TAB

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Biomedical innovations and clinical research

Summary

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SUMMARY

Clinical research is a central link in the development chain of new therapy methods. Scientifically speaking, it is located between basic research and application; it includes the first application of a substance to a human being as well as the main proofs of its efficacy and safety. Economically speaking, it requires ca. half of the total expenditure for research and development for a drug and represents a significant factor for the labour market for researchers and study personnel. In addition, through participation in the clinical tests, clinical trials allow patients early access to new treatment methods for diseases which could previously be only inadequately treated. Despite internationally recognized and to a large extent legally codified guidelines, significant national differences still exist in their implementation. Key aspects are still (in part) highly controversial.

Politics has undertaken significant steps to strengthen clinical research in Germany, but the (pharmaceutical) industry continues to complain about further competitive disadvantages here. Although the number of clinical trials has increased in recent years, the increase in several competing countries was significantly higher. This could in the long term affect employment and supplying patients with innovative medicines, as, according to the manufacturers, new products are preferably introduced in countries in which the clinical trials were already carried out. The traditional practices in clinical research are being called into question by novel, mainly biotechnological therapeutic methods, about which existing knowledge is still relatively small and which therefore could harbour particular risks for patients and trials volunteers.

The present report analyzes, on the basis of current regulations, scientific literature, statistics and interviews with experts, the framework conditions, current challenges and solution approaches for clinical research in an international comparison.

ACTORS AND PROCEDURES

In clinical research various interest groups interact: the two federal superior authorities, the Paul Ehrlich Institute (PEI) and the Federal Institute for Drugs and Medical Devices (BfArM) assess the applications for approval of clinical trials which are filed either by the manufacturers of a product to be tested or by academic researchers. The federal states are responsible for the approval of

study sites and the monitoring of the trials, as well as for the work of the regional ethics committees. As the proof of efficacy and safety, i.e. the harmlessness of a product, is an essential pre-condition for the commercialization of new drugs or medical devices and this proof is provided by clinical trials, most clinical trials are financed by and under the responsibility of the manufacturers of the products as approval studies. In order to limit the considerable financial outlay involved in the clinical trials as much as possible, and in order to market their product as fast as possible, the manufacturers are interested in a rapid approval of the study and to recruit trial participants quickly. The approval duration and the associated costs depend on the time schedule and the capacity of the authorities, their interaction with each other and the processing by the involved ethics committees.

Research questions which do not serve the purpose of market approval are usually not borne by private sector interests and must therefore be paid for from public funds. This non-commercial as well as the commercial clinical research depends on the cooperation with hospitals, partly also with outpatient physicians to find the requisite number of appropriate candidates for the studies. Patients are, on the one hand, somewhat reserved as far as participation in trials with new, not fully tested therapy methods is concerned, but on the other hand, they are interested to have access to new therapies as soon as possible, even in the shape of clinical tests, in particular if their illnesses could only be poorly treated with the methods available. Coordination centres for clinical trials have been opened at the university hospitals, funded by the federal government, which support clinical research and offer their services to public and private clients.

REGULATORY FRAMEWORK

Clinical research is largely standardized by international law, whereby in principle different regimes apply for medicines, on the one hand, and medical devices, on the other. As the regulation for drugs is much more complex than that for medical devices – unless medical devices are explicitly mentioned – the conditions for testing drugs are discussed in this report. Clinical research is in addition integrated in the respective national healthcare systems and limited by economic factors, such as the location decisions of the internationally operating pharmaceutical and medical device manufacturers as well as demographic conditions, e.g. the availability of large numbers of test persons, which can only be influenced by politics to a small extent.

Nevertheless, the states have tried to utilize the remaining leeway and to create the most favourable conditions for clinical research in their country. Through an advantageous implementation of the EU directives in national law and by means of many and varied forms of research promotion, Germany has gained a good position, by international comparison. The regulatory framework conditions and their implementation by the federal superior authorities are internationally competitive.

Certain administrative barriers can be determined with regard to the ethics committees which are under *Länder* jurisdiction, the recognition of the trial centres by the Regional Councils, and the approval of trials in accordance with the Radiation and X-ray Ordinance – if required. Thus the division of labour between the various ethics committees, which in a multi-centre study evaluate one study centre each, and the ethics committee in charge which assesses the trial plan as a whole, is not yet optimized. The certification of trial centres and trial monitoring must be carried out by the *Länder* or the Regional Councils, whereby a high burden falls on the sponsor due to the different evaluation criteria, and trials which include radiological examinations or radiation treatments must be in addition approved by the Federal Office for Radiation Protection, which often takes too long to complete because of lack of capacity at the Federal Office.

GERMANY AS A LOCATION FOR CLINICAL RESEARCH

The federal government has been promoting the clinical research infrastructure for several years; the most important instrument in this context are the coordination centres for clinical research. Project funding takes place in the framework of a joint programme of the German Research Association (DFG) and the Federal Ministry for Education and Research (BMBF). Various committees of experts have analyzed the situation of clinical research in Germany in the past years on behalf of the Federal Ministries for Education and Research and of Health. The recommendations have been partially implemented in the meantime.

The general conditions for clinical research in Germany are good, and contrary to the trend in many other countries, the number of clinical trials has increased again in Germany in recent years. This is due among other factors to the growth rates in pre-clinical research, which supplies drug candidates that must subsequently be clinically tested. Moreover, the quality of the clinical trials in Germany is highly regarded, with respect to the reliability of results and safety of the trial participants. Although the costs are high compared with competitors like

China and India, in an intra-European comparison the costs were still comparably modest, at least at the beginning of this decade.

According to the absolute number of clinical trials as well as the number of facilities which conduct them, Germany clearly lies ahead of the other European countries. With reference to the population size, however, in 2007 Germany occupied only the eighth place (with a clear gap after the USA, Belgium, Canada, Denmark, the Netherlands, Sweden and the Czech Republic, at approximately the same level as France, but clearly ahead of the United Kingdom).

Clinical trials in Germany are certified as being of high quality, which represents a significant location advantage in international competition. The emerging competitors such as China, India and several eastern European countries can not yet adequately guarantee this quality and the related safety for the test persons and reliability of the data gained. They possess other locational advantages, however, in particular lower costs and the availability of a large number of potential test persons. A relocation of clinical research to emerging nations is taking place, but only to a limited extent. An essential part of the clinical research will also have to remain in Germany in the future, even if the quality will gradually disappear: data is required which at least partially stems from the population in the target market; at the same time studies also serve to familiarize the users in the target market with a new method.

An important site condition in Germany is also the access to test persons who are willing to take part in clinical trials. Further improvements are possible regarding the willingness to participate and the access to studies, in particular through a better integration of clinical research in the health care structures and by trials which reflect the need from the perspective of the patients and the public health system. In addition, the availability of well educated test persons is significant; there are already programmes to promote this. The evaluation of these programmes and a systematic integration of research knowledge in the education syllabus of medical doctors is however still outstanding. For the location factors, further need for improvement is seen in the appreciation of clinical research among scientists and with regard to integrating clinical research into other health research.

CHALLENGES POSED BY INNOVATIVE THERAPIES

Because their mechanisms of action are often poorly understood, but highly effective, novel therapeutic procedures involve particular risks, which in clinical

research mainly concern the trial volunteers. This emerges clearly from the example of the drug TGN1412 of the Würzburg firm TeGenero. In these tests, which were carried out in the United Kingdom, but would also have been approved for Germany, the test persons suffered severe health effects. The European approval authorities thereupon raised the requirements for the testing of high risk substances, which was regarded by the scientists as an appropriate and adequate reaction to increase the safety of the trial volunteers. Risks for test volunteers or patients in clinical studies cannot be completely ruled out. Balancing these risks and the resulting stricter conditions for clinical trials against the chances of an early access of concerned sufferers to innovative therapies, and the economic interests of the manufacturers and the economy is difficult. For the patients and users there is a dilemma between a fast improvement of the treatment possibilities and a minimization of the risks; for the manufacturers an early market introduction means an increased profit opportunity, but they too want to keep risks for the users to a minimum and avoid market withdrawals. The discussion about balancing benefits against risks should be further encouraged in society as a whole and in the expert forums, also with a view to increasing patient participation and patients' sovereignty. Depending on their classification into risk categories, different requirements apply to prove the efficacy and safety of medical devices. But also in drug testing, some trials are more risky than others. Also tests to optimize therapy with already approved drugs must be approved as clinical trials, so that they do not differ from studies with new drugs in terms of outlay in costs. It is proposed to examine at which points the requirements for clinical trials can be reduced, depending on the related risks.

INTERNATIONAL APPROACHES TO SOLUTIONS

The previous and still running public measures promoting clinical research in Germany have had a good effect. However, there is still need for extensive promotion to optimize the infrastructure as a basis for non-commercial clinical research as well as a cooperation partner for commercial trials. In an international comparison, centres for clinical research have proved favourable, as they are able to accumulate a high level of competence in specific research fields. Examples for this in Germany are the Interdisciplinary Centres for Clinical Research. Compared to the United Kingdom or the USA, however, their number is relatively small and they are financially less well equipped. In the United Kingdom the integration of such centres in the regional, even ambulatory health care proved to attract patients for trials. A register of information about clinical tests is already being set up in Germany, but with hitherto uncertain financing after the end of the start-up promotion. Moreover, in Germany the question is being controver-

sially debated whether an obligation to report studies to the register is required. The proponents of a mandatory solution promise a better controllability of the course of the trial and complete documentation, also of trials which do not reach an outcome favourable for the sponsor; the opponents consider the necessary effort to be counterproductive. In other countries, registers for treatment data of patients with certain indications from routine health care which can be used to evaluate therapy procedures have also proved to be valuable complements.

INTEGRATION OF CLINICAL RESEARCH IN THE HEALTHCARE SYSTEM

In addition to promoting the infrastructure, clinical research is also supported via project promotion; above all, research issues profit from this which are not of commercial interest to a manufacturer, but rather of purely clinical relevance. A body which determines the need for clinical trials from the perspective of the public health system and commissions the relevant studies, as is the case in other countries, does not exist in Germany. In general, clinical research is still too little connected with health care practice, as it is either guided by the marketing interests of industry or by uncoordinated applications for promotion from academic researchers. This makes it difficult to recruit study participants, contributes to the low reputation of clinical research in the academic environment and limits the utilization of the results of clinical research in clinical practice. A body which coordinates the activities of the university teaching hospitals with the nation-wide activities and the need from the viewpoint of the public health system, including the patients‘ perspective, could support the systematic recording of health care needs and coordination across hospital and federal state borders.

Clinical research depends on new procedures which should be examined in studies for their suitability for health care practice. It can only develop maximum benefits if it is well coordinated with basic research, on the one hand, and with health care research and practice on the other hand. This should include both the planning of clinical trials as well as the utilisation of their results. The various promotional programmes should therefore be better coordinated than previously, in the framework of an overall concept for translational research (as a translation of research results to practice and definition of research issues from practice-relevant concerns). The users in clinical practice should receive access to the research results in an easily usable form and the acquisition of corresponding user skills facilitated. A joint body could be created which coordinates the evaluation of clinical studies and the processing of results for the different target groups (e.g. patients, healthcare professionals, hospitals, health insurance providers). For the use of the results in practice it would also be helpful to re-

cord, besides the hard result criteria like mortality rates, also those which are of greater relevance for the practitioner and those concerned, such as e.g. the improvement of the quality of life.

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