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ORIGINAL ARTICLE

Status of clinical research in neurology in Germany—A national survey

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Abstract

Background and purpose: To provide an overview on the status of clinical research in neurology in Germany.

Methods: German university hospitals, nonuniversity hospitals, and neurological medical practices were surveyed regarding their clinical research activities during the period 2013 to 2017.

Results: Fifty percent of university hospitals, 10.6% of nonuniversity hospitals, and 5.2% of medical practices in Germany responded to our questionnaire. More than 80% of the clinical studies conducted have been phase III/IV and noninterventional trials (NISs), whereas <1% have been phase I and 3.5% investigator-initiated trials (IITs). University hospitals have conducted most of the phase II–IV trials. NISs have been predominantly performed by medical practices. Fifty-six percent of the university hospitals and less of the nonuniversity institutions confirmed the implementation of standard operating procedures (SOPs).

Abbreviations: DGN, German Neurological Society; GCP, good clinical practice; IIT, investigator-initiated trial; MS, multiple sclerosis; NIS, noninterventional trial; SOP, standard operating procedures.

Luisa Klotz and Sven G. Meuth contributed as co–senior authors.

In university hospitals, on average, 11 physicians had acquired a good clinical practice certificate. Overall, 43% of all trials have been performed in neuroimmunology.

Conclusions: The status of clinical research in neurology in Germany is predominated by NISs and late-phase trials, potentially due to a general lack of easily accessible funding, which leads to a highly competitive environment and fewer opportunities to perform early-phase clinical trials as well as IITs. Our results indicate that there is substantial need for structured support for creating and implementing SOPs to maintain quality standards and guarantee uniformity of performance. This survey assessed many aspects of clinical research and serves as guidance for providing ideas for structured improvement of clinical research in neurology in Germany.

KEYWORDS
clinical research, Germany, good clinical practice, survey

INTRODUCTION

Treatment options in neurology have fundamentally developed over the last few decades. From cerebrovascular to neuroinflammatory and neuromuscular diseases, clinical research is the key factor for improvement of patient care and progress in therapeutic success. However, to be able to conduct clinical trials that meet certain quality standards, sufficient infrastructure and skilled personnel are necessary. High quality in clinical research cannot be provided only by project-specific financial funding, it requires experienced researchers, adhering to the guidelines of good clinical practice (GCP), as well as key instruments providing navigation in the process of conducting clinical studies such as the implementation of standard operating procedures (SOPs).

However, data providing a comprehensive overview of active participation of neurology departments in hospitals and neurologic outpatient practices in the conduction of clinical trials and assessment of respective quality criteria in Germany have been lacking. For this purpose, we created a focused questionnaire that should provide an overview of the significance and quality of clinical research in neurology in Germany.

METHODS

In June 2017, the clinical studies committee of the German Neurological Society (DGN) [1] sent out a systematic survey on clinical research, including a fill-in assistance sheet, to neurological departments of university and nonuniversity hospitals as well as to medical practices specializing in neurology all over Germany (see Table S1; for original copy see File S2). A university hospital was defined as an academic hospital linked to a medical school of the university of the respective city. A nonuniversity hospital was defined as an academic or nonacademic hospital without a direct link to a university. Medical practice was defined as an autonomic institution for treatment of outpatients. Ethics approval was not required for this study. The questionnaire included 10 questions focusing on the overall activity in clinical research over the period of the previous 5 years, aspects of the research environment (e.g., infrastructure, human resources, availability of time), types of clinical studies, as well as the neurological diseases investigated. Furthermore, the questionnaire addressed measures of quality assurance.

The survey was distributed via an email list from the DGN, and recipients were asked to forward the questionnaire to the study centers of their facility. The completed surveys had to be returned via email or fax to a given address by August 1, 2017. Evaluation was performed by the neurological department of the University Hospital of Münster. Descriptive statistics were used to summarize data. Analyses were performed using GraphPad Prism.

RESULTS

In total, we sent out surveys to 36 university hospitals, 403 nonuniversity hospitals, and 640 medical practices that are members of the DGN and received feedback from the neurological departments of 18 university hospitals (response rate of 50%), 43 nonuniversity hospitals (response rate of 10.6%), and 33 neurological practices (response rate of 5.6%) in Germany. Referring to the regional distribution of the participating centers, we obtained responses from 35% of the centers from the west, 25% from the south, and 20% each from the north and the east of Germany. Regarding the type of studies, our results show that within the previous 5 years (2013–2017), more late-phase (phase III/IV) than early-phase (phase I/II) trials have been conducted. Furthermore, about 30% of all neurological clinical studies carried out in German hospitals and practices had been noninterventional trials (NIS) (Table 1).

Overall, university hospitals have conducted more phase I–IV and investigator-initiated trials (IITs) as compared to nonuniversity hospitals and medical practices. More than 20% of the overall clinical study activity during 2013 to 2017 consisted of NISs performed by medical practices (Figure 1).

TABLE 1 Respondents' characteristics

	Response rate, % (*n*)
Institution	
University hospitals	50 (18)
Nonuniversity hospitals	10.6 (43)
Medical practices	5.2 (33)
Type of clinical study[a]	
Phase I	0.7 (9)
Phase II	11.7 (151)
Phase III	34.6 (449)
Phase IV	17.5 (226)
NIS	31.2 (414)
Patient numbers 2013–2017	
Phase I	0.3 (43)
Phase II	5.4 (664)
Phase III	17.2 (2118)
Phase IV	17.8 (2199)
NIS	55.0 (6787)
IIT	4.3 (528)

Abbreviations: IIT, investigator-initiated trials; NIS, noninterventional studies.

[a]Studies conducted over the 5-year period of 2013–2017.

Concerning the number of patients who had been recruited over this 5-year period, more than 50% of all patients participated in NISs (Table 1). Of the total number of patients, 5.7% were recruited in phase I and II trials, whereas about 35% participated in phase III and IV trials. Eighty percent of the respondents indicated that patient recruitment had been conducted via their own patient databases. Moreover, external referral of patients was an additional recruiting strategy for 90% of the university hospitals.

Furthermore, we assessed the infrastructural conditions in German hospitals and medical practices in our survey. Thirty percent of the university hospitals interviewed owned a phase I unit. Most of the hospitals had their own local laboratories and radiology department, whereas the medical practices depended on external facilities (Table 2).

Regarding human resources, in 40% of the university hospitals, at least one physician was working exclusively in clinical research. In contrast, this was the case for 14% of the nonuniversity hospitals and only 6% of the medical practices (Table 3). In most of the hospitals and medical practices interviewed, specialized study nurses had been available to work on clinical trials.

Furthermore, in university hospitals, research-specific tasks were performed >5 days per week on average; in nonuniversity hospitals and medical practices, the average was 3 to 4 days per week. In over 95% of the cases, a physician had been present on the respective days. However, in about 50% of the cases the physician was recruited from other areas of activity to perform study-related tasks (Table 3).

In the neurology departments of university hospitals, there was an average number of nine physicians with experience in clinical studies and 11 with a valid GCP certificate. Fifty-six percent of the university hospitals confirmed that studies were conducted according to local SOPs. This was the case in 37% of the nonuniversity hospitals and 21% of medical practices (Table 4).

Finally, we created an overview of the study activities in the different neurological fields. Overall, 43% of the clinical studies dealt with inflammatory diseases of the central nervous system, 20% with cerebrovascular diseases, and 10% with movement disorders (e.g., Parkinson's disease) (Figure 2). Regarding the different institutions, studies in neuroimmunology constituted about one third of the overall study activity in university hospitals and almost two thirds in medical practices. In university hospitals, cerebrovascular diseases, neuromuscular diseases, and neurooncological diseases each covered about 15% of the overall study activity. On the other hand, in medical practices about 15% of the clinical studies investigated movement disorders. In nonuniversity hospitals, over one third of the clinical trials had been related to cerebrovascular diseases.

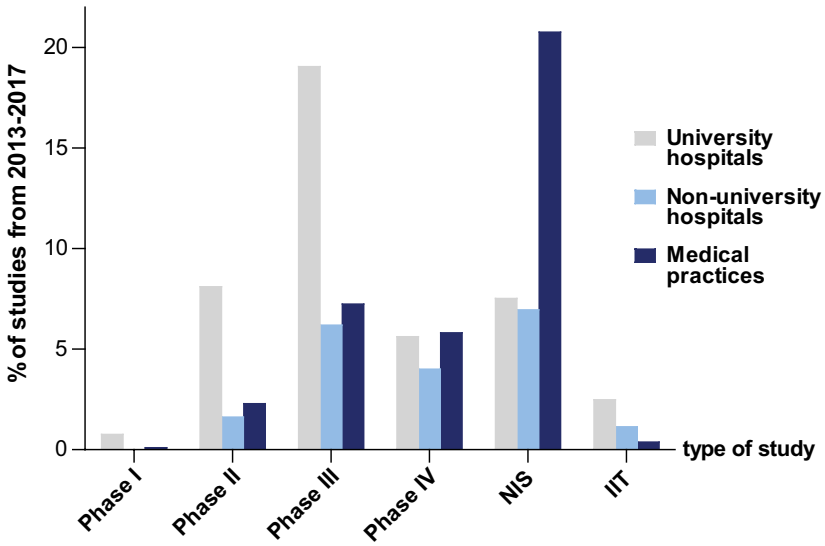

FIGURE 1 Distribution of clinical studies. Distribution of types of clinical trials conducted in the different institutions from 2013 to 2017. IIT, investigator-initiated trials; NIS, noninterventional studies. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Infrastructure

	Value, % (*n*)
Local radiology department	
University hospitals	100 (18)
Nonuniversity hospitals	86 (36)
Medical practices	43 (13)
Local laboratory	
University hospitals	100 (18)
Nonuniversity hospitals	83 (35)
Medical practices	17 (5)

TABLE 3 Human resources

	Value, %
≥1 physician exclusively working in research	
University hospitals	40
Nonuniversity hospitals	14
Medical practices	6
Recruitment of physician from clinical duty	
University hospitals	56
Nonuniversity hospitals	63
Medical practices	33
Specialized study nurses available	
University hospitals	100
Nonuniversity hospitals	84
Medical practices	84

TABLE 4 Quality management

	Value
Physicians with GCP certificate, mean, *n*	
University hospitals	11
Nonuniversity hospitals	4
Medical practices	2
Study nurses with GCP certificate, mean, *n*	
University hospitals	3
Nonuniversity hospitals	2
Medical practices	1
SOP available, %	
University hospitals	56
Nonuniversity hospitals	37
Medical practices	21

Abbreviations: GCP, good clinical practice; SOP, standard operating procedure.

DISCUSSION

The objective of this survey was to create an overview of the current state of clinical research in neurology in Germany. Our results show that on the one hand, over the period of 2013 to 2017, significantly more phase II/III clinical trials had been performed in university hospitals than in nonuniversity hospitals and neurological medical practices, presumably due to accessible funding as well as local availability of infrastructure, interdisciplinary cooperation, and human resources. On the other hand, outpatient medical practices had been predominantly conducting NISs. Looking at the overall research activity, the NISs conducted in the neurological field in Germany had mainly been performed on behalf of and funded by pharmaceutical companies. In contrast to interventional clinical trials, European NISs are regulated by guidelines provided by the respective country and are therefore not subject to the Clinical Trial Regulation (EU/536/2014) [2]. Hence, recruitment of participants and the conduct of the study itself are less restricted. GCP, including expenses for medical monitoring, is not required. As a result, NISs are less expensive and easier to implement in clinical practice.

The complexity of interventional clinical trials may be a reason why only a small number of phase I trials have been conducted in Germany. Phase I trials are frequently run by contract research organizations on behalf of pharmaceutical companies. Most notable contract research organizations are located in the United States and China [3] As illustrated by our survey results, a relevant number of university hospitals in Germany can provide necessary infrastructure and resources to perform phase I trials. However, this is rarely used by funders, which leads to the question of whether resources in German institutions might be too expensive to be able to compete internationally.

Regarding clinical trials addressing their own research questions, our results show that only a few IITs had been performed, which might result from a relative lack of appropriate funding opportunities in Germany. One of the main reasons IITs are so expensive is the demand for permanent monitoring. For clinical researchers in Germany, there are only a few funding options provided (e.g., by the German Research Foundation [4] or the Federal Ministry of Education and Research [5]). Here, the application process is highly competitive and difficult to access. Extension of funding options would be an incentive for clinical researchers to proactively set up IITs.

As our results indicate, lack of financial support is also one of the reasons why most physicians are not able to exclusively work in research and must be recruited from non–research-related tasks or work simultaneously in in-patient care and dedicate their spare time to clinical research. This leads not only to a delay of progress due to shortage of time but might potentially cause a loss of quality.

However, these are issues that are not exclusively affecting clinical studies in neurology but do seem to concern the state of German clinical research in general, as observations in the field of oncology demonstrate [6] The establishment of clinical research coordination centers and central organizations, such as the Institute for Quality and Efficiency in Health Care, serve to improve quality standards, which are also necessary to be able to fulfill the evolving standards of German medicine law [7] Nonetheless, these requirements are a crucial factor for a significant increase in costs, which again leads to

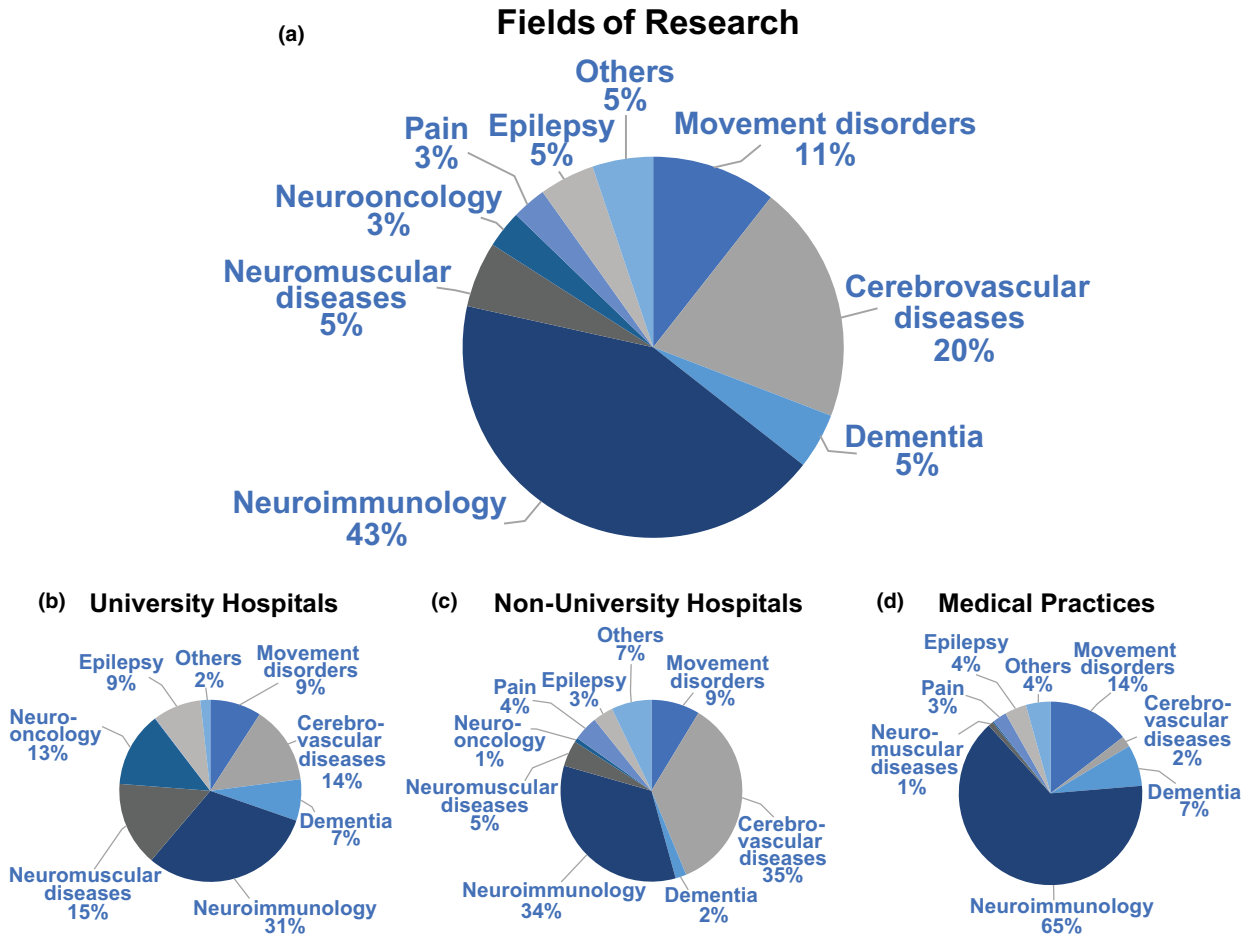

FIGURE 2 Fields of research. Depiction of the percentages of the different fields of research relating to (a) the overall clinical research activity and (b–d) the activity in the different institutions in Germany. [Colour figure can be viewed at wileyonlinelibrary.com]

a dependency on funding by pharmaceutical companies. Off-label use, an essential basis for the development of oncological therapies in clinical trials and utilized as a way to generate financial support from health insurance funds and reduce costs, has been challenged by central boards in German health care [8] As a result, these actions for raising quality standards lead to a substantial increase in costs while funding and financing options become more exclusive.

Another significant objection concerns the long period of time from designing a clinical study to its publication, which seems to represent a burden for medical doctors because it prolongs the academic pathway. A survey study in clinical research in neurology from the United States shows that especially the time to conduct clinical studies as well as recruitment and administrative challenges are major barriers for researchers and ultimately lead to a decrease in research interest and applications for funding [9] The demand and interest for young medical doctors to get involved and invest time in clinical research is evident, whereas offers of specialized training in clinical research methodology and, as mentioned previously, adequate funding are not sufficiently provided [10,11] Apart from financial support, the academical infrastructure and knowledge provided are crucial factors for the quality of research centers. Young neurologists should be encouraged to not only pursue a fast-track academical pathway but also to build a career on conducting more IITs that might be smaller and take longer but in the end are the basis for progress in research.

Addressing the issue of quality management, implementation of and adherence to SOPs are essential for providing efficiency, quality output, and uniformity of performance, not only in research in neurology in Germany but worldwide. The results of our survey reveal that in both nonuniversity and university institutions, there is still a lack of sufficient guidance by SOPs. This might consequently lead to a susceptibility to failures and miscommunication compromising GCP.

Our results show that not all medical doctors involved in clinical trials had a valid GCP certificate, which is becoming an increasingly important issue because, for example, sponsors are asking for available SOPs and GCP certificates as eligibility criteria to serve as a trial site. However, these quality measures are mostly only locally implemented and do not apply on a general basis. In some instances, local centers for clinical trials that are part of the network of the Coordination Center for Clinical Studies [12] can be helpful in creating SOPs. However, it would be preferable to provide general and nationwide guidelines that enable clinical researchers to create and establish reliable SOPs for their specific purposes. Support from a

network providing SOPs that can be adapted to local requirements and education in the field of clinical trials in neurology for study coordinators and study nurses may improve quality and numbers of recruited patients. This would raise quality standards and support clinical research in Germany in international competition. In addition, cooperation with innovative biostatisticians should be promoted to improve trial design, the trial process and data analysis.

Regarding patient recruitment, our results demonstrate that medical practices mainly recruited via their own patient databases, which explains why trials are primarily conducted in the field of neuroimmunology, because neuroinflammatory diseases such as multiple sclerosis (MS) are often treated in the outpatient sector on a long-term basis. The same applies for nonuniversity hospitals that conduct their clinical research mainly in neuroimmunology and cerebrovascular diseases. Here, MS outpatient facilities and stroke units serve as primary sources of patient recruitment. Acute-phase stroke trials go one step further with an excessive demand for human resources to realize 24/7 enrolment.

Besides recruitment from their own patient databases, university hospitals frequently work with internal as well as external referrals. It should be taken into consideration to promote outpatient departments with a higher number of external referrals, especially in the field of neuroimmunology, as experienced and already established research groups could be an advantage to the clinical study landscape in Germany. Because patient recruitment is also crucial to the time frame of conducting clinical studies, another approach could be the development of a nationwide, accessible online database as a recruitment strategy to overcome local limitations and improve efficiency[13].

It must be acknowledged that our results cover only a minority of institutions conducting clinical trials in neurology in Germany and might therefore not be fully representative. Furthermore, the results of this survey are susceptible to bias, because active participants in the survey are more likely to be involved in clinical research. However, the overall response rate could also be a realistic reflection of the actual distribution of clinical research activity in Germany.

To sum up, our inquiry served the purpose of providing the first comprehensive overview of the activities in clinical research in neurology in Germany to identify promising approaches for quality improvement as well as to sustain and encourage clinical research activities in neurology.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Concept and survey: Luisa Klotz and Sven G. Meuth; data acquisition and analysis: Anna Lammerskitten, Luisa Klotz, Melanie Korsen, and Lisa Lohmann; data interpretation: Luisa Klotz and Lisa Lohmann; drafting of the manuscript and figures: Luisa Klotz and Lisa Lohmann; editing and revision of the manuscript: all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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