Germany

**Question 1:** What laws or regulations apply to an application for conducting a clinical trial in Germany?

Clinical trials involving drugs are covered by the German Drug Law (Arzneimittelgesetz, AMG); further details are provided in the GCP Decree (GCP-Verordnung). An amendment is expected for July 2012.

Medical Devices are covered by the German Medical Device Law (Medizinprodukte-Gesetz, MPG); further details are provided in the MPKP Decree (Medizinprodukte-Klinische Prüfungsverordnung) and in the DIMDI Decree (DIMDI-Verordnung, DIMDI = Deutsches Institut für Medizinische Dokumentation und Information). The last amendment dates for March 2010.

For radioactive compounds there is a radiation protection decree (Strahlenschutzverordnung; Decree for protection against ionising radiation) and a radiology decree (Röntgenverordnung; Decree for protection against x-ray radiation); both were amended in November 2011.

In addition, there are data protections laws and overall civil and criminal legislation coverage.

Genetic research: Gendiagnostik-Gesetz (genetic diagnostics law) entered into force 2009; however, its regulations do not apply for research projects.

For other biomedical research there is no special legislation. However, physicians in Germany have to follow their Medical Association’s Professional Code of Conduct which becomes a legally binding instrument by a decree of the Federal States governments and can slightly differ among the different Federal States (“Bundesländer”).
Question 2: Which government, legal or authoritative body or bodies is or are responsible for the establishment and/or accreditation of (research) ethics committees for IMPs, and for their supervision and quality? Are there different (research) ethics committees reviewing other projects?

By the “Law for the Amendment of Provisions concerning Regulations in the Drug Field” (Gesetz zur Änderung arzneimittlerleichtlicher Vorschriften), operative from 17th July 2009; RECs are entitled, and obliged, to withdraw a favourable opinion if adverse aspects come to their knowledge. They are, however, not obliged to perform any kind of active monitoring.

The same regulation is given in the revised “Law on Medicinal Devices (Medizinproduktesgesetz) operative from 29th of July 2009. The latter law also prescribes that, for the assessment of research projects on medicinal devices after the 21st of March 2010, only RECs established on the States law (Landesrecht) are permitted. Free or commercial RECs are not now legally competent for this kind of research. The new regulation harmonizes the research on drugs and medicinal devices.

The competent REC which is responsible for the coordinating investigator in multi-site trials, or for the principal investigator in single site trials, is defined by different States legislations: either the REC at the Medical Association or at the university, or a REC attached to a States government depending on the location of that investigator.

RECs are competent for all biomedical research projects including research using removed biological materials of human origin and/or using personal (including pseudonymized= coded) data for epidemiologic research.

Question 3: What is the process for achieving clinical trial authorisation from the competent authority in Germany?

The sponsor submits a CTA request to the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) or the PEI (Paul-Ehrlich-Institut) (both are federal competent regulatory authorities responsible for CTAs for different types of IMPs), containing the elements required by the GCP Decree (GCP-Verordnung, for trials with pharmaceutical drugs) or the MPKP Decree (for trials with medical devices) respectively; for clinical trials involving radiation the competent authority is the Bundesamt für Strahlenschutz (BfS).

Question 4: What is the process for obtaining ethical review of a clinical trial protocol by a competent (research) ethics committee in Germany?

The sponsor must submit a request for a favourable opinion to the competent REC; the request has to contain the elements of the GCP Decree for trials with pharmaceutical drugs and of the MPKP Decree for trials with medical devices:
In general the REC of the regional Medical Association to which an investigator is attached, is the competent REC, according to States legislation. In few States, RECs are attached to the Local Government. For studies conducted by an investigator attached to a university, in several states the REC of the Faculty of Medicine is the competent REC.

In a multicenter trial, the sponsor nominates one investigator as the lead investigator (Leiter der klinischen Prüfung, LKP). Then the REC of this LKP becomes the master REC which combines the opinions of the local RECs into a single opinion.

There is no central REC for the review of individual biomedical projects.

The members of the “Deutscher Ethikrat”, as established by legislation of the “Deutscher Bundestag” on April 26, 2007, are appointed by the “Deutscher Bundestag”. The “Deutscher Ethikrat” may give general ethical recommendations which are not binding and which only seldom apply to research and the work of the research ethics committees.

There is also the Central Ethics Committee of the German Medical Association (Zentrale Ethikkommission bei der Bundesärztekammer) which gives opinions on general ethical issues and which may give advice to the Ethics Committees of the Medical Associations at their request. Again, the advice is not binding on the research ethics committees.

**Question 5:** Is there a single organisation to which to apply for ethical review of a clinical trial for an investigational medicinal product, regardless of whether this is for a single site or multiple sites?

No (it is all organised in a federal mode/way).

**Question 6:** What is the website for the organisation that issues guidelines on the ethical review of a clinical trial for an investigational medicinal product?

There is no single website that provides this information. However, harmonized information can be found on the website of the “Permanent Working Party of German Research Ethics Committees” (Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland), [http://www.ak-med-ethik-komm.de](http://www.ak-med-ethik-komm.de), and on the websites of the individual Research Ethics Committees.

The website of the Federal Ministry for Health is at [http://www.bmgs.bund.de/](http://www.bmgs.bund.de/).

The website of the Federal Institute for Drugs and Medical Devices is at [http://www.bfarm.de/de/index.php](http://www.bfarm.de/de/index.php).

The website of the National Council for Ethics is at [http://www.ethikrat.org/](http://www.ethikrat.org/).
**Question 7:** Is there a procedural interaction between the national or local competent authority and the (research) ethics committee during the approval process?

Interaction is possible, but not in an established procedure.

**Question 8:** Does the application to the REC and to the competent authority have to be submitted in parallel, or, if not, in which order?

No order is required, i.e. the applications may be made either sequentially (in either order) or in parallel.

**Question 9:** How many (research) ethics committees are there in Germany?

Germany has a total of 53 research ethics committees for all kind of biomedical research including clinical trials with pharmaceutical drugs and medical devices, and clinical research with radiation (for the last the REC must be registered at the Bundesamt für Strahlenschutz, BfS).

**Question 10:** How are RECs funded in Germany? Do they charge fees? If yes, what is their scale of fees?

All RECs charge fees for their work in the range €1000 – 6000 for clinical trial assessments and €200–1000 for substantial amendments. For trials initiated by investigators requests for reduction of fee are possible.

The amounts of the fees are not fixed by the RECs but by their establishing institution or by State law.

**Question 11:** Who is responsible for submitting the request for ethical review to the competent (research) ethics committee for single-site and for multi-site clinical trials?

For the submission of requests for trials with pharmaceutical drugs, medical devices or radiation research the sponsor is responsible. For other research project the investigator himself is responsible, but in general he can delegate this also to the sponsor. The competence of RECs is determined by the fixed affiliation of the principal investigator (single centre trial) or the co-ordinating investigator (multi-centre trial) to their REC.

**Question 12:** How is a “single opinion” achieved for multi-site studies?

The REC of the coordinating investigator becomes the master or coordinating REC is responsible for the assessment of the project. This assessment is achieved in cooperation with all RECs who assess qualification of local sites and investigators and whose assessment regarding their local sites and investigators should be respected by the coordinating REC. The local RECs may also comment on the protocol, but the
coordinating REC is exclusively responsible for the decision on the content, i.e. the single opinion.

**Question 13: How many members serve on a REC?**

From 7 up to 15 (rather seldom), depending on states legislation or university policy. However, many committees have several substitute members in order to cover several medical specialties and also comply with deadlines.

**Question 14: How many members constitute a quorum?**

Differently – according to bylaws or (university) policies. Minimum is usually 5 members.

**Question 15: How are REC members appointed?**

For RECs at the Medical Associations directly by their members or via their board; in universities by their academic authority (Senate).

**Question 16: How is the independence of members ensured?**

By bylaws and statutes in accordance with the States law.

**Question 17: How are conflicts of interest of REC members avoided?**

By declaration of potential conflict of interest as requested by bylaws and statutes, and – if the submitting investigator is a member of the REC - by exclusion of this investigator or his/her co-workers from the respective decision making.

**Question 18: What backgrounds and/or qualifications of members are actively sought?**

There is a standard exemplary bylaw from the Permanent Working Party of German Research Ethics Committees which has been used as a guideline by most RECs. This exemplary bylaw suggests at least 6 members and an adequate number of replacements. One member should be a jurist with the qualification to be a judge. One member should have scientific or professional experience in medical ethics. At least three should be clinicians with experience in clinical research. There should also be experience in study design and statistics within the REC. Both genders should be adequately represented, but in reality this is not always achieved.

The members are elected/appointed usually for 4 years; re-election/re-appointment is possible and the chair and the vice-chair(s) are elected amongst the members of the REC. However, the composition of the RECs varies from State to State: Bavaria has adopted the standard exemplary bylaw literally. Some States require a clinical pharmacologist, others a pharmacist, a statistician or several lay persons. One State requires that the chair is alternating between female and male.
**Question 19: How do RECs obtain specialist expertise?**

Seeking external expertise is compulsory for all drug trials with xenogenic drugs and gene therapeutics. Seeking external expertise is also compulsory for all drug trials in paediatrics, unless the REC does not have members who are specialists in paediatrics. Moreover, RECs can and do seek external expertise if there are questions which cannot be answered by the members of the REC themselves.

**Question 20: What are the training requirements for members of RECs?**

There are no legal requirements. Only persons well recognized and experienced in their discipline can become a member of a REC. Few RECs have requirements put down in their constitution and/or in an agreement with their establishing institution or supervising authority.

Some RECs organise introductory seminars for new members, some also organise continuous training by annual seminars. In the last 3-4 years the Permanent Working Party of German Research Ethics Committees has established 1-2 times per year a training day for beginning or advanced REC members with a wide range of topics (e.g. research with children, with incapacitated persons, radiation, specifics of clinical trials with medical devices, bio-banking, genotyping, data management etc.). Furthermore, especially new members learn just by taking part.

Administrative and technical aspects are covered by the experience of the permanent staff (office) of the RECs.

**Question 21: What training programmes are available for REC members in Germany?**

In addition to the above mentioned seminars the Permanent Working Party of German Research Ethics Committees organises twice a year a workshop to discuss difficult ethical issues and to exchange experiences. In addition, it is helpful and possible for REC members to participate at seminar/workshops for investigators and sponsors, initiated by universities and institutes.

**Question 22: What are the timelines for the assessment of single- and multi-site studies?**

For mono-site trials it is 30 days for pharmaceutical drug trials, 60 days for medical device trials.

For multi-site trials (with pharmaceutical drugs or medical devices) it is 60 days after receipt of complete application documents.

For radiation research it is also 60 days. Other biomedical research projects do not have timelines for assessment.
However, for trials on somatic cell or gene therapy the timeline is 90 days. This can be extended by another 90 days if gaining external advice requires this.

For substantial amendments the timelines are 20 days for pharmaceutical drug trials, 30 days for medical device trials and 35 days for trials on somatic cell or gene therapy.

**Question 23: How are substantial amendments submitted during the review process dealt with?**

Submission of substantial amendments during the review process is usually not accepted – in line with the practice of the competent authorities. However, sometimes it would reduce the work of the REC and the competent authority, therefore sometimes a requesting phone call is advisable.

**Question 24: How does a REC assess the suitability of investigators and of sites?**

According to the checklist adopted by all German Research Ethics Committees in 2004. In addition, meanwhile 1-2 day GCP courses are demanded for investigators, half-day refresher or more detailed courses are recommended after 3 years. Recommendations for a curriculum for basic and advanced GCP courses are in preparation.

**Question 25: How are the requirements for (research) ethics committees to review the contractual or financial arrangements in clinical trials for both investigators and hospitals handled?**

RECs must request and evaluate information according to the requirements of the GCP-Decree: “all relevant elements of the contract between sponsor and investigative site” and “agreements on compensation of the investigators”.

**Question 26: How are the requirements for (research) ethics committees to review the compensation arrangements for study subjects handled?**

Information requested according to the requirements of the GCP-Decree: “information on reimbursement for the trial subjects”.

**Question 27: Is there an ongoing quality assurance process (e.g. audits, inspections, internal SOP) for (research) ethics committees in Germany?**

Most RECs have SOPs. Regular audits are performed only in very few RECs. Inspections are not legally prescribed. However, it can happen that, in combination with the inspection of an investigational site, the statements of the REC are re-checked.
**Question 28: Is there an appeal mechanism?**

There is no specific appeal mechanism. Theoretically, a decision taken by an REC could be looked on by a court of administration in the respective State.

**Question 29: How do RECs deal with SUSAR reports and Annual Safety Reports?**

Discussion on this is ongoing.

Some RECs do not want to see SUSARs, but only periodic safety reports and listings.

Some RECs want to see only the SUSARs regarding the specific trial in their country, few want to see all SUSARs regarding the IMP.

A consultation group has been established with representatives from BfArM, Paul-Ehrlich-Institut, Robert-Koch-Institut (German federal authorities), VFA, BPI (associations of the German pharmaceutical industry), and of the “Permanent Working Party of German Research Ethics Committees” to come to a common approach. A working group has also been established at the Federal Medical Association (Bundesärztekammer).

**Question 30: How are ‘substantial amendments’ defined?**

Discussion ongoing, within the groups described in 29 above.

Presently, in the GCP Decree the same (not helpful) definition can be found as in the Guidance CT2.

**Question 31: What are the indemnity insurance requirements for research projects?**

Risk-adapted coverage according to § 40 (3) AMG (pharmaceutical drug trials): for each case of death or permanent disability at least € 500 000 per person, regardless of fault/blame (“verschuldensunabhängig”). For medical device trials it is regulated respectively, see § 20 (3) MPG.

**Question 32: What are the indemnity insurance requirements for (research) ethics committee members themselves?**

In case of liability issues of RECs, i.e. members and permanent staff, it has to be proven that members or staff acted grossly negligently and with intention.

In some States the government has taken the liability with a right of recovery.

In other States, the institution responsible for the REC has to take the liability to a certain amount (the limit being different in different States) and has therefore distinctly increased its liability insurance. In liability claims above that certain amount the State government takes over.
**Question 33: How is informed consent obtained from vulnerable subjects who are potentially to be involved in a clinical trial?**

Information to the vulnerable subjects has to be provided by a physician.

For minors: consent must be given by the legal representative(s), usually both parents. Assent of the minor has to be sought if possible, refusal must be accepted.

For incapacitated adults: the consent has to be provided by the legal representative. Assent of the incapacitated adult has to be sought if possible, refusal must be accepted.

For emergency situations: If consent cannot be obtained, treatment which is necessary without delay to save the life of the person concerned, to restore good health or to alleviate suffering, can be dispensed immediately. Consent for continued participation must be obtained as soon as it is possible and reasonable”; German Drug Law § 41 (1).

Clinical trials with pharmaceutical drugs or medical devices or radiation research on persons deprived of liberty are not allowed.

**Question 34: How do RECs assess the progress and outcome of research projects that they have approved?**

No processes are in place. At present the assessment of the outcome is not the task of RECs in Germany. During a clinical trial RECs are obliged to evaluate submitted substantial amendments and are entitled, and obliged, to withdraw a favourable opinion if adverse aspects come to their knowledge. They are, however, not obliged to perform any kind of active monitoring (see also answer to question 2).

**Question 35: How does the REC ensure reception of the Annual Safety Report and the Summary of the Final Report of a research project that it has approved?**

It is not the duty of RECs to ensure reception, rather it is the duty of the sponsor to ensure provision of these documents to RECs (according to GCP Decree § 13).

**Question 36: Do national regulations in Germany allow research on healthy volunteer children (subjects under 16)?**

No (no national regulations allowing research with healthy volunteer children).

Diagnostic or preventive clinical trials with pharmaceutical drugs or medical devices on healthy children can only be performed when among other restrictions [see § 40 (4) AMG, § 20 (4) MPG] each participating child has an *individual benefit* (e.g. vaccination studies: each child receives vaccination, no placebo-group).
**Question 37:** Do national regulations in Germany allow payment, (other than expenses), to children taking part in research?

No. According to German Drug Law § 41, paragraph 3 No.4: “advantages with the exception of adequate compensation must not be provided”.

**Question 38:** Do RECs invite or allow a) applicants or b) observers to attend committee meetings?

Applicants are invited to present and to explain their project to the REC; some RECs practice this in general, others only invite the applicants when clarification to the protocol is needed. The invited applicants are excluded from any internal discussion and of decision making procedure. Observers are not allowed.

**Question 39:** Are the minutes of (research) ethics committee meetings made public?

No. the minutes are confidential.

An annual “business” report is sent to the establishing body (University, Faculty of Medicine or States government), but this is done without details which might enable the reader to identify projects, sponsors, researchers and/or patients.

**Question 40:** Is there any scope for Chairman’s actions in between meetings?

Yes, but that must be in accordance with the constitution of the individual REC: e.g. RECs can usually transfer not essential decisions which do not need the plenary onto the chairman or other members.

**Question 41:** Do (research) ethics committees ever appoint subcommittees for any specific purpose?

No, usually not. If it is done, it must be in accordance with the RECs constitution.

**Question 42:** Is there a national policy on the registration of clinical trials before they start?

It depends what kind of trial. In detail:

a) For trials with pharmaceutical drugs it is legally required to register in the EudraCT data base of EMA (see also GCP Decree; according to Directives 2001/20/EC and 2005/28/EC).

b) For trials with medical devices it is legally required to register in the DIMDI data base (Deutsches Institut für Medizinische Dokumentation und Information; see also DIMDI Decree).

c) For other trials there is no national policy, but a strong recommendation to register any clinical trial in one of the established international registries or the
WHO-associated Deutsches Studienregister (German study register) at the University of Freiburg. More and more universities have the internal policy that their researchers must register their studies in a WHO-associated national or international register.

**Question 43:** If the answer to Question 42 is ‘yes’, do (research) ethics committees have any role to play in reviewing such registration?

No. However, some university RECs recommend registration on their website or oblige their researchers. Also the Permanent Working Party of Germany Ethics Committees strongly recommends registration in a register.

**Question 44:** If the answer to Question 42 is ‘yes’, is this register of clinical trials made available to the public?

The DIMDI data base for trials with medical devices is not available to the public. The Deutsches Studienregister is public and free of charge.

**Question 45:** With regard to Clinical Trial Insurance, do research ethics committees in Germany work to a set template of requirements?

See also answer to question 31.

The applicant must submit
- the confirmation of the insurer or a copy of the insurance policy,
- which must show that the *individual* trial is covered,
- that the beginning and the end of the insurance period fit to the planned trial schedule,
- that the maximum insurance sum per person for each case of death or permanent disability is at least € 500 000 per person
- that the insurance covers regardless of fault/blame (“verschuldensunabhängig”)
- the general and specific conditions of the insurance contract
- The provisions for radiation research are regulated respectively.

However, a REC cannot evaluate whether the risk estimation for the overall insurance contract is sufficient (or too low or too high!?): i.e. if there are 100 participants, then the complete insured sum is not 100 x € 500 000, according to the risk-based estimation mathematics of the insurance companies.

**Question 46:** If the answer to Q45 is ‘yes’, how are these requirements a) Decided upon?

The Permanent Working Party of German Ethics Committees had formed an insurance working party which developed this template and is in regular contact with the insurance industry.
b) Cross referenced to statutory requirements?

The requirements are in compliance with the national laws, i.e. AMG (Arzneimittelgesetz, Drug Law), MPG (Medizinproduktegesetz, Medical Device Law), StrlSchV (Strahlenschutzverordnung, Decree for protection against ionising radiation), RöV (Röntgenverordnung, Decree for protection against X-ray radiation).

c) Updated?

According to amendments to the laws cited in 46b.

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