Chapter 16
Risk Management in Radiation Medicine: Administrative, Legal and Ethical Aspects of Research in Radiation Medicine in Germany

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Key Messages

Research is a key to assess and minimize risks in medicine. Therefore, clinical trials are a prerequisite. However, their legal framework has intersections between conflicting risk cultures. Hereby, research is hampered and significant risks (e.g. lethal complications after combination of radiation and new drugs in oncology) may not be well addressed.

Clinical Trials in Radiation Medicine

Medical research is the cornerstone of evidence-based medicine, minimizing treatment risks by the knowledge obtained in clinical trials. In order to minimize the risk to patients within trials versus other, for example commercial interests, a large legal framework has been established and recently internationally harmonized. Similarly, radiation protection of individuals and society must be maintained and is regulated by another internationally harmonized legal framework regulating the use of radiation in medicine. As clinical radiation medicine research is touching both topics, the problems of intersecting risk cultures can be learned here.

In the following, we point out three examples for such problems: the risk for the research landscape in Germany, the combination risks of radiation and drugs in oncology, and the changing position of ethics committees.

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Research Involving Radiation Medicine in Germany

The requirements for the conduction of clinical trials do not make a difference between commercial and non-commercial research. The legal framework is driven by the highly relevant idea to protect individual patients when participating in a trial. Clear standards and safety requirements (e.g. the guideline on good clinical practice of the international conference of harmonization; ICH-GCP) guide researchers to high-quality conductance of studies, ideally leading to valid answers to relevant questions. These guidelines regulate the application of a drug tested alone or in the context of other drugs, and their aim is to internationally standardize the requirements for drug approval.

On the other side, the application of radiation in medicine underlies respective laws (e.g. Euratom and consecutive national regulations), which aim at the protection of individuals and society against radiation. Research involving radiation in medicine, e.g. on evaluation of new tracers for diagnostic imaging or new treatment methods involving radionuclides or percutaneous radiotherapy, is regulated here.

When trials include both drug application and medical radiation exposure, they underlie both regulatory frameworks and hence must respect both risk philosophies. This leads to a situation in which the same scientific question may be assessed and regulated twice, with different requirements. As an easy example, a scientific project addressing the use of a drug together with standard radiotherapy may be regarded as research in the drug administration context and not as research in the radiation protection context. However, when both frameworks regard a project as research, the administrative organization of the study approval processes in Germany, together with different risk focuses and philosophies, may lead to conflicting constraints and to multiple reviews and revisions before the approval of the trial. Sometimes, different regulatory bodies are not informed about the requirements of their counterpart and propose conflicting corrections. Due to this time-consuming process, German researchers are often not included in international research projects, because the regulatory frameworks of other countries offer more efficient solutions for this dilemma.

Beyond the obvious disadvantage for German researchers, the problem is that patients will here be advised using data from trials conducted in foreign countries, possibly underlying less strict safety and quality control.

Risk of the Combination of Drugs and Therapeutic Radiation

For the approval of drugs in oncology, it is not mandatory to test the drug in the context of therapeutic radiotherapy. Furthermore, due to the administrative obstacles, additional trials on the combination of drugs and radiation therapy are often omitted by the research community. After approval of a drug, its combination with therapeutic radiation medicine in clinical reality is, however, often inevitable.

A patient with multiple painful metastases needing effective pain control, for example, may need both stabilization by radiotherapy for local palliation and systemic treatment to prevent or slow progression at other sites. Both treatments can then be regarded as standard approaches and are approved or even recommended by international guidelines.

Recently, after the approval of a new generation of anti-cancer drugs, there are increasing numbers of reports about severe complications after their intended or even accidental simultaneous or sequential combination with therapeutic radiotherapy. From a regulatory view, these complications are subject to individual reports to the authorities. However, prospective comprehensive data would be needed to assess the actual incidence and hence the severity of this problem. Obviously, there is no commercial interest to obtain such data after successful drug approval. The instrument of health services research (*Versorgungs-forschung*) would therefore be appropriate, which however lacks initiative and funding. We here see an urgent need for action due to the severe risk potentially affecting thousands of patients with cancer.

Changing Position of Ethics Committees

In the recent harmonization of European laws, the position of ethics committees assessing clinical trials has significantly been changed. Now, only one ethical committee, in the country of choice of the investigator, is responsible for the approval of a trial. Together with the time limits given (if not kept, the trial is regarded as approved), this places enormous pressure and responsibility on the ethics committees. On the other side, in order to be able to give independent statements, the committees are usually manned by honorary persons with limited time resources. Furthermore, they may still be somehow dependent on university bodies. This situation may lead to a lack of thorough discussion of proposed trials, and hence increase the risks for patients in clinical trials.

In the context of radiation medicine research, there is an additional issue: for an ethics committee confronted with complex radiation-related scenarios, the presence of committee members with respective know-how should be mandatory. Due to the recent regulatory changes, this is not guaranteed, posing an additional risk to patients—and researchers—involved in trials, as outlined above.

Conclusions

Radiation medicine research in Germany faces several urgent issues involving the process of administrative approval of clinical trials, the problem of combination toxicities between new oncologic drugs and therapeutic radiotherapy, and the shortage in manpower and expertise of ethical committees confronted with recent regulatory demands.