Clinical Trial Application – EudraCT - Germany

Pertinent EU regulations

- EU Clinical Trial Directive 2001/20/EC ("on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use")
- EU GCP Directive 2005/28/EC ("laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products")
- EudraLex Volume 10-CT1 ("Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) - (2010/C 82/01)")
- EudraLex Volume 10-CT2 ("Communication from the Commission — Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (CT-2) - (2010/C 82/01)")

Pertinent German regulations

- German Drug Law ("Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz – AMG) - Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das durch Artikel 2 des Gesetzes vom 20. Dezember 2016 (BGBl. I S. 3048) geändert worden ist").
- 3. Bekanntmachung zur klinischen Prüfung von Arzneimitteln am Menschen. Gemeinsame Bekanntmachung des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts zum Antrag auf Genehmigung einer klinischen Prüfung bei der zuständigen Bundesoberbehörde nach § 40 Abs. 1 Satz 2 Arzneimittelgesetz (AMG) sowie § 7 der Rechtsverordnung nach § 42 Abs. 3 AMG (GCP-V), zur Anzeige nachträglicher Änderungen während der Durchführung klinischer Prüfungen nach § 10 sowie zur Anzeige der Beendigung einer klinischen Prüfung nach § 13 Abs. 8 und 9 dieser Rechtsverordnung vom 10. August 2006
- German GCP Implementing Ordinance ("GCP-Verordnung [GCP-V]")

Pertinent guidelines and standards

- EMA/CHMP/ICH/135/1995 – ICH Topic E6(R2): Guideline for good clinical practice
- EMA/CPMP/ICH/291/95 – ICH Topic E8: General Considerations for Clinical Trials

Documents needed

Specification	Reference	CA	EC
Cover			
Cover letter	GCP-V Section 3 §7 (2) 2	X	X
Table of contents of application and cross-reference to GCP-V	GCP-V Section 3 §7 (2) 2	X	X
Authorisation			
Power of Attorney assigning Legal Study Representative (if applicable)		X	X
Letter of authorisation of the Applicant by the sponsor		X	X
Administrative			
List of responsibles & contacts – Sponsor	GCP-V Section 3 §7 (2) 4	X	X
List of responsibles & contacts – Trial Sites & Laboratories	GCP-V Section 3 §7 (2) 5	X	X
List of responsibles & contacts – Investigators	GCP-V Section 3 §7 (2) 7	X	X
List of responsibles & contacts – Delegates (CRO, DM, PV, etc.)	GCP-V Section 3 §7 (2) 5	X	
List of Ethics Committees	GCP-V Section 3 §7 (2) 5	X	
Financing, budgets, contracts			
Declaration re. financing of the study	GCP-V Section 3 §7 (3) 5	X	
Declaration of accepting procedural costs/fees		X	X
Specification of the remuneration of the investigator	GCP-V Section 3 §7 (3) 14		X
Specification of the remuneration of the trial participants	GCP-V Section 3 §7 (3) 14		X
Contract with the investigators	GCP-V Section 3 §7 (3) 16		X
EudraCT			
Copy of the e-mail that confirms EudraCT-Nr.	GCP-V Section 3 §7 (2) 1	X	X
EudraCT Application Form – Module 1 (incl. xml)	Eudralex X CT-1	X	X
Name of sponsor's contact EudraCT Item B.1	Eudralex X CT-1	X	X
Specification of past SA EudraCT D.2.6	Eudralex X CT-1	X	X
IMP used previously in the EEA Eudra CT 2.4	Eudralex X CT-1	X	X
National Application Form – Module 2 (national language)	Eudralex X CT-2		X
Correspondence re. past Scientific Advice		X	
Correspondence re. past Review of the Trial	GCP-V Section 3 §7 (2) 14	X	X
Investigator's Brochure (IB)	GCP-V Section 3 §7 (2) 7	X	X
Investigational Medicinal Product Dossier (IMPD-Q)	GCP-V Section 3 §7 (4) 1	X	
Specification that parts of the IMPD are contained in the IB	GCP-V Section 3 §7 (4) 1	X	
IMPD-Q Pharmaceutical Quality – for each IMP (possibly SmPC)	GCP-V Section 3 §7 (5)	X	
For each IMP – Manufacturing Authorisation - Product	Eudralex IV	X	
For each IMP – GMP-Certificate - Product	Eudralex IV	X	
For each IMP – Manufacturing Authorisation - Substance	Eudralex IV	X	
For each IMP – GMP-Certificate - Substance	Eudralex IV	X	
Statement by EU IMP-Site QP	EMA/334808/2014	X	
IMP-label (national language)	Eudralex IV 13	X	
Clinical Trial Protocol (CTP)			
Clinical trial Protocol	GCP-V Section 3 §7 (2) 3	X	X
Clinical trial Protocol – Signature page - Sponsor	GCP-V Section 3 §7 (2) 3	X	X
Clinical trial Protocol – Signature page - Investigator	GCP-V Section 3 §7 (2) 3	X	X
Clinical trial Protocol – Tabulated summary in national language	GCP-V Section 3 §7 (3) 19		X
Clinical Trial Protocol (CTP) – declarations **Separate declarations and/or cross-reference to CTP-sections**			
Explanation re. the rationale and relevance of the trial	GCP-V Section 3 §7 (3) 1		X
Summary of the benefit:risk-considerations	GCP-V Section 3 §7 (3) 2		X
Objectives of the trial	GCP-V Section 3 §7 (2) 9	X	X
Number, age, and gender of the trial participants	GCP-V Section 3 §7 (2) 10	X	X

Specification	Reference	CA	EC
Eligibility criteria and considerations re. sample size	GCP-V Section 3 §7 (2) 11	X	X
Considerations re. appropriateness of sex distribution	GCP-V Section 3 §7 (2) 12	X	X
Considerations re. inclusion of subjects that require legal representation	GCP-V Section 3 §7 (3) 3		X
Procedures re. recruitment and avoidance of overlapping/competing participation in other trials	GCP-V Section 3 §7 (3) 11		X
If applicable: test procedures used to evidence participants to be healthy	GCP-V Section 3 §7 (3) 12		X
Specification of the trial test procedures with regard to those that not common in medical practice in particular	GCP-V Section 3 §7 (3) 10		X
Specification of criteria leading to interruption or premature discontinuation of the trial	GCP-V Section 3 §7 (3) 17		X
Considerations re. treatment and medical management of the trial participants after the end of the trial	GCP-V Section 3 §7 (2) 13	X	X
Considerations re. data protection and re. non-inclusions of subjects who do not provide consent therewith	GCP-V Section 3 §7 (2) 15 GCP-V Section 3 §7 (3) 15	X	X
List of ongoing trials with the same IMP within the EEA		X	
Informed consent			
Patient information form – template (national language)	GCP-V Section 3 §7 (3) 9		X
Patient consent form – template (national language)	GCP-V Section 3 §7 (3) 9		X
Any written information/instruction to the trial participants (as applicable)			
Written scheduling or compliance instructions	GCP-V Section 3 §7 (3) 9		X
Written agreements or contracts to be signed by the participants	GCP-V Section 3 §7 (3) 9		X
Any written or published information re. trial participation (as applicable)			
Trial's participation ID-card	GCP-V Section 3 §7 (3) 9		X
Information letter to the participants' GP	GCP-V Section 3 §7 (3) 9		X
Recruitment advertisements – hand-outs	GCP-V Section 3 §7 (3) 9		X
Recruitment advertisements – newspapers	GCP-V Section 3 §7 (3) 9		X
Recruitment advertisements – web	GCP-V Section 3 §7 (3) 9		X
Any written material to be used by the participant for data capture			
Diary template (national language)	GCP-V Section 3 §7 (3) 9		X
Source forms for test scores (national language	GCP-V Section 3 §7 (3) 9		X
Documentation by investigational site			
Lead investigator - CV	GCP-V Section 3 §7 (3) 6		X
Lead investigator – GCP-Certificate	GCP-V Section 3 §7 (3) 6a		X
Lead investigator – Financial disclosure	GCP-V Section 3 §7 (3) 7		X
Lead investigator – CTP-receipt	GCP-V Section 3 §7 (2) 2		X
Lead investigator – IB-receipt			X
Deputy investigator - CV	GCP-V Section 3 §7 (3) 6		X
Deputy investigator – GCP-Certificate	GCP-V Section 3 §7 (3) 6a		X
Deputy investigator – Financial disclosure	GCP-V Section 3 §7 (3) 7		X
Deputy investigator – CTP-receipt	GCP-V Section 3 §7 (2) 2		X
Deputy investigator – IB-receipt			X
Detailed qualification report of the site/investigator	GCP-V Section 3 §7 (3) 6a GCP-V Section 3 §7 (3) 8		X
If applicable: declaration re. qualification of non-medically qualified lead or deputy investigators	GCP-V Section 3 §7 (2) 6	X	X
Insurance			
Insurance policy/certificate – Trial participation	GCP-V Section 3 §7 (3) 13		X
Insurance conditions – Trial participation	GCP-V Section 3 §7 (3) 13		X
Insurance policy/certificate – 'accident en route'	GCP-V Section 3 §7 (3) 13		X
Insurance conditions – 'accident en route'	GCP-V Section 3 §7 (3) 13		X

How to submit?

- CA: CDROM plus two printed hardcopies (acc. GCP-V §7 Abs.1)
- EC: CDROM plus printed hardcopies (number varies by EC)

Procedural timelines

- CA:
  - Formal check re. completeness and appropriateness of the submitted documentation: within 10 days after submission (acc. GCP-V §9 (1))
  - Resolution of formal deficiencies by the sponsor within 14 days after receipt of the queries (acc. GCP-V §9 (1))
  - Once the application is accepted to be formally OK, the BfArM undertakes a content check and informs the sponsor of its content queries (if any) within
    - 30 days: normal case (AMG § 42 Abs. 2)
    - 14 days: special case (phase I trials that are part of a global project or that are an extension thereof – acc. GCP-V §9 (3))
    - 60 days (possibly longer) in the event of special medications (medicinal products which fall under Number 1 of the Annex to Regulation (EC) No. 726/2004, which are advanced therapy medicinal products, xenogenic medicinal products, which contain genetically modified organisms, or the active substance of which is a biological product of human or animal origin, contains biological components of human or animal origin or requires such components in its manufacture)
  - Within 90 days after receipt of the content queries, the sponsor should respond (one reply and/or update of the submission permitted at this stage)
  - Within 15 days after receipt of the sponsor's reply to the content queries, a decision will be issued by the BfArM.
- EC:
  - Formal check re. completeness and appropriateness of the submitted documentation: within 10 days after submission (acc. GCP-V §8 (1))
  - Resolution of formal deficiencies by the sponsor within 14 days after receipt of the queries (acc. GCP-V §8 (1))
  - Once the application is accepted to be formally OK, the lead EC is bound to express its vote on the application within the following time-limits:
    - 60 days: normal case (AMG § 42 Abs. 2 and GCP-V §8 (2)) [for multi-centre trial]
      Note: if multi-centre/multi-EC the subsidiary ECs must communicate their vote or queries to the lead EC within 30 days after the submission has been formally accepted to be OK (GCP-V §8 (5)).
    - 30 days: normal case for single-centre trials (GCP-V §8 (3))
    - 14 days: special case (phase I trials that are part of a global project or that are an extension thereof – acc. GCP-V §8 (3) and GCP-V §9 (3))
    - 90 days (possibly longer) in the event of special medications (medicinal products which fall under Number 1 of the Annex to Regulation (EC) No. 726/2004, which are advanced therapy medicinal products, xenogenic medicinal products, which contain genetically modified organisms, or the active substance of which is a biological product of human or animal origin, contains biological components of human or animal origin or requires such components in its manufacture) – see GCP-V §8 (4)
  - Within these limits the EC can raise content queries once; such query 'stops the clock' and the clock starts ticking again once the sponsor has submitted his reply.

EudraCT-Application TOC - CA

01	Cover letter	
02	Copy of E-mail assigning EudraCT-number	
02	EudraCT-application form (and .xml) – Module 1	
03	Clinical Trial Protocol (CTP)	
03	CTP-signature pages	
03	CTP-summary in national language	
04	Investigator's Brochure	
05	IMPD-Q(s)	
06	Benefit:risk Statement	
07	Documentation of NIMP	
08	GMP: Manufacturing authorisation / GMP-Certificate – IMP-Site	
08	GMP: Manufacturing authorisation / GMP-Certificate – Substance manufacturing	
08	GMP: Manufacturing authorisation / GMP-Certificate – Product manufacturing	
08	GMP: QP-Statement by IMP-Site	
09	GMP: IMP-Labelling	
10	Administrative: POA Legal Study Representative (if applicable)	
10	Administrative: Declaration of AMG-, GCP, CTP-adherence by Sponsor/LSR	
10	Administrative: Authorisation of Applicant	
10	Administrative: Declaration of sponsorship (who finances the study?)	
10	Administrative: Declaration of acceptance to pay CA-processing fees	
10	Administrative: List of responsibles & contact data: ethics committees	
10	Administrative: Declaration re. sex/gender distribution	
10	Administrative: Declaration re. post-study follow-up treatment	
10	Administrative: Declaration re. data protection and use of pseudonymised patient data	
11	Documentation of past scientific advice within the EU/EEA (pertinent to the study)	
12	GMO: --	
13	Xenogenic products: --	
14	Other documents: List of responsibles & contact data: sponsor	
14	Other documents: List of responsibles & contact data: CRO	
14	Other documents: List of responsibles & contact data: Sites/investigators	
14	Other documents: Insurance documentation (policies, conditions, etc.)	
15	Clinical Study Report	

EudraCT-Application TOC – EC

[as per EK LÄK-BAY 2017]

00	Table of contents	
01	Letter of application	
01	POA of legal study representative (if applicable)	
01	Letter of authorisation of applicant	
02	Check-list of documents contained in the application	
03	Copy of E-mail assigning EudraCT-number	
04	EudraCT-application form (and xml) – Module 1	
05	EudraCT-application form – Module 2 (national language)	
06	Clinical Trial protocol (& signature pages)	
06C	Clinical Trial Protocol Summary (national language)	
06D	Declaration re. post-study follow-up treatment acc. GCP-V §7 (2) 13	
06E	Declaration re. sex/gender distribution acc. GCP-V §7 (2) 12	
07	Investigator's Brochure	
08	Template of patient information and informed consent form	
09A	Template of diary (if applicable)	
09A	Template of on-site questionnaires (if applicable)	
09B	Patient trial ID-card	
09C	Template information letter to the participants general practitioners	
09D	Template trial information advertisements	
09D	Template trial information leaflets	
10	Insurance (policies, certificates, conditions)	
11	Declaration re. data protection acc. GCP-V §7 (2) 15 | §12 | §13	
12	Declaration re. data protection acc. GCP-V §7 (3) 15	
13	Declaration of non-inclusion of dependent persons acc. GCP-V §7 (3) 4	
14	Declaration of who finances the study acc. GCP-V §7 (3) 5	
15A	List of responsibles & contact data: sponsor	
15B	List of responsibles & contact data: CRO & laboratories	
15C	List of responsibles & contact data: Trial sites & investigators	
15D	List of responsibles & contact data: Ethics committees	
16-01	Specifications by trial site: CV of investigator	
16-02	Specifications by trial site: GCP-certification of investigator	
16-03	Specifications by trial site: Site qualification questionnaire	
16-04	Specifications by trial site: Declaration of AMG- and GCP-Adherence – Investigator	
16-05	Specifications by trial site: Declaration of data protection adherence – Investigator	
16-06	Specifications by trial site: Declaration of receipt of IB and CTP - Investigator	
16-07	Specifications by trial site: Declaration of absence of financial conflicts acc. GCP-V §7 (3) 7 - Investigator	
16-11	Specifications by trial site: CV of Deputy	
16-12	Specifications by trial site: GCP-certification of Deputy	
16-14	Specifications by trial site: Declaration of AMG- and GCP-Adherence – Deputy	
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19	Specification of investigator remuneration/honorary	
20	Investigator Contract – Lead Investigator	
20	Investigator Contract – Investigator	
21	Declaration of acceptance to pay EC-processing fees	