Critical Reviews in Oncology / Hematology 134 (2019) 82–86

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

# Ready for Germany's revised radiation rules?

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ARTICLE INFO

*Keywords:*
Oncology
Clinical trials
Ionising radiation
X-ray
Authorisation
Germany
BfS
Radiation protection
Law
Companion diagnostics
Medical imaging
EU
AMG
StrlSchG

ABSTRACT

The assessment of the benefit-risk ratio of investigational medicinal products (IMPs) and the approval of clinical trial applications (CTAs) conducted in the European Union (EU) is a remit of national competent authorities (NCAs) of the 28 member states.

The aim of this article is to shed light on clinical studies for oncology drugs carried out in Germany which involve diagnostic radiation tests. The authorisation process surrounding diagnostic radiology accompanying clinical investigations and used for measuring IMP related treatment effects is not well understood. The procedure appears to be complicated because the scientific evaluation of the application is carried out by an independent agency, the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz, BfS). To avoid delays and failures in conducting studies in Germany knowledge of the scope, procedural steps and associated timelines is crucial for project management purposes. Reliable planning is a pre-requisite for timely study initiation. Novelties of the recently implemented law and key aspects relevant to CTAs should facilitate obtaining BfS clearance. Integrating this additional regional requirement in drug development plans is of importance for timely commencement of multi-national clinical trials.

## 1. Initiation of clinical trials in the EU

According to the clinical trial directive (2001/20/EC) (Anon1, 2018), which currently regulates clinical studies on medicinal products for human use in the EU, approvals by NCAs and Ethics Committees (ECs) are imperative for initiating a clinical study.

The typical CTA consists of study protocol, and investigator's brochure on the IMP, as well as appropriate summaries of clinical, non-clinical and quality information in the form of an Investigational Medicinal Product Dossier. The documentation is submitted to concerned NCAs and relevant ECs. Upon assessment of the data and after granting authorisation / favourable opinions from regulators / investigators the study may proceed.

Oncology clinical trials often include imaging tests to diagnose the presence of a tumour or to visualize its location, size and shape. Methods for detecting, evaluating and measuring tumours include:

- computed tomography (CT) scans with oral or intravenous contrast to produce pictures (Anon3, 2018)
- positron emission tomography (PET) for assessment of cancer spread
- magnetic resonance imaging (MRI) scans

Table 1 presents data from the EU clinical trial database (The EU Clinical Trials Register). As shown, approximately one-third of all oncology trials involve CT, followed by MRI and PET.

Imaging using CT and PET involves the use of x-ray / ionizing radiation (IR) and the biological effect translates into ionization of water molecules through creation of hydroxyl radicals or other reactive oxygen species. These can induce DNA single/double strand breaks or DNA base damages (Anon5, 2018; Anon6, 2018).

MRI, primarily used for soft tissue scans (Anon7, 2018) and functioning via magnetic fields is not subject to the additional radiation law obligations.

Tumour assessment is in general based on RECIST (Response Evaluation Criteria In Solid Tumours), which is defined as a set of validated and consistent criteria to assess quantitative changes in tumour burden, primarily measuring changes in tumour size as the main response criteria (Anon8, 2018; Anon9, 2018). Imaging encompasses the entire study therapy period from screening, treatment, end of treatment and follow up stages, and targets different body parts depending on the location of the tumour.

As part of a clinical study protocol, initial response assessment is determined by investigators based on a fixed schedule. Subsequently, these scans are sent to a central imaging laboratory for independent review and archiving. At the time of early (first line or second line) oncology treatment with single anti-cancer medicines or combination drugs, more frequent monitoring of responses is done. During maintenance, treatment scanning is scheduled less frequently. The distinct

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https://doi.org/10.1016/j.critrevonc.2018.11.012
Received 15 June 2018; Received in revised form 7 October 2018; Accepted 29 November 2018

**Table 1**
Overview of oncology clinical studies - EU Clinical Trials Register (Anon4, 2018).

| | |
|---|---|
| Total number of clinical trials in the EU Clinical Trials Register | > 32,000 |
| Number of oncology clinical trials | > 2,100 |
| Number of oncology trials and CT | > 650 |
| Number of oncology trials and MRI | > 474 |
| Number of oncology trials and PET | > 180 |

[accessed: 01/05/2018].

number and frequency of diagnostic imaging procedures must be justified. There may also be variability in terms of the actual dose. For a global protocol, especially in the case of rare cancers, key opinion leaders and clinicians must be consulted not only on the primary objective but also on diagnostic examinations. All study investigators should agree upon on what is appropriate in clinical practice, taking into account recommendations of regional oncology guidelines and local medical practices (Anon10, 2018).

Exposure of the human body to harmful IR is often unavoidable when participating in an oncology clinical study. However, exposure of patients, whose condition is already affected by cancer and several prior lines of treatments, must be minimized to reduce radiation-induced damages, particularly if the protocol suggests multiple exposures (Anon11, 2018). At the same time the radiation dose must be sufficient to obtain the required diagnostic information (Anon12, 2018; Anon13, 2018; Anon14, 2018).

All radiological study procedures and interventions are part of the 'Informed Consent Form' (ICF) which every subject must read, acknowledge and sign to be able to enrol in a study. The ICF informs about the imaging that will be used, including brief descriptions and warnings of the potential risks, discomforts and unwanted effects.

Furthermore, radiation exposure is controlled by a regulatory body to assure the protection of patients participating in a trial. Remembering that the EU clinical trial directive has been nationally implemented, country specific elements are applicable. Therefore, different types of radiation supervision are set up across the EU. A radiation expert is frequently a member of the CTA assessment team assigned as needed within the NCA. If the IR exposure exceeds to the usual standard care, approval by an advisory committee may be required (e.g. UK's Radioactive Substances Advisory Committee, ARSAC) (Anon15, 2018; Anon16, 2018).

In Germany, and as per the regulatory landscape, the CTA evaluation engages the national authority for radiation protection (BfS) (Anon17, 2018). Provided an authorisation is needed, the BfS opinion always matters, whether or not the radiation examinations are consistent with the standard care for radiographic monitoring. The essential aspects of the radiation law covering the use of IR are described in the following paragraphs.

## 2. Study initiation in Germany

In Germany, clinical trials are authorised by one of the two competent federal higher authorities. For CTAs with small molecules or recombinant proteins the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) (Anon18, 2018) is responsible, whereas the Federal Institute for Vaccines and Biomedicines (Paul Ehrlich Institute, PEI) (Anon19, 2018) is in charge of approving clinical trials for allergens, vaccines, blood products, recombinant antibodies, and advanced cell therapies.

If a CTA includes besides an investigational therapeutic antibody, an unlicensed, small molecule radioactive PET ligand used for assessment of an end point in a trial, the PEI is responsible for the IMP whereas the BfArM is assessing the quality and safety of the PET tracer, which is regarded as non-IMP (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/imp_03-2011.pdf).

**Table 2**
List of clinical studies as published in German clinical database (DRKS).

| | |
|---|---|
| Total number of clinical trials in the DRKS | > 6970 |
| Number of radiation trials | > 150 |
| Number of oncology trials and radiation | > 130 |
| Number of oncology trials and MRI | > 80 |

[Accessed: 3 June 2018].

As mentioned previously, regulatory green light from one of these agencies as well favourable opinions from the concerned ECs are necessary prior to study start. An overview of completed and ongoing cancer trials in Germany can be found in the portal 'PharmNet.Bund' (Anon20, 2018) or in the 'German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS) (Anon21, 2018). Against the background that the DRKS is the approved WHO Primary Register (Anon22, 2018) with public access, information on clinical studies was extracted from this database. Table 2 shows the majority of studies currently ongoing are radiation oncology trials.

The federal agency's (e.g. BfArM or PEI) oversight is to check the IMP quality / safety and efficacy along with its benefit-risk profile, whereas ECs evaluate ethical aspects of the clinical investigation (Anon23, 2018; Anon24, 2018)

The local law defining CTA requirements and approval timelines is described in the German Medicinal Products Act (Deutsches Arzneimittelgesetz, AMG) (Anon25, 2018). In addition, the ordinance on the implementation of Good Clinical Practice (GCP) in the conduct of clinical trials on medicinal products for use in humans (GCP-Verordnung) (Anon26, 2018) is relevant. Having transitioned the rules originating from the clinical trial directive, it contains language on the approval and conduct of clinical trials with medicinal products in humans.

The AMG covers radio-pharmaceuticals and medicinal products treated with IR (radioactive drugs and ionizing radiation-treated drugs (§7 AMG). It also requires alignment with the federal ministry for Environment, Nature Conservation, Building and Nuclear Safety, when placing radiopharmaceuticals on the market or using IR radiation in the manufacture of medicines. But the AMG makes no provisions for a study that includes IR for diagnostic or therapeutic purposes. These cases are regulated by another agency, the BfS.

## 3. The third pillar in the control of clinical studies in Germany: BfS

The BfS (Anon17, 2018) is an organisationally independent, scientific-technical higher federal authority within the ministry for the Environment, Nature Conservation and Nuclear Safety. The agency's mission is to serve for the safety and protection of humans and the environment against damage due to ionising and non-ionising radiation. It pools competencies in the area of radiation protection integrated across the Department for Radiation and the Environment and Department for Radiation and Health (Anon27, 2018; Anon28, 2018).

As regards medical radiation protection, the BfS assesses the safety of a clinical trial in terms of radiation exposure. The corresponding legal framework relates to a special law, the Radiation Protection Act, which contains statues on companion diagnostics / radiation therapy and governs the authorisation procedure.

Of note, the GCP-V includes (refer to the Chapter 4 Documentation and notification obligations, databases, inspections - §12 Notification, documentation and information obligations of the investigator) a requirement that investigators shall inform in accordance with §67 of the AMG to the competent authority on whether provisions of the laws on [….,] radiation protection are to be taken into consideration […..] (Anon29, 2018).

## 4. The new law on radiation protection in the context of diagnostics / medical imaging

Having transposed the European Directive (2013/59/Euratom - protection against ionising radiation) (Anon30, 2018) from 2013 into national law, the German x-ray and Radiation Protection Acts were integrated in the new radiation protection law (Strahlenschutzgesetz, StrlSchG) (Anon31, 2018), which covers all areas of protection from IR.

The federal ministry for the Environment, Nature Conservation and Nuclear Safety, which historically owns radiation expertise, was driving this legislative procedure in Germany. The new Radiation Protection Act from 27 June 2017 came into force on 01 October 2017. It represents a step forward in providing consistency and thus simplifying the clinical trial regulation in Germany, while assuring protection of subjects participating in clinical research involving potentially harmful radiation diagnostic tests or radiation therapy.

It must be borne in mind that the radiation-related risks measured against the expected significance of the results for the development of medical science / treatment procedures are medically justified, taking into account the medical benefits for the subject (§§31 (4)1).

Particulars on medical research are provided in Section 5 (§§31 - 37 StrlSchG). In principle the use of x-ray radiation on humans in medical research requires approval by BfS (§31) unless x-ray examinations meet criteria of a simplified notification procedure as specified in §32 (Anon32, 2018).

## 5. §32 simplified radiological companion diagnostics [diagnostic imaging]

This section relates to research that examines the safety or effectiveness of a method (e.g. low-dose radiological companion diagnostics) for the treatment of patients if:

- the application of radioactive substances or IR itself is not the subject of the research project
- the application of radioactive substances or IR corresponds to an accepted standard method of medical care
- type and frequency of the application of radioactive substances or IR corresponds to the purpose of the research project.

In addition, insurance coverage and ICF signatures are needed in line with the standard practices for clinical research.

This notification procedure is not applicable for radiation oncology research comprising the medical use of IR as part of cancer treatment to control malignant tumour cells.

Although the content of the new StrlSchG is identical with the previous x-ray law, the ordinance now lays down timelines for the notification and authorisation procedures for studies within the scope of ‘medical research” as defined in the radiation law [§ 33 StrlSchG].

As a concrete example, reference is made to an established radiation application (CT scans), incorporated into a randomized phase 2 trial conducted to assess the efficacy and safety of a new anti-cancer drug combination, consisting of an investigational therapeutic monoclonal antibody and different standard doublet chemotherapies. The schedule of assessments of the protocol includes several tumour assessments. Radiation uses are intended prior to treatment, during combination treatment, frequent checks during maintenance. One scan is recommended at the end of the treatment plus one treatment if participating in an extension study.

In this context, the planned diagnostic imaging examinations involve nuclear medicine that do not correspond to the standard of care, and authorisation by means of a simplified notification procedure is mandatory.

## 6. Application of IR research on humans in medical research

Detailed instructions and explanations as well as examples illustrating the use of IR within the framework of a clinical study are available on the BfS website (Anon33, 2018), (Anon34, 2018)

First and foremost, it must be checked if the use of radiation at all requires a BfS license. This depends if the planned radiation use is primarily intended for the examination or treatment of individual patients but not for advancement of medicine / medical research. If the same type and scope of use of radiation is administered to study participants on the basis of the inclusion and exclusion criteria, as would be given to patients, not participating in the study, then no BfS approval is needed. If the type and scope of radiation use is outside the scope of the current standard of care (e.g. higher frequency than used in clinical practice) approval for the use of radiation is required (Simon et al., 2015; Anon36, 2018).

If a BfS license is endorsed and considered to be essential, the application requires provision of detailed information on type of radiation (beam quality), dose, schedule, target etc. and on the clinically established and recognized procedures. Several forms need to be completed, which can be downloaded from the BfS website. The key documents for radiation companion diagnostics are summarized in Tables 3 and 4 (Anon37, 2018).

The procedural timelines can be summarized as follows (Anon38, 2018):

- Validation: the agency has 14 days to formally review the completeness of the submission. In case of deficiencies the sponsor has 10 days to provide additional information. The agency checks the supplemental information within 12 days.
- Assessment: once validated, the BfS has 28 days to assess the application. If there are grounds for non-acceptance (GNA), the agency issues a deficiency letter. The sponsor has 21 days to respond. The agency evaluates the response document within 21 days and decides if all issues raised in the deficiency letter have been adequately addressed and the responses were satisfactory.

For radiation therapy research, a 90 day period is applied for determination of the authorisation. If needed, the deadline can be extended once for another 90 days [§31].

**Table 3**
Scope of BfS application.

| Document | Content |
|---|---|
| Form sheet A | Administrative company information and specifying if application relates to simplified notification or detailed authorisation procedure |
| Form sheet C (only multi centres studies) | Table of participating centres including information on the use of x-ray |
| Form sheet D | Medical scientific study information, x-ray examinations, study population, study duration etc. |
| Appendix 1 | Information must be provided on the type of radiation and its frequency at the different stages as summarized in Table 4 |
| Appendix 2 (not needed for simplified notification) | Technical implementation of the X-ray |
| Form sheet B (for each study centre) (not needed for simplified notification) | Personnel and equipment information required to perform the study. It is key that participating facilities require an establishment license and participating physicians must have the specialist knowledge in radiation protection |

**Table 4**
BfS Appendix 1 - radiological information.

| Type of radiation use | Number or frequency of uses in relation to the intervention | | | |
|---|---|---|---|---|
| Beam source | Prior of commencing treatment` (screening or baseline) | During treatment | End of treatment | Follow up |
| e.g. CT | × | × | × | × |

- Approval: the simplified notification application of x-ray research on humans in medical research is approved as specified in §33 StrlSchG:
- after expiry of the deadline (implicit approval), or the BfS has notified to the sponsor that the agency will not require the full timeline.
- EC approval: the BfS has informed the sponsor of the receipt of a positive opinion from EC. Implementation of this additional measure may be a consequence of parallel submissions to EC and BfS. The EC must be registered with the BfS. An overview of ECs entitled to use in the context of IR on humans can be found on the BfS homepage: Registered ECs (Anon39, 2018).

A flow chart of the BfS approval process is shown in Fig. 1. Changes to the authorised use of x-ray must be reported in Form sheet A.

Approval notification is usually obtained if the type of medical use of radiation is in line with the acknowledged standard procedures in human medicine. The actual use of radiation in patients depend on inclusion and exclusion criteria, which are not reliant on approved radiation uses.

The BfS authorisation on the use of radiation is valid for the study duration only but does not extend to cover treatment after disease progression.

In order to obtain a consolidated opinion on radiological assessment for a multi-centre clinical investigation, each participating investigator, coordinating investigator and qualified physician(s) (according to the German radiation protection law) (Anon40, 2018) must certify that the radiological tests as proposed in the study protocol are justified and consistent with the standard of care. No detailed authorisation is needed; only a submission using the simplified notification procedure (companion diagnostics) and assessment by BfS is adequate.

The standard of care appropriate for diagnostic imaging may not always be evident, even to the qualified physician. Likewise, radiologists may need to adapt parameters from a global study protocol to available instruments at the site, which can conflict with the local standards. The settings in the protocol may more reflect the lowest common denominator requiring optimization and experimental work (Anon41, 2018; Anon42, 2018). If there is any doubt about the adequacy of the imaging frequency, it is recommended to consult with an independent panel of experts at the Germany Radiological Society (DRG) (Anon47, 2018). This organisation can advise if the proposed radiation used is in agreement with current medical practice. A short description of the sudy is needed including primary objectives and endpoints along with the type of radiological interventions to be used. Also relevant is whether the study serves as a basis for a new diagnostic test or as companion diagnostics in context of a therapeutic study. Additionally, the scope of an application and use of IR can be discussed with the German Society for Radiation Oncology (DEGRO) (Antoch et al., 2014; https://www.degro.org/). The advice obtained from DRG/DEGRO is not legally binding.

## 7. Conclusions

The BfS is a specialised agency in Germany designed to provide state of the art technical expertise relating to IR. Thus, patient safety in a clinical trial is assured by evaluating protocols and associated radiation measures to establish appropriate exposure. The BfS complements the assessments of the federal agency (PEI / BfArM), which assess the quality of IMP along with toxicology and clinical efficacy, and ECs who look into ethical standards of a study.

The split of responsibilities between agencies provides a high level of specific, scientific know-how for thorough evaluation, applying what is considered appropriate regulatory oversight for imaging methods or radiological oncology.

Despite these strengths, lack of flexibility and cumbersome administrative procedures impair proper planning and timely approval procedures. There appears to be little cross-talk between the various regulatory committees in Germany, although the BfS collaborates with the WHO in protection against harmful effects of ionizing and non-ionizing radiation (Anon45, 2018).

The new radiation law promises to improve the overall performance of IR authorisation procedures by BfS (Anon50, 2018). The law now contains binding approval timelines and the duration for processing and approving applications ranges between 42 days (if there are no validation issues and agency questions) and up to 106 days (in case of validation requests and responding to a deficiency letter). This should make the application more predictable. Previously, the agency operated without time limits leading to procedures that varied between several months and more than one year. As a consequence, the number of radiation oncology studies conducted in Germany are estimated to have

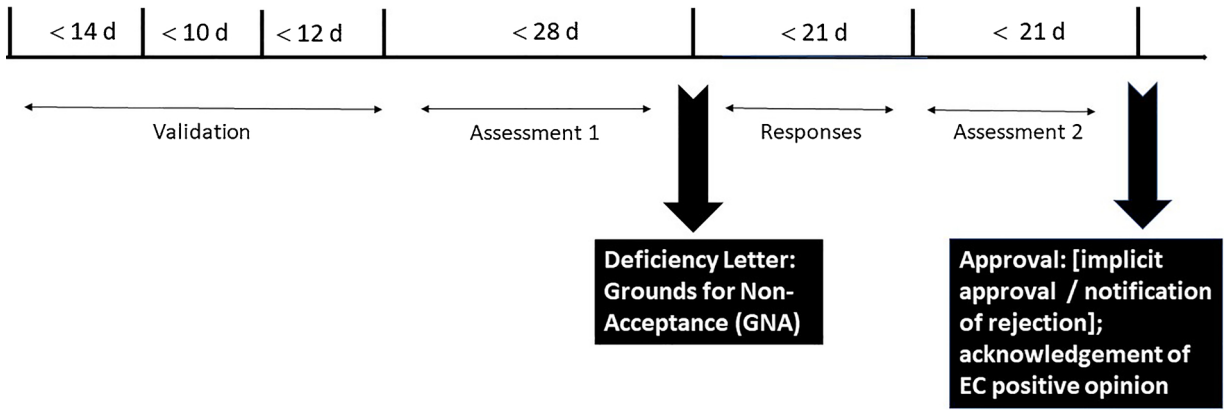


**Fig. 1.** Overview: BfS approval timelines.

dropped by around 15% in the past years (Anon51, 2018; Anon52, 2018) It remains to be seen if the new law attracts sponsors.

However, further changes and improvements can be envisaged and more streamlined procedures imagined. The new ordinance failed to transfer responsibilities for medical research to federal health agencies with in depth knowledge and competencies in overseeing clinical studies. There is also no centralised submission, nor a joint and coordinated assessment with the NCA / EC.

In view of the upcoming clinical trial regulation (CTR, 536/2014) (Anon54, 2018; Anon55, 2018) and advanced collaboration requirements, the continued operation of the BfS as an autonomous organisation does not foresee to yield synergies or value creation. In fact, besides the interaction with the WHO, the BfS is not really connected to the national or EU agency network. The BfS therefore is not compatible with the CTR, which will replace the clinical trials directive during 2019 (excluding the 3 years transition period) (Anon49, 2018). The CTR introduces an authorisation procedure based on a single submission via a single EU portal, and an assessment procedure leading to a single decision.

Likewise, to the joint pilot project between federal authorities (BfArM / PEI) and EC for processing of applications for the authorisation of clinical trials on medicinal products for human use in accordance with CTR (Anon56, 2018), it will be necessary to develop, test and optimise processes for a joint CTA assessment between federal agencies and BfS. If successful, an adjustment of the legal framework could be made. It is not clear why there seems to be reluctance to implement these changes at the government level. The intention should be to work effectively with industry to facilitate drug development in Germany and across the EU without compromising the regulatory oversight standards. The BfS should introduce transparency measures, such as publishing processing statistics (e.g. the number of applications and approval timelines), as is the usual practice with most agencies.

*Conflict of interest statement*

The views expressed are those of the author and should not be understood or quoted as being on behalf of the organization with which the author is affiliated. MK is an employee of H.Lundbeck A/S. The author has declared no conflict of interest.

## Acknowledgements

I am indebted to Dr Richard Peck and Mr Michael Sankey for their critical review of the manuscript.

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