# Medicinal Products for Human Use - GERMANY

## Competent authority

### Contact Details

**Contact Name 1**
Competent federal higher authority ("Bundesoberbehörde- BOB")

**Contact Name 2**
Federal Institute for Drugs and Medical Devices*: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

**Phone**
+49-228-20730

**Fax**
+49-228-2075207

**Email Department**
ct@bfarm.de

**Address**
Kurt-Georg-Kiesinger-Allee 3

**ZIP/City**
53175 Bonn

**Country**
Germany (DE)

**Web address**
http://www.bfarm.de/EN

### Additional Information

BfArM is the CA for medicinal products and MD!

### Regulatory and ethics bodies involved in approval process

- **Competent Authority/ies (CA)**
  - Ethics committee(s)

- **CA - Submission for authorisation mandatory for**
  - Clinical IMP trials
  - Clinical ATMP trials

- **CA - Registration/ notification without approval required for**
  -

- **CA - Submission required to**
  - National CA
  - Regional CA

- **Specific Competent Authority for ATMP trials in place**
  - Yes
Competent Authority for ATMP trials
Federal Institute for Vaccines and Biomedicine:

National trial registry
National public trial register in Germany: Deutsches Register Klinischer Studien DRKS

Submission of Application

Responsible for study submission
Sponsor
Legal representative domiciled in the EU/EEA

Entitled to study submission

Prerequisites for submission

Guidance on submission of application available
Yes

Guidance on submission of application
Further details concerning the application and the required documents are listed in section 7 GCP-V (e.g. EudraCT number confirmation etc.) and on the BfArM website (detailed guidance is provided in German, some in English) such as the guidance "3. Bekanntgabe zur klinischen Prüfung von Arzneimitteln am Menschen"

Applicable national legal framework/ Reference
Section 7 GCP-V

Submission Format

Format option(s)
1 paper hardcopy + 1 electronic copy on data carrier (CD Rom or DVD)

Preferred format

Guidance on submission format available
Yes

Guidance on submission format
Detailed guidance on Electronic submission of clinical trial applications is available on the BfArM website in section: Medicinal Products Licensing Clinical Trials Electronic Submission of Clinical Trial Applications

Language of Submission

Language(s) of application
German
English

Preferred language of application

English accepted
Partly, not for all documents

Documents mandatory to be in official national language
Cover letter
Protocol Summary
Information material, Documents and Forms intended for study participants and patient information
### Submission Fees

#### Fees for trial submission mandatory

Yes

#### Fees

Clinical trial authorisation:
- Initial submission - Phase I,II,III: 3800 EURO
- Follow-up trial without re-evaluation of dossier: 1500 EURO
- Follow-up trial with re-evaluation of dossier - Phase 1: 1900 EURO;
- Follow-up trial with re-evaluation of dossier - Phase II-III: 2100 EURO;
- Amendments with need for scientific evaluation: 1100 EURO;
- Other Amendments: 730 EURO

(Version March 2015)

Application for reduced fees is possible in special cases according to Art 3
AMG-Kostenverordnung - AMGKostV (de)

**Waiver for academic (non-commercial) studies possible**

Upon request

#### Applicable national legal framework/ Reference

Applicable authorisation fees are provided in the most recent version of the
AMG-Kostenverordnung - AMGKostV (de)

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### Timelines Authorisation

#### General timespan (max nr days)

30

#### Mode of approval (General)

Silent approval. Nevertheless, normally a written approval is sent to the sponsor

#### ATMP/GMO trials (max nr days)

90

#### Mode of approval (ATMP/GMO trials)

—

#### External expert advice required (max nr days)

180

#### Xenogeneic cell therapy (max nr days)

No time limit

#### Mode of approval (Xenogeneic cell therapy)

Explicit

#### Timespan counted from

Date of submission of valid application

#### National legal framework in place

Yes

#### Applicable national legal framework/ Reference

Section 9 GCP-V
Section 42 (2) AMG

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### Amendments/ Substantial Amendments (SA)

#### Notification mandatory for

—

#### Authorisation mandatory for

Any substantial amendments
Responsible for submission of SA
Sponsor

Standard notification form available
Yes

Standard notification form
"Substantial Amendment form" of Annex 2 of guideline ENTR/CT 1

Timeline for approval of SA (max nr days)
20
By silent (implicit) approval

Guidance on submission of SA
GCP-V (Section 10) provides definitions of substantial amendments as well as procedures and legal consequences

National legal framework in place
Yes

Applicable national legal framework/ Reference
Section 10 GCP-V

Safety Reporting

Responsible for AE reporting to CA
Sponsor

Sponsor must declare reportable events to
National CA
Regional CA
CA(s) of EU&EFTA Member States concerned
Relevant EC(s)
All investigators

Reportable AEs
SAE (Serious Adverse Event)
SUSAR (Suspected Unexpected Serious Adverse Reaction)

SUSAR being life-threatening or leading to death must be reported
Within a max of 7d upon first knowledge (+ 8d for additional information)

All other SUSARs
Within a max of 15d upon first knowledge

SAE /SADE must be reported
-

National standard reporting form available
-

Reporting format - Options
-

Preferred format
-

Provision of Annual safety report mandatory
Yes
Annual safety report shall be provided by sponsor to National CA CA(s) of EU&EFTA Member States concerned Relevant EC(s)

Guidance on AE reporting procedure
Detailed information about Pharmacovigilance issues including SAE and SUSAR reporting are provided on the BfArM website.

Applicable national legal framework/ Reference
Sections 12 and 13 GCP-V

Additional Information
Annual Safety report shall include a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects’ safety. Format: DSUR (Development Safety Update Reports). Guidance available on BfArM website in section: Medicinal Products > Licensing > Clinical Trials.

Investigator shall report SAE to

Reporting timeline

End of trial declaration mandatory for
All clinical trials requiring authorisation by CA

Responsible for End of trial declaration
Sponsor
Principal Investigator

Regular Termination - Declaration timespan (max nr days)
90

Timespan counted from

Early/premature Termination - Declaration timespan (max nr days)
15

Reasons for early termination shall be clearly stated
Yes

Applicable national legal framework/ Reference
Art 42 b AMG
Section 12 (2-3) & 13 (8-10) GCP-V

Additional Information
According to §42 b AMG, within a year after the end of the clinical trial, the sponsor shall send the CA and the competent EC a summary of the report on the clinical trial, covering all important results of the clinical trial. The report should be submitted electronically via the Drug Information Portal of the Bund (Federal Government) and the Laender (States).
Additional Information

Competent Authorities have published detailed Guidelines on clinical trials:
- 3. Bekanntmachung zur klinischen Prüfung von Arzneimitteln am Menschen
  (see the unofficial English translation: 3rd Announcement on clinical trials of medicinal products for human use): deals with general conditions of a clinical trial and
- Bekanntmachung zu nicht-kommerziellen klinischen Prüfungen (Notification on non-commercial clinical trials): deals with the conditions of investigator initiated trials.

### Ethics committee

#### Contact Details

**Contact Name 1**

List and contact details of competent ECs in Germany are provided on the website of "Arbeitskreis Medizinischer Ethikkommissionen in der Bundesrepublik Deutschland e.V."

**Web address**

http://www.ak-med-ethik-komm.de/index.php/de/mitglieder

**Additional Information**

About 52 local ECs. There is no central national ethics committee in Germany.

#### Ethical Review - General

**Submission for Ethical review mandatory for**

Clinical IMP trials
Clinical ATMP trials

**Submission to CA and EC to be performed in the following order**

In parallel

**Regulatory and ethics bodies involved in approval process**

- 

#### Single-Centre Studies - Ethical Review

**Ethical approval (favourable opinion) to be obtained from**

Local EC

**Additional Information**

There are about 52 local Ethics committees responsible for studies with human medicines. Local Ethics committees can be at the level of chamber of physicians (Ärztekammer) (EC-ÄK), at the level of the medical faculty (EC-MF), or at the country ministry of health (EC-HA).

Link to List of ECs: http://www.ak-med-ethik-komm.de/index.php/de/mitglieder

#### Multi-Centre Studies - Ethical Review

**Ethical approval (favourable opinion) required from**

Lead EC (authorised to issue a single opinion)

**Submission of application required to**

Lead EC + All concerned local ECs for site-specific assessment

**Additional Information**

This competent lead committee depends on the location of the coordinating or principal investigator ("Leiter der klinischen Prüfung") and is responsible for 'single opinion'. The assessment has to be achieved in cooperation with all ECs which are competent for local study sites (section 8, subsection 5 GCP-V). The local ECs will evaluate the qualification of the investigators and the suitability of the trial sites. Their opinion should be respected by the coordinating EC. Local ECs can comment on the protocol as well, but the coordinating EC is exclusively responsible for the decision on the content of the single opinion, which it creates independently.

Link to List of ECs: http://www.ak-med-ethik-komm.de/index.php/de/mitglieder
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<thead>
<tr>
<th>Submission of Application</th>
<th>Responsible for study submission</th>
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<tr>
<td></td>
<td>Sponsor</td>
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<td>Entitled to study submission</td>
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<td>Prerequisites for submission / approval</td>
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<td>Applicable national legal framework/ Reference</td>
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<td>Section 42 AMG</td>
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<td>Section 7 GCP-V</td>
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<td>Additional Information</td>
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<td>There is no consistent standard regarding requirements for application in different federal states or Ethics Committees (e.g. number of copies required for one application, amount of fees to be paid etc.) since this is regulated according to the different federal state law and to the statutes of the Ethics Committee concerned.</td>
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<td>Standard application form available</td>
<td>No</td>
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<td>Guidance on submission format</td>
<td>Information and documentation required by the ethics committee are provided in section 7 GCP-V.</td>
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<td>National legal framework in place</td>
<td>Yes</td>
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<tr>
<td>Applicable national legal framework/ Reference</td>
<td>Section 7 GCP-V</td>
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<td>Additional Information</td>
<td>The sponsor shall submit to the ethics committee all of the information and documents required by the EC to give its opinion (further details are provided in section 7 GCP-V). There is no consistent standard regarding requirements for application in different federal states or Ethics Committees (e.g. number of copies required for one application, amount of fees to be paid etc.) since this is regulated according to the different federal state law and to the statutes of the Ethics Committee concerned.</td>
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<td>English accepted</td>
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Documents mandatory to be in official national language

Additional Information
Form module 2 in German or English

Submission Fees

Fees for Ethical review mandatory
Yes

Waiver for academic (non-commercial) studies possible
Yes

Fees for Ethical review
The amounts of fees are not fixed by the ECs but by the establishing institution following States law

Additional Information
Applicable fees are provided on the EC's websites (some in English). Waiver or reduction of fees for non-commercial trials depends on EC concerned.

Timelines Ethical Review

General timespan for single-centre studies (max nr days)
30

General timespan for multi-centre studies (max nr days)
60

ATMP/GMO trials (max nr days)
90

External expert advice required: Timespan (max nr days)
180

Xenogeneic cell therapy: Timespan (max nr days)
No time limit

Clock-stop possible if complementary information requested
Yes

Timespan counted from
Date of submission of valid application

National legal framework in place
Yes

Applicable national legal framework/ Reference
Section 8 GCP-V

Additional Information
For multi-centre studies, the EC responsible for the principle investigator provides the favourable 'single opinion' after collaboration with the local ECs of the participating sites.
The local ECs have 30 days to issue their opinion on trial sites and qualification of investigators.

Amendments/
Substantial
Amendments (SA)

Ethical review mandatory for
Substantial amendments (SA) relating to aspects applicable to EC
Responsible for notification of SA

Timeline Ethical review of SA (max nr days)
20 resp. 35 (ATMP) - from receipt of the application

Applicable national legal framework/ Reference
Section 10 GCP-V

Additional Information
In case of multi-centre trials, the leading EC issues the opinion in cooperation with all other local ECs. The EC’s opinion has to be provided within the given timeframe to the sponsor and the CA.

Safety Reporting

Reportable AEs
SAE (Serious Adverse Event)
SUSAR (Suspected Unexpected Serious Adverse Reaction)

Investigator shall report SAE to

Reporting timeline
Immediately (without delay)
Within a max of 24h upon first knowledge

Responsible for AE reporting to relevant EC(s)
Sponsor

SUSAR being life-threatening or leading to death must be reported
Within a max of 7d upon first knowledge (+ 8d for additional information)

All other SUSAR must be reported
Within a max of 15d upon first knowledge

SAE/SADE must be reported

National Standard Reporting form available

Reporting format - Options

Preferred reporting format

Provision of Annual safety report mandatory
Yes

Guidance on AE reporting procedure
Detailed information about Pharmacovigilance issues including SAE and SUSAR reporting (according to Sections 12 and 13 GCP-V) are provided on the BfArM website.

Applicable national legal framework/ Reference
Sections 12 and 13 GCP-V (Safety reporting obligations)
Section 13 (6) GCP-V (Annual safety report)
### End of Trial

- **End of trial Declaration mandatory**: Yes
- **Responsible for End of trial Declaration**
  - Sponsor
  - Principal Investigator
- **Regular Termination - Declaration timespan (max nr days)**
  - 90
- **Timespan counted from**
- **Early/premature Termination - Declaration timespan (max nr days)**
  - 15
- **Reasons for early termination shall be clearly stated**: Yes
- **Applicable national legal framework/ Reference**
  - Section 12 & 13 GCP-V
- **Additional Information**
  - The duties of the PI and the sponsor regarding the completion of the trial can be found in section 12 subsection 2-3 and section 13 subsections 8-10 GCP-V.

### Additional Information & Specifics

- **Additional Information**
  - There are about 52 local Ethics committees responsible for studies with human medicines. Local Ethics committees can be at the level of chamber of physicians (Ärztekammer) (EC-ÄK), at the level of the medical faculty (EC-MF), or at the country ministry of health (EC-HA).

### Study specific Requirements

#### Sponsor

- **Sponsor - Definition available in national law**: Yes
- **Sponsor - Definition (pursuant to national law)**
  - Definition according to Art 4 (24) AMG:
  - The sponsor is a natural or legal person who assumes responsibility for the commissioning, organisation and financing of a clinical trial on human beings.
- **Sponsorship mandatory**: Yes
- **Sponsorship mandatory - Additional information**
  - It is mandatory to have a sponsor according the definition of the directive 2001/20/EC.

#### Investigator

- **Entitled to be principal investigator**
  - According to Art 4 (25) AMG
**Additional Information**

Definition of Investigator (pursuant to Art 4 (25) AMG):
"generally a physician responsible for the conduct of the clinical trial on human beings at a site or, in justified exceptional cases, another person whose profession, owing to the scientific requirements and the experience in the care of patients which it calls for, qualifies him/her to conduct research on human beings. If a clinical trial is being conducted at one site by a team of persons, the investigator shall be the person in charge of the team and responsible for conducting the trial. If a clinical trial is being conducted at various trial sites, the sponsor shallname one investigator as the chief investigator."

The duties of the PI regarding the completion of the trial can be found in section 12 GCP-V.

**IC is regulated by law**

Yes

**Informed Consent - Definition/ Requirements**

Definition provided in Art 4 (2b) GCP-V.
Requirements: The participant of a clinical trial must be informed by the investigator who must be a physician about the nature, significance, risks and implications of the clinical trial as well as about his/her right to withdraw from the clinical trial at any time; without reason; a generally comprehensible written information is to be handed out to him/her. The clinical trial may only be commenced after the participant has given his/her consent to participate in writing. The declaration of consent to participate in a clinical trial can be revoked at any time, orally or in writing, without disadvantaging the participant.

**Applicable national legal framework/ Reference**

Section 40 subsection 2 AMG
Art 4 (2b) GCP-V

**Study Participants - Vulnerable Population**

**Minors / Children - Studies allowed**

Yes

**Specific provision**

Informed consent form: For minors, additionally section 40 subsection 4 No. 3 AMG has to be considered. The consent is granted by the legal representative(s)/guardian(s) (generally both parents). The consent must correspond to the minor’s presumed will where such a will can be ascertained. If the minor is capable of understanding the nature, significance and implications of the clinical trial and able to form a rational intention in the light of these facts, his/her written consent is also necessary.

**Legal framework/Reference (Minors/Children)**

Section 40 subsection 4 No. 3 AMG

**Incapacitated persons - Studies allowed**

Yes

**Legal framework / Reference (Incapacitated persons)**

Clinical studies involving incapacitated persons are regulated by § 41 AMG

**Emergency situations - Studies allowed**

Yes

**Special provisions apply**
Specific provisions

Exceptions to the procedure of informed consent can be found in section 41 subsection 1 AMG (case of emergency) and section 3 subsection 2b GCP-V (consent in presence of a witness). However, there is no harmonised procedure accepted by ethics committees in case of informed consent in emergency.

Emergency situation without prior consent of patient or proxy - Studies allowed

With limitations

Conditions allowing trial participation in emergency setting without prior consent

NB! Court involvement might be needed.

Legal framework / Reference (Emergency Situation)

Section 41 subsection 1 AMG (case of emergency) and section 3 subsection 2b GCP-V (consent in presence of a witness).

Pregnant or breastfeeding women - Studies allowed

No national legal framework available

Specific provisions

No special provisions provided in German law

Data Protection

Notification to DP Authority/ Ombudsmann is mandatory

No

Approval/ authorisation required

Not specified

Specific notification timelines before operations start

—

Language of notification

—

Notification format

—

Additional Information

The participant in a clinical trial shall be informed of the purpose and scope of the recording and use of personal data, especially medical data. Further details concerning data protection are listed in section 40 subsection 2a AMG and the Bundesdatenschutzgesetz BDSG) - German Data Protection Act (see also the unofficial English version published in the Federal Law Gazette)

Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)

—

Insurance

Liability insurance or alternative arrangements for damages mandatory for

Study participants

Responsible for covering insurance

Sponsor
Insurance fee: A minimum coverage sum is defined
Yes

Minimum coverage sum
500,000 EURO

Applicable national legal framework/ Reference
Section 40 (subsection 1, sentence 3 No. 8) AMG
Section 40 (subsection 3) AMG

Additional Information
Pursuant to section 40 subsection 1 sentence 3 No. 8 AMG, an insurance has to be contracted. This insurance must be taken out in favour of the participant in a clinical trial with an insurance carrier authorised to conduct business in a Member State of the European Union or another State which is a member of the EEA (European Economic Area). Its scope must be reasonably commensurate with the risks involved in the clinical trial and determined on the basis of the risk assessment in such a way as to ensure that in case of the death or permanent disability of a participant, at least 500,000 EURO will be available (section 40 subsection 3 AMG).

Quality Assurance/ Quality Control (QA/QC)

Monitoring
Compulsory

Audit by sponsor
Optional

Standard Operating Procedures (SOPs)
Compulsory

Archiving & Data Management

Study documents must be kept at least (in years)
10

National legal framework in place
Yes

Applicable national legal framework/ Reference
Art 13 (10) GCP-V

Additional Information
Essential documentation must be kept by the sponsor.

National legislation

General Information: Applicable Legislation & Conventions

Official website providing relevant national legislation available
Yes

Official website providing relevant national legislation
Federal Institute for Drugs and Medical Devices/ Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

Official governmental legal database available
Yes

Official governmental legal database
Juris BMJ (Bundesministerium der Justiz und für Verbraucherschutz): Free database of the Federal Ministry of Justice and Consumer Protection covering most of the German federal law
Applicable national regulations

Transposition of (CT) Directive 2001/20/EC
Transposition of (GCP) Directive 2005/28/EC
Other

Transposition of (CT) Directive 2001/20/EC (or comparable national legal framework)

Medicinal Products Act (Arzneimittelgesetz AMG): (see also: unofficial English translation)

Transposition of (GCP) Directive 2005/28/EC

Available as separate legal text


GCP-Ordinance - GCP-V (GCP Verordnung)- currently only in German

Additional Information

In particular, sections 40-42a AMG in connection with the GCP ordinance are relevant for the conduct of a clinical trial.

Use of radiation or radioactive compounds - Specific requirements

Yes

Applicable legal framework

1. German X-ray Ordinance- Deutsche Roentgenverordnung/ RöV
2. Radiation Protection Ordinance -Strahlenschutzverordnung/ StrSchV

Additional Information

The 2 ordinances apply if radioactive compounds are used in a clinical trial.

For clinical trials involving the use of X-Rays an approval from the Federal Office for Radiation Protection- BfS (Bundesamt für Strahlenschutz) is required according to section 28 RöV (X-Ray Ordinance)

Specific requirements

Yes

Applicable legal framework

For clinical gene therapy, the Arzneimittelgesetz (AMG, Medicinal Products Act) and GCP-Verordnung (GCP-V, GCP ordinance) have to be considered. (see also: unofficial translations published in the Bundesgesetzblatt (Federal Law Gazette)): Medicinal Products Act (AMG), English version.

Gene transfer products are medicinal products according to section 2 subsection 1 AMG. Section 4 subsection 9 AMG contains a detailed definition. The legal procedure is generally the same as for medicinal products for human use, specific requirements are indicated in the related sections.

Additional Information

The German Gentechnikgesetz (Gene Technology Act) does NOT cover the issues of clinical gene therapy.

The GenTG only has to be applied for preclinical research including the construction, use and storage. In these cases an approval according to section 8 of the GenTG is necessary. The competent authority concerning this approval is the Landesbehörde (see ZLG-German register of the competent authorities responsible pursuant to Landesrecht)

As a matter of principle Good Manufacturing Practice (GMP) is required for the manufacture of medicinal products for human use.

The (1) German Arzneimittel- und Wirkstoffherstellungsverordnung (AMWHV) and the (2) EC-GMP-Guideline cover this issue.
Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)

National Data Protection Act

**National DP act**

German Data Protection Act - Bundesdatenschutzgesetz BDSG (see also: the unofficial English translation published in the Federal Law Gazette)

**Definition**

**IMP/IMP Study**

**IMP - Definition available in national law**

Yes

**IMP - Definition**

Definition according to Art 3 (3) GCP-V (English translation):
"a pharmaceutical form of active pharmaceutical substances and placebos that is tested in a clinical trial on humans or used as a comparator or that is applied to induce specific reactions in humans. This includes EU authorised drugs if they are investigated within a clinical trial, EU authorised drugs if they will be used as comparator, and EU non-authorised drugs"