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Bernhard Bührlen
Peter Georgieff
Horst Christian Vollmar

Clinical research in Germany with special focus on non-commercial studies

Summary

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SUMMARY

Besides commercial clinical research, which predominantly aims at obtaining marketing authorization for a new product, non-commercial clinical research responds to questions that originate from treatment practice. Frequently, medicinal products or medical devices that are already approved, or interventional ones, e.g. surgical or psychotherapeutic methods are investigated. Because research concentrates on the exact application procedures, e.g. the advantages or disadvantages of a combination of different cancer therapies, on the identification of long-term adverse effects, or on the comparison of two treatment methods, the manufacturers of the products often cannot expect economic gains from such studies. In this case, a non-commercial institution, frequently the medical faculty of a university, assumes responsibility for the study (that means, it becomes the »sponsor« of the study), and financial support is at least partially needed from public funds (from the university's budget or project funding), or from non-profit foundations. This kind of studies is called non-commercial clinical studies, investigator-driven trials (IDCTs) or investigator-initiated clinical trials (IITs), partially also as therapy-optimization studies.

Like all clinical studies, the non-commercial trials are regulated by the German Drug Law (»Arzneimittelgesetz«, AMG), as long as they analyse the efficacy, safety or metabolization of medicinal products, with the objective of testing their harmlessness or effectiveness, and if they include a comparison with a control group or a second treatment condition. This kind of clinical study is referred to as clinical trial (»Klinische Prüfung«).

The present report describes and evaluates the manifold factors which contribute to powerful non-commercial clinical research in Germany, and makes suggestions to further optimize the framework conditions. To this end, the medical faculties in Germany were surveyed and expert interviews as well as a final workshop were carried out.

The delineation of non-commercial and commercial clinical studies is not always trivial. It is, however, necessary when the governmental agencies have to decide about reducing or waiving the fees that have to be paid for the authorization of a trial, or if funding from public means is requested. An important criterion is the for-profit orientation of the sponsor and, related to that, the scientific aim of the study. This can be inferred among other factors from whether the data and results of the study can be published freely or if a company exerts influence

on the publication. In non-commercial studies, the substance being researched frequently already has marketing approval for the investigated indication group. The funding of the study, however, is often not an unequivocal criterion, because mixed financial support from companies as well as public funds is frequent. In addition, the economic benefit resulting from a study can only be assessed long after it has been completed, e.g. if the study led to an extended marketing authorization and thus to an increased market for the investigated product.

Non-commercial studies are indispensable for clinical practice for several reasons. It has been shown that the results of commercial clinical studies are partially biased towards too positive outcomes, e.g. because studies with positive outcomes are more frequently published, whereas negative outcomes are suppressed (so-called publication bias). Therefore, studies that are independent of the manufacturer are necessary, as control and correction. Furthermore, many questions are highly relevant for clinical practice, but do not promise increased revenues for the manufacturer, so his motivation to invest in a clinical trial is low. Such studies often imply the direct comparison of two or more treatment options (so-called head-to-head studies), the testing of approved medicines for effectiveness in daily clinical routine, or the development of new methods that do not promise a lucrative market. Furthermore, there are many therapeutic questions in which no medical products are applied at all, e.g. in surgery or psychotherapy, but also in lifestyle interventions or in the field of prevention. Whereas the results of such studies are highly relevant for health policy or for health insurance companies, they are inherently of no commercial interest to a producer.

Non-commercial clinical trials are not only required as thematic complements, but also as a correction for commercial studies, which are partially suspected of biasing the results in a direction which is unreasonably positive for the sponsor, who is mostly the producer of a new pharmaceutical product. Such biases emerge, among others, from the fact that the studies predominantly published are those that have led to positive results, while negative results could be dropped. In order to increase transparency, reduce publication bias and avoid unnecessary studies, obligatory and publicly accessible study registries, combined with the publication of the study results, are suggested.

The amount of non-commercial clinical research in Germany is in a range similar to that in other countries. Its share of all clinical research has not changed substantially in the last years, and also no large increase can be expected for the future. Four fifths of non-commercial studies at the medical faculties only recruit participants from Germany, so that the degree of internationalization is low. This distribution also roughly equals the international average.

Amongst the areas of medicine in which non-commercial studies are carried out, haematology/oncology is the strongest. These studies are frequently funded by the German Cancer Aid (»Deutsche Krebshilfe«). The second strongest disciplines in non-commercial clinical research are neurology/psychiatry/psychology.

In the view of the medical faculties, the financial support for non-commercial studies is the most problematic factor. On top of that, the following aspects are considered problematical: recruiting study patients, resource-intensive monitoring of the studies, validity of the data, qualification of the personnel, as well as problems with supervising authorities and independent ethics committee. To a smaller extent, the support in the phase of application for the authorization of a trial and patient safety are also regarded as problematic.

Even amongst the non-commercial studies, more than half of the trials are at least partially funded by companies. The second most important source of financial support is the joint funding programme of the Federal Ministry for Education and Research (BMBF) and the German Research Foundation (»Deutsche Forschungsgemeinschaft«, DFG), followed by other public funding and university funds. Foundations and the European Union (EU) only play a subordinate role.

The size of the BMBF and DFG funding programme is considered by the clinical researchers to be far too small. Other sources, e.g. the health insurance companies, should also contribute. However, even the funds available in the BMBF/DGF programme could not be expended in total, because the quality of the research proposals partially did not comply with the programme's quality standards. This gives strong evidence of an urgent need for methodological support for the researchers and improving their qualifications. The research infrastructure provided by the Coordination Centres for Clinical Studies (»Koordinierungszentren für Klinische Studien«, KKS) is regarded as very supportive; however, it is not available in all regions and needs additional flanking measures.

The regulations for clinical trials are still considered resource-consuming and partially prohibitive. Nationally and internationally, approaches are tested to graduate the requirements according to the risk for the study participants. In this context, in Germany, the BMBF is funding the ADAMON study. The results of this study, together with the researchers, should be used to establish criteria for the requirements for studies and eventually reduced fees and premiums for participants' insurance. Simplifications for studies with already approved drugs are already in place. This could be supported by an even more stringent implementation of the guidelines for ethical review boards. Compromises regarding patient

safety or the study quality should not be made, because despite the considerable efforts required, it is these two aspects in particular that are important assets of clinical research in Germany.

Clear criteria should also be established for the public benefit that is expected from a publicly funded study; these criteria should also be used for funding decisions. They could contribute to a more transparent procedure by which the Federal Joint Committee (»Gemeinsamer Bundesausschuss«, GBA) decides on the reimbursement of treatment costs for study patients by the statutory health insurance companies.

The at least partial funding of non-commercial clinical trials by companies is generally regarded as necessary and unproblematic in its implementation. In order to invest the resources for non-commercial clinical trials from the public as well as from private sources in a more targeted way, a joint fund for clinical studies should be discussed, to which the public, private funders, foundations, as well as service providers and insurance companies must contribute and which decides about the funding of projects according to the aforementioned criteria. Such an institution which should be guided by the societal need for research in specific fields, could also advise in the better integration of clinical research into broader health research, e.g. the coordination of funding decisions in Interdisciplinary Centres for Clinical Research (»Interdisziplinäre Zentren für Klinische Forschung«, IZKF), the clinical study centres (»Klinische Studienzentren«) or the integrated research and treatment centres.

In addition, funding and other support should be extended to more non-university hospitals and outpatient care. As recruiting study participants is still a problem, this should lead to an increase in potential study centres, facilitate the networking between centres and thus improve the patients' access to studies. To this end, however, it is also necessary that clinical professionals are motivated and qualified for research. A higher value placed on clinical research activities in staff selection and in post offerings – as opposed to the actual focus on basic research – combined with better training, could improve the personnel situation. A generally increased esteem for clinical research in society would also contribute to more patients volunteering to participate in a study. This should be supported by appropriate information for the public.

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BÜRO FÜR TECHNIKFOLGEN-ABSCHÄTZUNG BEIM DEUTSCHEN BUNDESTAG

KARLSRUHER INSTITUT FÜR TECHNOLOGIE (KIT)

Neue Schönhauser Straße 10
10178 Berlin

Fon +49 30 28491-0
Fax +49 30 28491-119

buero@tab-beim-bundestag.de
www.tab-beim-bundestag.de