EUFEMED Training Module 3 – Regulatory Issues / Ethics / GxP / Quality Assurance

Draft Programme

10 to 15 November 2023 and 20 November 2023 (1 day virtual, 3 days F2F, 1 day virtual)

Pre-reading to prepare course

Which documents are required for the Clinical Trial Authorisation Application?
Cover letter, EU application form, EU-CTR mit den wichtigsten Kapiteln (was muss im trial protocol, informed consent (in German) / in English, IB, IMPD aufgeführt sein, wie müssen die Dokumente aufgebaut sein), manufacturing authorization, site suitability template, labelling, recruitment arrangements, proof of insurance (in German), proof of insurance (in English), financial arrangements, proof of payment, compliance statement GDPR

Day 1: (Friday, virtual); 10. November 2023:

09:00-09:15	Introduction of faculty and participants
09:15-10:00	Historical development of ethical standards (Nuremberg Code, DoH, ICH-GCP, CIOMS) *Nadja Faisst*
10:00-10:45	What needs to be regulated in a clinical trial? (Clinical Trial Approval application dossier with protocol, IB, IMPD, etc., approval by CA and EC, Substantial modifications, IMP, Safety info, annual updates, results publication, QA, etc.) *Ingrid Klingmann*
10:45-11:00	**Break**
11:00-12:15	The structure of clinical trial legislation in the EU, UK, CH, and USA (CTD, CTR, MHRA, Swissmedic, FDA; legal texts and guidelines) *Birka Lehmann*
12:15-12:30	EudraLex Vol. 1,2,3,4,9,10 *Nadja Faisst*
12:30-13:15	**Lunch Break**
13:15-14:30	What is GxP? Overview of key elements of GCP (Good Clinical Practice) and GMP (Good Manufacturing Practice), GLP (Good Laboratory Practice), GcLP (Good clinical Laboratory Practice) including sample management *Kerstin Breithaupt* (GCP) (30 min); *Karl Kleine* (GLP, GcLP) (30 min); *Kerstin Breithaupt* (overview on other GxP like GLSP, GVP, GMP)
14:30-14:45	Discussion on the principles of GxP
14:45-15:15	**Break**
15:15-16:30	Principles of CTD, EU-CTR and transition period *Ingrid Klingmann*
16:30-16:45	**Break**

16:45-17:30 Case discussion: Informed consent process in Phase I - informed consent form from Tegenero trial will be discussed (Pre-reading of Tegenero case is mandatory!)
Ingrid Klingmann, Kerstin Breithaupt

Day 2: (Monday, face-to-face); 13. November 2023:

09:00-09:45 Regulatory development strategy options incl. central approval or country-specific approval, pre-approval scientific advice with EMA and/or FDA, abbreviated marketing authorisation, interaction with CA and ECs, paediatric development obligations in EU and USA
Birka Lehmann

09:45-10:30 From Phase 1 to marketing authorisation: formulations, PIP, interaction studies, conditional marketing authorisation options
Ingrid Klingmann

10:30-10:45 **Break**

10:45-12:00 Pharmaceutical specific regulations regarding an IMP (including API, validated analysis, manufacturing processes, certification, QP release and importation)
Rango Dietrich

12:00-12:45 Translational considerations of non-clinical experience to human studies (incl. M3, safety, bioavailability, pharmacokinetics, and metabolism)
Diane Sims-Silberman

12:45-13:45 **Lunch Break**

13:45-14:45 First-in-human guideline with focus on assessments of determination of first dose, process for dose escalation decisions, stopping rules, clinical safety (AE/SAEs), 'trend assessment processes' regarding safety, PK, and PD, institution of independent data monitoring committee
Kerstin Breithaupt

14:45-15:15 FDA guidance documents for first-in-human dose
Kerstin Breithaupt

15:15-15:45 **Break**

15:45-17:30 Trial preparation in Phase 1: the CTA application dossier (protocol, IB, IMPD), site selection, contracting and management of suppliers, investigator agreement, insurances
Diane Sims-Silberman

17:30-18:00 **Q&A;** What can Phase 1 contribute to prepare a (conditional) marketing authorisation?

Day 3 (Tuesday, face-to-face); 14. November 2023:

09:00-12:00 **Which documents are required for Clinical Trial Authorisation Application?**
- Cover letter, CTIS application structure in sandbox, trial protocol, informed consent, IB, IMPD, manufacturing authorization, site suitability template, labelling, recruitment arrangements, proof of insurance, financial arrangements, proof of payment, compliance statement GDPR,

- Redaction and Deferrals
Burkhard Kerlin

- Which information needs to be redacted? Break-out groups: redaction of trial protocol, informed consent, IB/IMPD taking into account the respective chapters of EU-CTR (Q&A Document, Eudralex guidances)

12:00-13:00 **Lunch Break**

13:00-17:00 **CTIS Training module:**
- Explanation of CTIS structure, available trainings, timelines, organisational aspects between regulatory and operations departments
- Upload of the mock CTA submission dossier according to the EU CTR; use of CTIS Sandbox
- Documents to be uploaded following the end of trial

Sybille Baumann, Kerstin Breithaupt, Sylvia Grebe, Nadja Faisst, Burkhard Kerlin Ingrid Klingmann, Maike Narten

Day 4 (Wednesday, face-to-face); 15. November 2023:

09:00-10:10 **Organisation and responsibilities of an early phase trial unit:**
Set-up of Phase I unit, infrastructure, how to be ready for a pre-qualification visit, subject recruitment, data protection, informed consent, housing conditions, ethical and technical aspects of assessments, data management, remuneration, follow-up (FiH guideline in practical application, Eudralex guidance for inspections)
Sybille Baumann

10:10-10:30 **Discussion / Short case study**
Sybille Baumann

10:30-11:00 **Break**

11:00-12:30 How to prepare the regulatory infrastructure for an early phase clinical trial incl. risk assessment and management? How to prepare inspection readiness?
Thomas Schillinger (perspectives of trial site)

Karin Köhler-Hansner (perspectives of sponsor)

12:30-13:30 **Lunch Break**

15:30-16:00 **Break**

16:00-16:30 Registration of clinical trials in EU and globally and reporting of results in data bases
Burkhard Kerlin

16:30-18:00 Evaluation and reporting of a Phase 1 trial in the EU (Statistical analysis plan, Clinical Study report, Start-End, Summary of Clinical Trials, Lay Summary)
Kerstin Breithaupt

17:45-18:00 Joint discussion: Challenges of transparency in Phase 1 trials

Home work day (individually / group work with up to 4 participants): Check the trial protocol that was developed under the EU Directive versus the requirements of the EU Clinical Trials Regulation and identify the required changes.

Day 5: (Monday, virtual); 20. November 2023:

09:00-09:45 Feedback from Home Work on trial protocol adaptation

09:45-10:30 Pharmacovigilance in practice (GPvP, Safety reporting, Serious breaches, MedDRA coding, SAE according to CIOMS, SUSAR reporting in EudraVigilance)
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10:30-11:00 **Break**

11:00-12:00 Quality management in Phase 1 trials (Quality manual, SOPs, work instructions, Documentation of qualification and training of site personnel, risk-based monitoring)
Thomas Schillinger

12:00-13:00 Validation (PK and PD assessments, bioanalytical methods, computerised systems and data capture)
Karl Kleine

13:00-13:45 **Lunch Break**

13:45-14:15 Document management (TMF, ISF, archiving conditions)
Diane Sims-Silberman

14:15-14:45 Sponsor's study oversight including cross-discipline due diligence and monitoring for all protocol-contracted out services
Karin Köhler-Hansner

14:45-15:00 **Break**

15:00-16:30 Audit, audit response (CAPA), inspection and inspection readiness
Auditor, Inspector, Quality Working Party
Karl Kleine

16:30-17:00 Feedback

17:00-18:00 Final Test

Case studies

- Review of the Informed Consent Form - blinded Tegenero case *(homework and virtual Day 1)*
- Prepare a mock submission dossier according to EU CTR *(on site on Day 3 at f2F meeting)*
- Homework: Review an 'old' protocol according to the new EU-CTR *(between Day 4 and 5)*
- Homework: Pre-reading and reading in-between course days; preparation of test

Pre-reading

- Declaration of Helsinki

- ICH-GCP
- EU-CTR specific chapters for trial protocol, informed consent, submission documents (incl. Annexes)
- FIH Guideline / FDA guidance documents for first-in-human dose
- Pre-course reading on marketing authorisation:
  - How are medicines evaluated at the EMA? booklet available from EMA
- - Clinical Trial Route Map – NIHR - http://www.ct-toolkit.ac.uk/routemap
- All documents for the mock submission dossier
- Blinded Tegenero informed consent form

Faculty

Dr. Sybille Baumann, CRS Clinical Research Services GmbH, Berlin

Dr. Kerstin Breithaupt-Grögler, -kbr- clinical pharmacology services, Frankfurt/Main

Dr. Rango Dietrich, PharmDev Innovations, Hamburg

Nadja Faisst, CRS Clinical Research Services GmbH, Mannheim

Dr. Sylvia Grebe, Socratec R&D GmbH, Oberursel

Burkhard Kerlin, Bayer AG, Wuppertal

Dr. Karin Köhler-Hansner, Consultant in Clinical Research, Niedernhausen

Dr. Karl Kleine, Quality Consultant, Weilheim

Dr. Ingrid Klingmann, Pharmaplex bv, Brussels

Dr. Birka Lehmann, Senior Expert for Drug Regulatory Affairs, Bonn

Dr. Maike Narten, Socratec R&D GmbH, Oberursel

Dr. Thomas Schillinger, CRS Clinical Research Services GmbH, Wuppertal

Dr. Diane Sims-Silberman, Janssen R&D, Düsseldorf