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)

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Additional Information

BfArM is the CA for medicinal products and MD!

Trial Authorisation / Registration / Notification

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

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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)
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
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-thereatening 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

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Reporting timeline

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End of Trial

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 & Specifics	**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

Submission of Application	**Responsible for study submission** Sponsor **Entitled to study submission** – **Prerequisites for submission / approval** – **Applicable national legal framework/ Reference** Section 42 AMG Section 7 GCP-V **Additional Information** 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.
Submission Format	**Format option(s)** Paper hardcopy Data carrier (CD-rom/DVD) **Preferred format** – **Standard application form available** No **Guidance on submission format** Information and documentation required by the ethics committee are provided in section 7 GCP-V. **National legal framework in place** Yes **Applicable national legal framework/ Reference** Section 7 GCP-V **Additional Information** 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.
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 – **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-thereatening 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 legalperson 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. **Co-Sponsor - Definition available in national law** No
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 trialis 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 investigatoras the chief investigator."

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

Study Participants - Informed Consent (IC)

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
Special provisions apply

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
Special provisions apply

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

Clinical Trials on IMPs in Humans	**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 **Act transposing (GCP) Directive 2005/28/EC** 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.
Radiation & Radiotherapy	**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)
Gene Therapy	**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.

Data Protection	**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"