ Sinje Gehr
sinje.gehr@charite.de

[1] Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

[2] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) (IQWiG), Im Mediapark 8, 50670 Köln, Germany

[3] Arzneimittelkommission der deutschen Ärzteschaft (Drug Commission of the German Medical Association), Herbert-Lewin-Platz 1, 10623 Berlin, Germany

## Background

Since the development of the first immunotherapy interferon beta-1b in 1995 (see Table 1), a number of immunomodulatory substances have been authorized for the disease-modifying treatment of multiple sclerosis (MS), namely by reducing relapse rates [13, 25, 58]. The mechanisms of action have been fully elucidated for only few of these drugs. While a positive effect on the autoreactive, inflammatory immune response is considered proven, direct neuroprotective effects are unlikely.

All drugs licensed to date were tested in 1- to 2-year (rarely longer) pivotal trials, mostly against placebo [20], although more recently, active comparators have also begun to be applied. From the patient's point of view, some of the primary and secondary endpoints of these studies have limited relevance [27, 65]. Moreover, methodologically sound data on these drugs' efficacy and safety (or detrimental effects), beyond the duration of these trials, are practically non-existent. The little data covering 3 years or more of application mostly derive from "extension studies" to initial phase III studies or from registers such as "MSBase" [36]. Specialized statistical analyses are applied to compensate for the poor methodological quality of "observational studies" in order to gain insight into the efficacy of immunomodulatory treatments (including compared with each other). However, the "real-world" data gathered in registers are generally not suited for such analyses [31]. Overall, these factors suggest a general approach to designing clinical MS trials that leaves room for improvement and which has hampered our understanding of the long-term benefits and risks of disease-modifying MS treatment. However, these deepened insights are urgently needed to enable neurologists to proceed from a mere "relapse-preventative" strategy when prescribing immunotherapies towards provision of personalized medical services that take the multiple facets of the disease and patient preferences into consideration [22, 45] and also adopts the aim of targeted prevention of adverse events.

## Investigative goal

The goal of this study is, firstly, to set out an overview of the primary and secondary endpoints of pivotal phase III trials in MS. Secondly, based on this summary, as well as our analysis of the shortcomings of clinical trial design to date, we propose a number of suggestions for improvement. Here, we also draw on the latest insights into MS pathophysiology, as well as aspects relevant for patients, particularly the implementation of "patient-reported outcome measures" (PROM). Moreover, we describe the ongoing, significant demand for trials with therapeutic agents that modify disease progression, for which there have been too few controlled studies to date.

## Materials and methods

Our research of the available literature yielded a systematic overview of published pivotal phase III MS trials performed to provide evidence for drug marketing approval (so-called pivotal trials). We took as a starting point an assessment of 21 randomized, controlled phase III trials on relapsing-remitting multiple sclerosis (RRMS) presented in Torkildsen et al. [74]. As all of the latter were completed prior to May 21, 2015, we augmented them with our own research into the literature, focusing on further *completed and published phase III MS trials* (inclusion criteria), as well as extending analysis of all the included trials to the disease courses relapsing multiple sclerosis (RMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and clinically isolated syndrome (CIS). Drugs not approved for the market despite phase III trial were not included (exclusion criteria). The literature was searched using PubMed, as well as the European public assessment reports (EPAR) of the European Medicines Agency (EMA) and the dossier assessments of early benefit assessments conducted by the German Institute for Quality and Efficiency in Health Care (IQWiG). The PubMed search was conducted using the keywords *Multiple Sclerosis*, *Phase 3*, *trial,* with last access on 2-15-2019.

The following characteristics of the phase III trials were analyzed: trial duration, sample size, comparator drugs (primary, secondary, MRI (magnetic resonance imaging) outcomes, as well as patient-reported outcome measures (PROM)).

## Results

Table 1 of the Appendix summarizes the characteristics of the 29 assessed pivotal phase III trials. Below we describe the key results of our investigation of the trials for the disease courses RRMS, RMS, SPMS, PPMS, and CIS.

### Trial duration

The analysis showed that the phase III RRMS trials conducted since the 1990s had a duration of approximately 2 years, with some few exceptions (e.g., EVIDENCE trial, interferon beta-1a, 1-year duration). For RMS, the trial duration was also generally 2 years. Exceptions here were

**Table 1** Published pivotal phase III trials

| Trial start | Approval (year, EU) | Indication trial | Test substance (trade name) | Trial duration, trial participants (N total) | Trial acronym | Comparator drug | Primary endpoints | Further endpoints & measurements | Online sources |
|---|---|---|---|---|---|---|---|---|---|
| 1988 | 1995 | RRMS | Interferon-β1b (Betaferon®) | 104 weeks, N 372 | MSSG | Placebo | REL | D, MRI, UE | [1, 2] |
| 1990 | 1997 | RRMS | Interferon-β1a IM (Avonex®) | 104 weeks, N 301 | MSCRG | Placebo | D | UE | [1, 6] |
| 1991 | 2001 | RRMS | Glatiramer acetate (Copaxone®) | 104 weeks, N 251 | CMSSG | Placebo | REL | D, MRI, UE | [1, 10] |
| 1994 | 1998 | RMS | Interferon-β1a SC (Rebif®) | 104 weeks, N 560 | PRISMS | Placebo | REL | D, O, UE | [1, 7] |
| 1996 | 1997 | CIS | Interferon-β1a SC (Avonex®) | 78 weeks, N 383 | CHAMPS | Placebo | O, D | MRI, PROM, UE | [33] |
| 1997 | 1995 | RRMS | Interferon-β1b (Betaferon®) | 104 weeks, N 188 | INCOMIN | Interferon β-1a IM | REL | D, MRI, UE | [1, 4] |
| 2001 | 2006 | RMS | Natalizumab (Tysabri®) | 104 weeks, N 942 | AFFIRM | Placebo | REL | MRI, D, UE | [1, 13] |
| 2002 | 1995 | CIS | Interferon-β1b (Betaferon®) | 104 weeks, N 468 | BENEFIT | Placebo | O, REL, D | MRI, UE | [5] |
| 2003 | 1995 | RRMS | Interferon-β1b (Betaferon®) | 104 weeks, N 2244 | BEYOND | Glatiramer acetate | REL | D, MRI, O, UE | [1, 3] |
| 2004 | 1998 | RMS | Interferon-β1a SC (Rebif®) | 96 weeks, N 766 | REGARD | Glatiramer acetate | REL | MRI, D, UE | [1, 8] |
| 2004 | 2001 | CIS[a] | Glatiramer acetate (Copaxone®) | 156 weeks, N 481 | PRECISE | Placebo | O | MRI, UE | [11] |
| 2004 | 2013 | RMS | Teriflunomide (Aubagio®) | 108 weeks, N 1088 | TEMSO | Placebo | REL | D, O, MRI, PROM, UE | [1, 36, 20] |
| 2005 | 2017 | RMS | Cladribine (Mavenclad®) | 96 weeks, N 1326 | CLARITY | Placebo | REL | D, MRI, UE | [27, 28] |
| 2006 | 1998 | CIS | Interferon β-1a (Rebif®) | 104 weeks, N 517 | REFLEX | Placebo | O | UE | [31, 32, 34] |
| 2006 | 2011 | RMS | Fingolimod (Gilenya®) | 104 weeks, N 1272 | FREE-DOMS | Placebo | REL | D, MRI, O, UE | [1, 14, 35] |
| 2006 | 2011 | RRMS | Fingolimod (Gilenya®) | 104 weeks, N 1083 | FREE-DOMS 2 | Placebo | REL | MRI, D, PROM, UE | [1, 35, 15] |
| 2006 | 2011 | RMS | Fingolimod (Gilenya®) | 52 weeks, N 1292 | TRANS-FORMS | Interferon β-1a i.m. | REL | MRI, D, UE | [1, 35, 16] |
| 2007 | 2013 | RRMS | Alemtuzumab (Lemtrada®) | 104 weeks, N 581 | CARE MS 1 | Interferon β-1a SC | REL, D | MRI, O, UE | [1, 20] |
| 2007 | 2013 | RMS | Alemtuzumab (Lemtrada®) | 104 weeks, N 840 | CARE MS 2 | Interferon β-1a SC | REL, D | MRI, O, UE | [1, 21] |
| 2007 | 2014 | RMS | Dimethyl fumarate (Tecfidera®) | 96 weeks, N 1234 | DEFINE | Placebo | REL | MRI, D, UE | [1, 22] |
| 2007 | 2014 | RRMS | Dimethyl fumarate (Tecfidera®) | 96 weeks, N 1417 | CONFIRM | Placebo/Glatiramer acetate | REL | MRI, D, O, UE | [1, 23] |
| 2008 | 2013 | RMS | Teriflunomide (Aubagio®) | 48 weeks, N 1169 | TOWER | Placebo | REL | D, O, PROM, UE | [1, 17, 36] |
| 2009 | 2013 | RMS | Teriflunomide (Aubagio®) | 96 weeks, N 324 | TENERE | Interferon-β 1a SC | REL | PROM, UE | [1, 36, 19] |
| 2009 | 2014 | RRMS | Peginterferon-1A (Plegidry®) | 104 weeks, N 1516 | ADVANCE | Placebo | REL | MRI, D, UE | [1, 24] |
| 2010 | 2016 | RRMS | Daclizumab (Zinbryta®) | 144 weeks, N 1841 | DECIDE | Interferon β-1a | REL | MRI, PROM, UE | [25, 26] |
| 2011 | 2018 | RMS | Ocrelizumab (Ocrevus®) | 96 weeks, N (I) 821 + N (II) 835 | OPERA I OPERA II | Interferon-β 1a SC | REL | D, MRI, PROM, UE | [29] |
| 2011 | 2018 | PPMS | Ocrelizumab (Ocrevus®) | 120 weeks, N 732 | ORATORIO | Placebo | D | O, MRI, PROM, UE | [30] |
| Unknown | 1998 | RRMS | Interferon-β1a SC (Rebif®) | 48 weeks, N 677 | EVIDENCE | Interferon-β-1a IM | REL | MRI, O, UE | [1, 9] |
| Unknown | 2003 | SPMS | Mitoxantrone (Ralenova®) | 104 weeks, N 194 | MIMS | Placebo | REL, D, O | UE, PROM | [1, 12] |

*D* disability progression (including EDSS score, EDSS progression), *MRI* MRI outcomes (including T1, T2 lesions, gadolinium-enhancing lesions, brain volume), *PROM* patient-reported outcome measures (including symptoms or quality of life, patient-related outcome such as fatigue), *REL* relapses (including relapse rate, relapse risk, annualized relapse risk), *O* other (including at least one MS-related admission to hospital, at least one MS-related steroid course, time to clinically definite MS, time to McDonald MS), *UE* undesired endpoints

[a] According to Teva product characteristics "Copaxone® 20 mg/ml", status July 2018, indicated for the treatment of relapsing multiple sclerosis

the 1-year TRANSFORMS trial (fingolimod, approved 2011) and the TOWER trial (teriflunomide, approved 2013), which had a variable duration, but was already completed 48 weeks after inclusion of the last patient. Alone, the PRECISE trial (glatiramer acetate for CIS, approved 2001) had a study duration of 3 years. Only recently have trials longer than 2 years been carried out, including the DECIDE trial (daclizumab for RRMS, 144 weeks, approved 2016, market withdrawal 2018) and the ORATORIO trial in PPMS (ocrelizumab, 120 weeks, approved 2018).

### Number of participants in MS pivotal trials

In recent years, the number of trial participants has increased significantly. While the first pivotal interferon beta 1b trial MSSG only included 372 patients, the DECIDE trial (daclizumab) recruited 1841 patients. One of the reasons for this is that relapse rates have decreased significantly over the last 20 years, for instance because many patients are already being treated with immunomodulatory agents and therefore patients with milder disease course are more likely to be recruited for drug trials. Thus, today significantly higher case numbers are needed to reach statistical significance using annual relapse rate as primary endpoint, with absolute differences between investigational medicinal product (IMP) and comparator drug sometimes averaging just < 0.2 relapses per year. Miniscule effects that only reach statistical significance by inflation of sample size suggests that such trial results are of questionable clinical relevance. However, it should be noted that one advantage of larger sample sizes is a greater chance of detecting rare side effects.

### Comparator drugs

The earliest RRMS trials tested the IMP against placebo as no other immunomodulatory agents had yet been developed. However, more recently, trials are increasingly carried out against active comparators, such as against interferon beta-1a in the RRMS trials CARE MS-1 (alemtuzumab), DECIDE (daclizumab), and EVIDENCE (SC vs. IM interferon beta-1a). Glatiramer acetate was used as comparator drug in the BEYOND trial (interferon beta-1b). In RMS, seven placebo-controlled trials and four trials (TRANSFORMS (fingolimod), CARE MS-2 (alemtuzumab), TENERE (teriflunomide), and OPERA I + II (ocrelizumab)) with interferon beta-1a as active comparator were carried out. In the RMS trial REGARD (interferon beta-1a) glatiramer acetate served as active comparator. The cytotoxic agent mitoxantrone for SPMS was tested against placebo in the MIMS trial, as was the monoclonal antibody ocrelizumab for PPMS in the ORATORIO trial. All four trials in CIS were also placebo-controlled: CHAMPS (interferon-β1a), BENEFIT (interferon-β1b), PRECISE (glatiramer acetate), and REFLEX (interferon-β1a).

### Endpoints

In RRMS trials, relapse rate was most frequently selected as primary endpoint. Disability progression, measured according to the "Expanded Disability Status Scale (EDSS)" for the quantification of neurological disability and confirmed after 12 or 24 weeks, was selected as primary endpoint in two trials (interferon-β1a, MSCRG, and alemtuzumab, CARE MS 1), but served only as secondary endpoint in most. Apart from adverse events, key secondary or explorative endpoints included MRI endpoints, such as number and volume of gadolinium-enhancing lesions and T2-hyperintense or T1-hypointense lesions in cranial MRI and, most recently, also the progression of cerebral atrophy [61]. For the 12 RMS trials, only relapse rate was selected as primary endpoint, albeit in the case of alemtuzumab (CARE MS 1 trial) in combination with disability progression. The pattern was similar for clinically isolated syndrome (CIS): the primary endpoints of the PRECISE trial (glatiramer acetate) were the rate of conversion to clinically definite MS as defined by a second clinical event, while the BENEFIT trial (interferon-β 1b) measured conversion to both clinically definite MS and McDonald MS, as well as the annual relapse rate and the degree of disability. Apart from the primary endpoint ("disability progression confirmed at 12 weeks"), the PPMS trial on ocrelizumab (ORATORIO trial) also investigated secondary endpoints such as "disability progression confirmed at 24 weeks", MRI endpoints, as well as a patient-reported outcome (quality of life according to the SF-36 (Short Form (36) Health Survey)).

### Patient-reported outcome measures (PROM)

In many cases, patients and physicians differ in the importance ascribed to particular symptoms and consequences of the disease [27, 65]. In general, patients tend to focus far more on disability progression impacting quality of life, rather than disease progression as measured by anatomical, biological, and clinical data. As such, patients generally understand disease progression as the worsening of symptoms, with fatigue, depression, cognitive impairment, pain, spasticity, sleep disturbance, loss of visual functioning, and mobility among those considered most burdensome [16, 17, 24, 27, 57, 60, 63, 65, 77, 78, 80]. Many of these symptoms can be easily quantified using internationally established and validated patient questionnaires.

Virtually, no drug approval trial has systematically investigated PROM. Where investigated, the focus is on fatigue, which is considered by many MS patients to be one of the most troubling symptoms [79]. Here, two examples are the TENERE and TEMSO trials (both teriflunomide, RMS), which investigated fatigue as secondary endpoint using the "Fatigue Impact Scale (FIS)". In the ocrelizumab trials (OPERA I, OPERA II, ORATORIO), health-related quality of life (HRQoL) was measured using the established, generic survey SF-36, which comprises the section vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Nevertheless, measuring HRQoL is far from standard in clinical MS trials, as evidenced by the CLARITY trial for the oral drug cladribine [34], which did not include any PROM parameters [21]. Overall, PROM are still investigated less frequently as primary or secondary endpoints than relapse rate, disease progression, or MRI parameters.

## Discussion

### Deficits in the design of phase III trials to date

Systematic analysis of the phase III trials included in this overview showed that the approval of new substances for the treatment of multiple sclerosis were as a rule randomized, controlled studies of at least 1 year and each included several hundred, sometimes over 1000, patients. This, in principle, suggests that an established approach to designing MS clinical trials exists to a greater extent than in other neurological disorders. However, on closer inspection, it becomes clear that our approach to MS clinical trial design urgently needs to redirect focus towards patient needs, as opposed to biological indicators and surrogate measures of dubious clinical importance.

In the EMA's "Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis" [30], relapse rate and disability progression are singled out as the most important primary endpoints. The guideline distinguishes between the "accumulation of disability" in terms of relapse rate in RMS and disability progression in SPMS or PPMS in phase III trials, with clinically measured prevention or delay of disability progression recommended as primary endpoint for SPMS and PPMS. For patients with RRMS or SPMS with relapsing MS (RMS), both relapse rate and the time to relapse are accepted as primary outcomes. Relapse rate, or that is, the proportion of relapse-free patients along with the progression of disability should, in addition to MRI outcomes, be investigated as secondary endpoints, insofar as they have not already been examined as primary endpoints. Furthermore, the EMA guideline calls for more emphasis on PROM, as symptoms such as subjective visual function, pain, bladder control, depression, sleep disorder, fatigue, and cognitive dysfunction are enormously important for quality of life and are considered more crucial by some patients than purely somatic outcomes [26, 65].

Analysis of the phase III trials to date highlights significant deficits in pivotal MS trials. These include a treatment duration that is often too short, discrepancies between the hypothesized mechanism of action and inclusion criteria (inclusion of patients with little disease activity or very long disease duration in trials with substances that have strong anti-inflammatory effect), premature confirmation of disease progression (already after 12 weeks), or the lack of relevant PROM. The attempt to obtain statistical significance with high patient numbers despite often only minimal absolute differences in the relapse rate between IMP and comparator drug are both of questionable clinical relevance and of dubious cost-effectiveness (insofar as these resources are then not available for other trials).

Investigating outcomes that are particularly important to patients has been the exception in drug approval trials to date and where the case, they only serve as secondary or explorative endpoints. These approaches are methodologically inadequate to some extent, for example because the PROM explorative endpoints were usually not surveyed using validated measurement instruments (e.g., measurement of fatigue in the TRANSFORMS trial on fingolimod with the unvalidated questionnaire "draft 39-item version of the U-FIS") [35].

### Suggestions for improving phase III MS trial design

The hypothesized mechanism of action should be clearly described at the beginning of the trial and should be taken into consideration when designing the study. For immunomodulatory drugs intended for treatment in (highly) active disease stages (e.g., natalizumab, ocrelizumab), this would mean that relapse rate could continue to serve as endpoint. However, aspects such as the severity of the relapse or the functional disability and the remission should also be taken into account. To establish the added benefit of a new drug, a clinically significant effect on functionally debilitating relapses (e.g., visual functioning, mobility, physical strength) should be demonstrated. As the timing of relapses is difficult to predict, the duration of observation in trials that take relapse rate as endpoint should be at least 2 years.

For substances with a hypothesized effect on disability progression, the observation period should be of suitable

duration (at least 3 years, ideally up to 5 years). Currently, disability progression is commonly established after only 12 or 24 weeks. However, recovery from relapse can take up to 6 or even 12 months, and temporary disability changes stemming from previous relapses can lead to overestimation of long-term disability progression. Consequently, disability progression should only be confirmed after 12 months, which reduces confounding effect of incomplete recovery from recent relapses [42].

The inclusion criteria for the trial subjects should take into account the expected effect of the active substance and be compatible with the primary endpoint. For example, validation of a drug with hypothesized effect on disability progression should include patients whose progression is confirmed prior to inclusion in the trial. Otherwise, the danger exists of including significant numbers of "stable" patients or those with only slow progression. In such cases, the drug being tested might indeed have an effect in the subpopulation, but this might not be detected in the sample due to the mild natural history of the cohort (false negative result for the subpopulation in question). Conversely, a "positive" effect could be the result of the actual subpopulation of interest, but be mistakenly extended to include patients with mild natural history (false positive result for the subpopulation with mild natural history, see ORATORIO trial, ocrelizumab).

For drugs with strong anti-inflammatory effect, focus should be placed on including patients in early disease phases with higher disease activity, instead of—as was most recently the case in the CLARITY trial—a very broad enrolment of the population, including patients with low disease activity and extremely long disease duration. By ensuring the inclusion criteria is compatible with the hypothesized mode of action, it might be possible to achieve clinically relevant results with smaller case numbers, thereby sparing patients the risks involved in testing new immunotherapies. The subjects should also cover a wide age range (up to 60 or 65 years, as opposed to the currently usual age limit of 55) and age effects should be investigated, as a recent meta-analysis demonstrated that age can affect the efficacy of an immunomodulatory therapy [82]. Apart from EDSS, it is imperative that a functional test of low-contrast sensitivity (e.g., low contrast letter acuity using Sloan charts) and mobility (e.g., 6-min walk test) be performed to quantify disability, as vision and mobility are the most important bodily symptoms from a patient point of view [27].

The EMA guideline [30] recommends evaluating health-related quality of life, although lack of data precludes recommending any specific instruments. Indeed, using established assessment instruments to quantify health-related quality of life, as well as fatigue and cognition, should become standard practice. Tools for measuring quality of life include MSQOL 54 (Multiple Sclerosis Quality of Life-54) [38], HAQUAMS (Hamburg Quality of Life Questionnaire in Multiple Sclerosis) [66], MSQLI (Multiple Sclerosis Quality of Life Inventory) [39], or the recently developed Neuro-QoL [51]. Fatigue and cognition can be measured using the Fatigue Severity Scale (FSS) [37, 46] and BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis) [32, 48], respectively. A simple further screening instrument for cognition is the SDMT (Symbol Digit Modalities Test) [75]. The effect of limited vision and mobility on quality of life should be quantified using the established measurement instrument NEI-VFQ25 (National Eye Institute Visual Functioning Questionnaire 25) [40] or the MSWS-12 [23], as applies.

Cerebral or spinal MRI parameters can serve as secondary or explorative outcomes (e.g., T2 lesions, spinal cord atrophy [2, 83]); however, the repeated application of gadolinium-based MRI contrast agents should be avoided due to safety concerns [14, 67]. Moreover, brain atrophy measurements, although technically feasible in a clinical study with rigorous standardization of assessments, are not recommended as they are not yet transferable to gauge prediction and monitoring of disease course in individual patients, thus currently not supporting personalization of medical services [3, 28, 61, 62, 81]. The same applies to other advanced imaging modalities such as diffusion tensor imaging, ultrahigh field MRI and others [47, 56, 59, 64, 69, 70, 72]. Most recently, the use of retinal optical coherence tomography (OCT) for the quantification of axonal and neuronal damage caused by MS is increasing [4, 10, 50, 52–54, 84]. This technique has been occasionally used as outcome measure in clinical trials and might serve as predictive diagnostics for disease course and response to immunotherapy both in trial cohorts and individual subjects in the future. A further suitable secondary or explorative outcome that might be established in the near future both for clinical studies and individualized prediction is the identification of neurofilaments in serum as surrogate marker of axonal damage in the CNS [1, 6, 7, 12, 43, 49, 73, 76].

Exclusively placebo-controlled trials with a duration of more than 6 months that test disease-modifying drugs in RRMS are ethically problematic. Moreover and importantly, the advantages and disadvantages of individual treatment options cannot be identified by means of placebo-

controlled studies. When selecting appropriate active comparators, care should be taken that the trial's inclusion criteria reflect both the study population and the active comparator's approval status. In trials with a PPMS population, the lack of approved drugs (with the exception of ocrelizumab) justifies the use placebo-controlled trials. Ocrelizumab, which was recently approved, likely only benefits a small subgroup of younger PPMS patients (up to 45 years) with short disease duration (up to 15 years) and disease activity in MRI (new T2 lesions, gadolinium-enhancing lesions), and trialing against this substance in other PPMS populations (older patients, longer disease duration, no MRI activity) makes little sense and is moreover not ethically acceptable.

Overall, the high demand of patients for studies in progressive MS (SPMS, PPMS) continues. A significant number of drugs, including some approved for treatment of RRMS, were unsuccessfully tested in patients with progressive MS. The reasons for this are manifold and include an incomplete understanding of the pathophysiology of progression, an insufficiently detailed grasp of the mechanism of action of the drug, and the shortcomings of the applied outcomes (such as the EDSS with high inter-rater variability and disproportionate weighting allocated to lower extremity functioning, or more generally, the ability to walk).

The suggestions for improvement presented here build to some extent on those recently published by Ontaneda et al. ([55], see Text Box 5b). Importantly, clinical researchers planning a trial should make use of the EMA's advice service, and ideally also involve the European HTA (Health Technology Assessment) institutions [29], of which the Federal Joint Committee (G-BA) is the primary body in Germany [33]. The aim of the consultation process should be ensuring that the trial is designed to not only meet the requirements necessary for market approval, but also to inform treatment decisions and to perform an assessment of the added benefit of the new drug compared to standard treatment. The results of the consultation should be published to ensure transparency.

Pharmaceutical companies in Germany sometimes complain that the recommendations of drug approval agencies and HTA institutions (IQWiG and G-BA) diverge to some extent and that data from a single phase III trial is interpreted differently by the EMA, on the one hand, and the committees participating in the early benefit assessment (IQWiG and G-BA), on the other. However, this perspective does not take into account the fact that the questions posed by the approval agencies ("Does the new substance have a positive benefit-risk balance?") and the benefit assessment ("Does the new substance have an added benefit compared to a 'standard therapy'?") are very different. By necessity, this leads to diverging demands on the trial design in the first instance, and ultimately leads to different interpretation of the obtained results in the final instance.

Despite our criticism of MS studies to date, we are aware that planning a clinical trial and improving quality and patient focus as discussed above also (have to) take into account a wider health policy and regulatory framework, as well as financial considerations. This complicates and could even hobble design of a study that focuses exclusively on achieving scientific insights into MS.

## Expert recommendations

Fortunately, the therapeutic landscape for people with MS has significantly broadened over the past 15 years. In parallel to the increasing number of available immunotherapies, treatment strategies in MS have shifted from a mere "relapse-prevention" approach to a personalized provision of medical care as to the choice of the appropriate drugs and their sequential application over the course of the disease. This personalized provision should take patient preferences as well as disease-related factors into consideration such as objective clinical and radiographic findings but also very burdensome symptoms such as fatigue, depression, and cognitive impairment. This change in perspective on what physicians want to accomplish for their patients has not only been endorsed by clinicians and researchers but has also been adopted by regulatory bodies such as EMA. Therefore, future trial designs in MS should assign higher relevance to these patient-reported outcomes and should aim at implementing measures that can serve as predictive markers for individual treatment response to new and investigational immunotherapies. This is an indispensable prerequisite to maximize the benefit of individual patients when participating in clinical trials and when starting on an immunotherapy post approval. Moreover, such appropriate trial designs and suitable enrolment criteria that correspond to the mode of action of the study drug will facilitate targeted prevention of adverse events, thus mitigating risks for individual study participants. Finally, personalized provision of medical services prior to enrolment into clinical trials must encompass utmost accuracy when diagnosing MS and ruling out relevant differential diagnoses given that newer and highly efficacious immunotherapies for MS might cause harm in other MS mimics such as neuromyelitis optica spectrum disorders and many others [5, 8, 9, 11, 15, 18, 19, 41, 44, 53, 68, 71].

5a Text box "Suggestions for improving the design of (R)RMS[1]/CIS trials"

Duration: Not less than 2 years, active comparator
Outcomes: Relapse rate, only functionally debilitating (relapse involving EDSS worsening of at least 1 point) relapses with full or partial recovery should be included
Disability progression: in RRMS trials involving patients with short disease duration, it makes little sense to investigate after 12 or 24 weeks; instead the number of functionally debilitating relapses and their remission should be examined; comparing disability at the end of a 2-year trial compared to baseline recommended
Additional for CIS: Time to conversion to CDMS (Clinically Definite Multiple Sclerosis)
Further outcomes/measurement instruments:
- General: EDSS, MSFC (Multiple Sclerosis Functional Composite)
- Vision: Snellen Visual Acuity Test and LCLA (Low Contrast Letter Acuity), e.g., using Sloan charts)
- Mobility: 6-min walk test
- Cognition: BICAMS or at a minimum SDMT
- PROM: Fatigue (FSMC (Fatigue Scale for Motor and Cognitive Functions)) or FSS), depression BDI-II (Beck Depression Inventory II); general quality of life: HAQUAMS (Hamburg Quality of Life Questionnaire in Multiple Sclerosis), SF36 or MSQoL; vision-related quality of life: NEI-VFQ25; mobility-related quality of life: MSWS-12 (Multiple Sclerosis Walking Scale); sleep-related quality of life: PSQI (Pittsburgh Sleep Quality Inventory); pain-related quality of life: Brief Pain Inventory (BPI)
- MRI: Repeated administration of gadolinium-based contrast agent to be avoided, T2 lesions recommended, brain atrophy not recommended as clinical value unclear, spinal cord atrophy as potentially promising imaging marker
- OCT (Optical Coherence Tomography) with GCIPL (Ganglion Cell-inner Plexiform Layer) and RNFL (Retinal Nerve Fiber Layer)

5b Text box "Suggestions for improving the design of PPMS/SPMS[2] trials"

Prerequisite: Inclusion only of patients with proven clinical progression PRIOR to inclusion (e.g., at least 1 EDSS point in prior 1–2 years)
Duration not less than 3 years, preferably up to 5 years, placebo may need to be justified
Endpoints: Confirmed disability progression after 12 months
Further endpoints/measurement instruments:
- General: EDSS, MSFC (Multiple Sclerosis Functional Composite)
- Vision: Visual Acuity Test and LCLA (Low Contrast Letter Acuity), e.g., using Sloan charts)
- Mobility: 6-min walk test
- Cognition: BICAMS or at a minimum SDMT
- PROM: Fatigue (FSMC (Fatigue Scale for Motor and Cognitive Functions)) or FSS), depression BDI-II (Beck Depression Inventory II); general quality of life: HAQUAMS (Hamburg Quality of Life Questionnaire in Multiple Sclerosis), SF36, MSQoL or Neuro-QoL; vision-related quality of life: NEI-VFQ25; mobility-related quality of life: MSWS-12 (Multiple Sclerosis Walking Scale); sleep-related quality of life: PSQI (Pittsburgh Sleep Quality Inventory); pain-related quality of life: Brief Pain Inventory (BPI)
- MRI: Repeated administration of gadolinium-based contrast agent to be avoided, T2 lesions recommended, brain atrophy not recommended as clinical value unclear, spinal cord atrophy as potentially promising imaging marker
- OCT (optical coherence tomography) with GCIPL (ganglion cell-inner plexiform layer), and RNFL (retinal nerve fiber layer)

[1] RMS also includes patients with SPMS and relapse activity
[2] Particularly patients without relapse activity

**Abbreviations** *AMNOG*, The Act on the Reform of the Market for Medical Products; *BDI-II*, Beck Depression Inventory II; *BICAMS*, Brief International Cognitive Assessment for Multiple Sclerosis; *BPI*, Brief Pain Inventory; *CDMS*, Clinically definite multiple sclerosis; *CIS*, Clinically isolated syndrome; *EDSS*, Expanded Disability Status Scale; *EMA*, European Medicines Agency; *EPAR*, European Public Assessment Reports; *FIS*, Fatigue Impact Scale*vFSMC*, Fatigue Scale for Motor and Cognitive Functions; *FSS*, Fatigue Severity Scale; *G-BA*, Federal Joint Committee; *GCIPL*, plexiform layer; *HAQUAMS*, Hamburg Quality of Life Questionnaire in Multiple Sclerosis; *HTA*, Health technology assessment; *IQWiG*, German Institute for Quality and Efficiency in Health Care; *LCLA*, Low Contrast Letter Acuity; *MRI*, Magnetic resonance imaging; *MS*, Multiple sclerosis; *MSFC*, Multiple Sclerosis Functional Composite; *MSWS-12*, Multiple Sclerosis Walking Scale; *MSQLI*, Multiple Sclerosis Quality of Life Inventory; *MSQOL-54*, Multiple Sclerosis Quality of Life-54; *NEI-VFQ25*, National Eye Institute Visual Functioning Questionnaire 25; *Neuro-QoL*, Quality of Life in Neurological Disorders; *OCT*, Optical coherence tomography; *PPMS*, Primary progressive multiple sclerosis; *PROM*, Patient-reported outcome measure; *PSQI*, Pittsburgh Sleep Quality Inventory; *RMS*, Relapsing multiple sclerosis; *RNFL*, Retinal nerve fiber layer; *RRMS*, Relapsing-remitting multiple sclerosis; *SDMT*, Symbol Digit Modalities Test; *SF36*, 36-Item Short Form Survey; *SPMS*, Secondary progressive multiple sclerosis

## Compliance with ethical standards

**Conflicts of interests** Sinje Gehr, Thomas Kaiser, and Wolf-Dieter Ludwig declare that they have no competing interest. Friedemann Paul received lectures fee/research support from Bayer/Novartis/Biogen Idec/TEVA/Sanovi–Aventis–Genzyme/Merck Serono, Alexion/Chugai/Medimmune/Roche/Chugai/Guthy Jackson Foundation. Furthermore, Friedemann Paul took part in the advisory boards of Novartis and Medimmune. Reinhold Kreutz declares that he consulted Bayer Pharma, Berlin–Chemie, Daiichi Sankyo, Ferrer, Sanofi, Servier. Additionally, he did research for Bayer Pharma.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors. The consent of the publication is not applicable. Ethical approval is not applicable.



## References

1. Akgun K, Kretschmann N, Haase R, et al. Profiling individual clinical responses by high-frequency serum neurofilament assessment in MS. Neurol Neuroimmunol Neuroinflamm. 2019;6:e555.
2. Alcaide-Leon P, Cybulsky K, Sankar S, et al. Quantitative spinal cord MRI in radiologically isolated syndrome. Neurol Neuroimmunol Neuroinflamm. 2018;5:e436.
3. Amiri H, De Sitter A, Bendfeldt K, et al. Urgent challenges in quantification and interpretation of brain grey matter atrophy in individual MS patients using MRI. Neuroimage Clin. 2018;19:466–75.
4. Ayadi N, Dorr J, Motamedi S, et al. Temporal visual resolution and disease severity in MS. Neurol Neuroimmunol Neuroinflamm. 2018;5:e492.

5. Beekman J, Keisler A, Pedraza O, et al. Neuromyelitis optica spectrum disorder: Patient experience and quality of life. Neurol Neuroimmunol Neuroinflamm. 2019;6:e580.
6. Bergman J, Dring A, Zetterberg H, et al. Neurofilament light in CSF and serum is a sensitive marker for axonal white matter injury in MS. Neurol Neuroimmunol Neuroinflamm. 2016;3:e271.
7. Bjornevik K, Munger KL, Cortese M et al. Serum Neurofilament Light Chain Levels in Patients With Presymptomatic Multiple Sclerosis. JAMA Neurol. 2019. https://doi.org/10.1001/jamaneurol.2019.3238.
8. Blaabjerg M, Ruprecht K, Sinnecker T, et al. Widespread inflammation in CLIPPERS syndrome indicated by autopsy and ultra-high-field 7T MRI. Neurol Neuroimmunol Neuroinflamm. 2016;3:e226.
9. Borisow N, Hellwig K, Paul F. Neuromyelitis optica spectrum disorders and pregnancy: relapse-preventive measures and personalized treatment strategies. EPMA J. 2018;9:249–56.
10. Cellerino M, Cordano C, Boffa G, et al. Relationship between retinal inner nuclear layer, age, and disease activity in progressive MS. Neurol Neuroimmunol Neuroinflamm. 2019. https://doi.org/10.1212/NXI.0000000000000596.
11. Cook LJ, Rose JW, Alvey JS et al. Collaborative International Research in Clinical and Longitudinal Experience Study in NMOSD. Neurol Neuroimmunol Neuroinflamm. 2019;6:e583
12. Dalmau J. Neurofilament light chain levels in MS: At the doorstep of clinical application. Neurol Neuroimmunol Neuroinflamm. 2019. https://doi.org/10.1212/NXI.0000000000000601.
13. Dorr J, Paul F. The transition from first-line to second-line therapy in multiple sclerosis. Curr Treat Options Neurol. 2015;17:354.
14. El-Khatib AH, Radbruch H, Trog S, et al. Gadolinium in human brain sections and colocalization with other elements. Neurol Neuroimmunol Neuroinflamm. 2019;6:e515.
15. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, de Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019;142:1858–75.
16. Finke C, Schlichting J, Papazoglou S, et al. Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue. Mult Scler. 2015;21:925–34.
17. Gaede G, Tiede M, Lorenz I, et al. Safety and preliminary efficacy of deep transcranial magnetic stimulation in MS-related fatigue. Neurol Neuroimmunol Neuroinflamm. 2018;5:e423.
18. Gahlen A, Trampe AK, Haupeltshofer S, et al. Aquaporin-4 antibodies in patients treated with natalizumab for suspected MS. Neurol Neuroimmunol Neuroinflamm. 2017;4:e363.
19. Geraldes R, Ciccarelli O, Barkhof F, et al. The current role of MRI in differentiating multiple sclerosis from its imaging mimics. Nat Rev Neurol. 2018;14:199–213.
20. Gerardi C, Bertele V, Rossi S, et al. Preapproval and postapproval evidence on drugs for multiple sclerosis. Neurology. 2018;90:964–73.
21. Gesundheitswesen IFQUWI (2018) [A17-62] Cladribin (multiple Sklerose) - Nutzenbewertung gemäß § 35a SGBV.
22. Golubnitschaja O, Baban B, Boniolo G, et al. Medicine in the early twenty-first century: paradigm and anticipation - EPMA position paper 2016. EPMA J. 2016;7:23.
23. Grobelny A, Behrens JR, Mertens S, et al. Maximum walking speed in multiple sclerosis assessed with visual perceptive computing. PLoS One. 2017;12:e0189281.
24. Hasselmann H, Bellmann-Strobl J, Ricken R, et al. Characterizing the phenotype of multiple sclerosis-associated depression in comparison with idiopathic major depression. Mult Scler. 2016;22:1476–84.
25. Havla J, Warnke C, Derfuss T, Kappos L, Hartung HP, Hohlfeld R. Interdisciplinary Risk Management in the Treatment of Multiple Sclerosis. Dtsch Arztebl Int. 2016;113:879–86.
26. Heesen C, Bohm J, Reich C, et al. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. Mult Scler. 2008;14:988–91.
27. Heesen C, Haase R, Melzig S, Poettgen J, Berghoff M, Paul F, et al. Perceptions on the value of bodily functions in multiple sclerosis. Acta Neurol Scand. 2018;137:356–62.
28. Hemond CC, Healy BC, Tauhid S, et al. MRI phenotypes in MS: Longitudinal changes and miRNA signatures. Neurol Neuroimmunol Neuroinflamm. 2019;6:e530.
29. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/07/Wc500230375.pdf. Accessed 10 Sept 2019.
30. http://www.ema.europa.eu/docs/en_gb/document_library/scientific_guideline/2015/03/wc500185161.pdf. Accessed 10 Sept 2019.
31. https://www.aerzteblatt.de/archiv/188027/Patientenregister-fuer-die-Nutzenbewertung-Kein-Ersatz-fuer-randomisierte-Studien. Accessed 10 Sept 2019.
32. https://www.bicams.net/. Accessed 10 Sept 2019.
33. https://www.g-ba.de/Institution/Presse/Pressemitteilungen/695/. Accessed 10 Sept 2019.
34. https://www.iqwig.de/De/Projekte-Ergebnisse/Projekte/Arzneimittelbewertung/2017/A17-62-Cladribin-Multiple-Sklerose-Nutzenbewertung-Gemaess-35a-Sgbv.8401.html. Accessed 10 Sept 2019.
35. https://www.iqwig.de/download/A14-21_Fingolimod-Neues-Anwendungsgebiet_Nutzenbewertung-35a-Sgb-V.pdf. Accessed 10 Sept 2019.
36. https://www.msbase.org/. Accessed 10 Sept 2019.
37. https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-(Fss)-and-Expanded-Disab. Accessed 10 Sept 2019.
38. https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Multiple-Sclerosis-Quality-of-Life-54-(Msqol-54). Accessed 10 Sept 2019.
39. https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Multiple-Sclerosis-Quality-of-Life-Inventory-(Msql). Accessed 10 Sept 2019.
40. https://www.psycharchives.org/Handle/20.500.12034/353. Accessed 10 Sept 2019.
41. Kaisey M, Solomon AJ, Luu M, Giesser BS, Sicotte NL. Incidence of multiple sclerosis misdiagnosis in referrals to two academic centers. Mult Scler Relat Disord. 2019;30:51–6.
42. Kalincik T, Cutter G, Spelman T, Jokubaitis V, Havrdova E, Horakova D, et al. Defining reliable disability outcomes in multiple sclerosis. Brain. 2015;138:3287–98.
43. Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, Gattringer T, et al. Neurofilaments as biomarkers in neurological disorders. Nat Rev Neurol. 2018;14:577–89.
44. Kleiter I, Gahlen A, Borisow N, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm. 2018;5:e504.
45. Koduah P, Paul F, Dorr JM. Vitamin D in the prevention, prediction and treatment of neurodegenerative and neuroinflammatory diseases. EPMA J. 2017;8:313–25.
46. Krupp LB, Larocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46:1121–3.
47. Kuchling J, Brandt AU, Paul F, Scheel M. Diffusion tensor imaging for multilevel assessment of the visual pathway: possibilities for personalized outcome prediction in autoimmune disorders of the central nervous system. EPMA J. 2017;8:279–94.

48. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler. 2012;18:891–8.
49. Leppert D, Kuhle J. Blood neurofilament light chain at the doorstep of clinical application. Neurol Neuroimmunol Neuroinflamm. 2019;6:e599.
50. Martinez-Lapiscina EH, Arnow S, Wilson JA, Saidha S, Preiningerova JL, Oberwahrenbrock T, et al. Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: a cohort study. Lancet Neurol. 2016;15:574–84.
51. Miller DM, Bethoux F, Victorson D, et al. Validating Neuro-QoL short forms and targeted scales with people who have multiple sclerosis. Mult Scler. 2016;22:830–41.
52. Oberwahrenbrock T, Traber GL, Lukas S, et al. Multicenter reliability of semiautomatic retinal layer segmentation using OCT. Neurol Neuroimmunol Neuroinflamm. 2018;5:e449.
53. Oertel FC, Zimmermann H, Paul F, Brandt AU. Optical coherence tomography in neuromyelitis optica spectrum disorders: potential advantages for individualized monitoring of progression and therapy. EPMA J. 2018;9:21–33.
54. Oertel FC, Zimmermann HG, Brandt AU, et al. Novel uses of retinal imaging with optical coherence tomography in multiple sclerosis. Expert Rev Neurother. 2018:1–13.
55. Ontaneda D, Fox RJ, Chataway J. Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives. Lancet Neurol. 2015;14:208–23.
56. Pasquier B, Borisow N, Rasche L, et al. Quantitative 7T MRI does not detect occult brain damage in neuromyelitis optica. Neurol Neuroimmunol Neuroinflamm. 2019;6:e541.
57. Paul F. Pathology and MRI: exploring cognitive impairment in MS. Acta Neurol Scand. 2016;134(Suppl 200):24–33.
58. Paul F, Ruprecht K. Current immunotherapy of multiple sclerosis. Nervenarzt. 2015;86:1031–42 quiz 1043-1034.
59. Pawlitzki M, Neumann J, Kaufmann J, et al. Loss of corticospinal tract integrity in early MS disease stages. Neurol Neuroimmunol Neuroinflamm. 2017;4:e399.
60. Penner IK, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. Nat Rev Neurol. 2017;13:662–75.
61. Radue EW, Sprenger T, Gaetano L, et al. Teriflunomide slows BVL in relapsing MS: A reanalysis of the TEMSO MRI data set using SIENA. Neurol Neuroimmunol Neuroinflamm. 2017;4:e390.
62. Rahn AC, Kopke S, Stellmann JP, et al. Magnetic resonance imaging as a prognostic disability marker in clinically isolated syndrome: A systematic review. Acta Neurol Scand. 2019;139:18–32.
63. Reen GK, Silber E, Langdon DW. Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review. J Neurol Sci. 2017;375:107–22.
64. Rissanen E, Tuisku J, Vahlberg T, et al. Microglial activation, white matter tract damage, and disability in MS. Neurol Neuroimmunol Neuroinflamm. 2018;5:e443.
65. Rothwell PM, Mcdowell Z, Wong CK, et al. Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. BMJ. 1997;314:1580–3.
66. Schaffler N, Schonberg P, Stephan J, et al. Comparison of patient-reported outcome measures in multiple sclerosis. Acta Neurol Scand. 2013;128:114–21.
67. Schlemm L, Chien C, Bellmann-Strobl J, et al. Gadopentetate but not gadobutrol accumulates in the dentate nucleus of multiple sclerosis patients. Mult Scler. 2017;23:963–72.
68. Sepulveda M, Delgado-Garcia G, Blanco Y et al. Late-onset neuromyelitis optica spectrum disorder: The importance of autoantibody serostatus. Neurol Neuroimmunol Neuroinflamm. 2019. https://doi.org/10.1212/NXI.0000000000000607.
69. Sinnecker T, Kuchling J, Dusek P, et al. Ultrahigh field MRI in clinical neuroimmunology: a potential contribution to improved diagnostics and personalised disease management. EPMA J. 2015;6:16.
70. Sinnecker T, Schumacher S, Mueller K, et al. MRI phase changes in multiple sclerosis vs neuromyelitis optica lesions at 7T. Neurol Neuroimmunol Neuroinflamm. 2016;3:e259.
71. Solomon AJ, Corboy JR. The tension between early diagnosis and misdiagnosis of multiple sclerosis. Nat Rev Neurol. 2017;13:567–72.
72. Spano B, Giulietti G, Pisani V, et al. Disruption of neurite morphology parallels MS progression. Neurol Neuroimmunol Neuroinflamm. 2018;5:e502.
73. Thebault S, Tessier DR, Lee H, Bowman M, Bar-Or A, Arnold DL, et al. High serum neurofilament light chain normalizes after hematopoietic stem cell transplantation for MS. Neurol Neuroimmunol Neuroinflamm. 2019;6:e598.
74. Torkildsen O, Myhr KM, Bo L. Disease-modifying treatments for multiple sclerosis - a review of approved medications. Eur J Neurol. 2016;23(Suppl 1):18–27.
75. Van Schependom J, D'hooghe MB, Cleynhens K, et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. Eur J Neurol. 2014;21(1219-1225):e1271–12.
76. Varhaug KN, Barro C, Bjornevik K, et al. Neurofilament light chain predicts disease activity in relapsing-remitting MS. Neurol Neuroimmunol Neuroinflamm. 2018;5:e422.
77. Veauthier C, Paul F. Sleep disorders in multiple sclerosis and their relationship to fatigue. Sleep Med. 2014;15:5–14.
78. Veauthier C, Gaede G, Radbruch H, Wernecke KD, Paul F. Sleep Disorders Reduce Health-Related Quality of Life in Multiple Sclerosis (Nottingham Health Profile Data in Patients with Multiple Sclerosis). Int J Mol Sci. 2015;16:16514–28.
79. Veauthier C, Hasselmann H, Gold SM, et al. The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue. EPMA J. 2016;7:25.
80. Von Bismarck O, Dankowski T, Ambrosius B, et al. Treatment choices and neuropsychological symptoms of a large cohort of early MS. Neurol Neuroimmunol Neuroinflamm. 2018;5:e446.
81. Wang C, Barnett MH, Yiannikas C, et al. Lesion activity and chronic demyelination are the major determinants of brain atrophy in MS. Neurol Neuroimmunol Neuroinflamm. 2019. https://doi.org/10.1212/NXI.0000000000000593.
82. Weideman AM, Tapia-Maltos MA, Johnson K, et al. Meta-analysis of the Age-Dependent Efficacy of Multiple Sclerosis Treatments. Front Neurol. 2017;8:577.
83. Zeydan B, Gu X, Atkinson EJ, et al. Cervical spinal cord atrophy: An early marker of progressive MS onset. Neurol Neuroimmunol Neuroinflamm. 2018;5:e435.
84. Zimmermann HG, Knier B, Oberwahrenbrock T, Behrens J, Pfuhl C, Aly L, et al. Association of Retinal Ganglion Cell Layer Thickness With Future Disease Activity in Patients With Clinically Isolated Syndrome. JAMA Neurol. 2018;75:1071–9.

## Further References (only to Table1: Published pivotal phase III trials)

1. Torkildsen O, Myhr KM, Bo L. Disease-modifying treatments for multiple sclerosis - a review of approved medications. Eur J Neurol. 2016;23(Suppl 1):18–27.

2. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993;43:655–61.
3. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8:889–97.
4. Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet. 2002;359:1453–60.
5. Freedman MS. Evidence for the efficacy of interferon beta-1b in delaying the onset of clinically definite multiple sclerosis in individuals with clinically isolated syndrome. Ther Adv Neurol Disord. 2014;7:279–88.
6. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol. 1996;39:285–94.
7. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998;352:1498–504.
8. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008;7:903–14.
9. Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002;59:1496–506.
10. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45:1268–76.
11. Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374:1503–11.
12. Hartung HP, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet. 2002;360:2018–25.
13. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899–910.
14. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362:387–401.
15. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:545–56.
16. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362:402–15.
17. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:247–56.
18. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365:1293–303.
19. Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler. 2014;20:705–16.
20. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380:1819–28.
21. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380:1829–39.
22. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367:1098–107.
23. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367:1087–97.
24. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13:657–65.
25. Kappos L, Wiendl H, Selmaj K, Arnold DL, Havrdova E, Boyko A, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2015;373:1418–28.
26. Liu Y, Vollmer T, Havrdova E, Riester K, Lee A, Phillips G, et al. Impact of daclizumab versus interferon beta-1a on patient-reported outcomes in relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2017;11:18–24.
27. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362:416–26.
28. Giovannoni G, Soelberg Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. Mult Scler. 2018;24:1594–604.
29. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376:221–34.
30. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med. 2017;376:209–20.
31. De Stefano N, Comi G, Kappos L, et al. Efficacy of subcutaneous interferon beta-1a on MRI outcomes in a randomised controlled trial of patients with clinically isolated syndromes. J Neurol Neurosurg Psychiatry. 2014;85:647–53.
32. Comi G, De Stefano N, Freedman MS, et al. Subcutaneous interferon beta-1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing frequency-blind

multicentre REFLEXION study. J Neurol Neurosurg Psychiatry. 2017;88:285–94.

33. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med. 2000;343:898–904.
34. Comi G, De Stefano N, Freedman MS, et al. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. Lancet Neurol. 2012;11:33–41.
35. https://www.iqwig.de/download/A15-12_Fingolimod_Nutzenbewertung-35a-SGB-V.pdf
36. https://www.iqwig.de/download/A13-38_Teriflunomid_Nutzenbewertung-35a-SGB-V.pdf

# 4 CV

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht. Sinje Gehr

# 5 COMPLETE LIST OF PUBLICATIONS

## PUBLICATIONS

**Gehr S,** Garner CC, Kleinhans KN. Translating academic careers into industry healthcare professions. Nature Biotechnology. 2020;38(6):758-63.

**Gehr S,** Kaiser T, Kreutz R, Ludwig WD, Paul F. Suggestions for improving the design of clinical trials in multiple sclerosis-results of a systematic analysis of completed phase III trials. Epma j. 2019;10(4):425-36.

**Gehr S,** Garner CC. Rescuing the Lost in Translation. Cell. 2016;165(4):765-70.

**Gehr, S**. (2014). „Trust in Translation.“ f&w 10/2014, 918-919.

## MONOGRAPH

**Gehr, S**. (2013). „Das Gesetz der Wölfe? – Strategische Unternehmensentwicklung in der Pflegebranche.“ Akademiker Verlag:

# 6 ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisor, Prof. Dr. Craig Curtis Garner from the Neuroscience Research Center. His guidance, support, enthusiasm and, most vitally, friendship, have made this journey an inspiring and truly unique experience for me.

My second supervisor, Prof. Dr. Friedemann Paul from the Experimental and Clinical Research Center, guided me with trust and patience and shared his profound knowledge on Multiple Sclerosis with me.

The research on the institutions within the translational ecosystem was critically discussed by the team from SPARK-BIH in Berlin. Prof. Dr. Daria Mochly-Rosen and Prof. Dr. Kevin Grimes from Stanford University, USA, offered insights into the origins of the SPARK program and invited me to their vital events.

Concerning the research project on the users I would like to say a very special thank you to Dr. Thomas Kaiser from the Institute of Quality and Efficiency in Health Care for his integrity and critical voice on behalf of patients as well as his final review of my thesis. I also thank Prof. Dr. Wolf-Dieter Ludwig from the Drug Commission of the German Medical Association and Prof. Dr. Reinhold Kreutz, Institute of Clinical Pharmacology and Toxicology, for sharing their deep knowledge on the process of drug development. Hence, my thanks also go to all members of the Charité Initiative for MS Patients, a joint endeavor by various government institutions, pharmaceutical industries, the German Multiple Sclerosis Society and, most importantly, dedicated patients.

The research project on the actors was supported and frequently discussed by members of the Career-Development–Initiative of the Einstein–Center of Neurosciences. Abigail Garner helped me continuously frame the questionnaire and proofread drafts. I would also like to thank the members of SPARK-BIH and SPARK Global who helped spread the questionnaire at an international level as well as all

314 respondents who participated in the survey on career development in biomedicine.

I would like to express my thanks to Dr. Sophie Pieper from the Institute of Biometry and Clinical Epidemiology who helped a lot with the interpretation of data. Dr. Jens Steinbrink from Charité Corporate Development accompanied and challenged me during this journey. Finally, I would like to add a sincere thank you to Martin Vere-Jones and Prof. Dr. Joshua Shannon for their diligent proofreading.

*snj.*