Curriculum „Clinical Research Physician“ Overview

Definitions

- *Clinical Research Physician*
  - *carries out independently a clinical drug trial or*
  - *takes part in the planning and execution of clinical trials*

- *Clinical Trial*
  - *is a systematic evaluation of a new drug or medical therapy in healthy volunteers or patients in a strictly scientifically controlled setting*
  - *Background: A new medicine must be proven to be therapeutically effective and safe and better than current standard care before being licenced for prescription in clinical practice*

Aim of training programme „Clinical Research Physician“:

- *Overview about the planning, conduct and evaluation of clinical trials as well as some relevant background knowledge*

- *Emphasis on topics especially relevant for clinical research physicians*

Main Topics (Total 60 hours; thereof 48 hours face-to-face and 12 hours E-learning)

I Planning and Organization (14 hours face-to-face, 4 hours E-learning)

II Biometry (10 hours face-to-face, 2 hours E-learning)

III Law and Ethics (10 hours face-to-face, 2 hours E-learning)

IV Preclinical and Clinical Basics (14 hours face-to-face, 4 hours E-learning)

Curriculum „Clinical Research Physician“ Details

I Planning and Organization (14 hours face-to-face, 4 hours E-learning)

Pre-study Activities

- Agreements (Confidentiality, Investigator, Financial)
- Investigator`s Brochure (IB)
- Clinical Trial Protocol
- Patient Information, Informed Consent Form (IC)
- Volunteer / Patient Insurance
- Case Report Form (CRF)
- Trial Master File
- Investigator Site File
- Registration to EudraCT (database of all clinical trials in EU)
- Submission to Ethics Committee (positive vote)
- Submission to Competent Authority (permission)

Study Activities

- Study Initiation
  - To assure thorough knowledge of protocol, of study drug, to solve problems
- Study Conduct
  - Investigator: Planning of study activities, of measures to safeguard subjects
  - Reporting responsibilities of AEs of investigator, sponsor
  - SOPs
- Study Monitoring
  - Monitor: Overseeing study progress: checking of recruitment rate, of adherence to protocol, of recording and reporting of AEs, of availability of study material, of reasons for drop outs, performing drug accountability,
- Study Closure
  - Monitor: returning/destroying study medication, returning CRFs, archiving of investigator file

Post-Study Activities

- Data Management
- Statistical Analysis
- Statistical Study Report
  - Summary of results of statistical analysis, tables, figures, listing of data
- Clinical Study Report
  - Description of complete study from planning to outcome
  - Medical and statistical methods
  - Deviations from protocol
  - Group analyses, individual data (to allow reanalyses e.g. by authorities)
  - Efficacy and safety overview
  - Appendices

Quality Control: parallel to study, all phases

- Monitoring, audits, inspections

II Biometry (10 hours face-to-face, 2 hours E-learning)

Definition and Principles

- **Definition of biometry**
  - application of statistics in medicine
- **Forms of Bias**
  - selection bias → unequal structure of groups
  - performance bias → unequal medical care to groups
  - detection bias → unequal examination of groups
- **Principles to avoid Bias**
  - randomisation
    - simple, block, stratified
  - blinding
    - open, single, double blind, doubly dummy

Biometrical Planning

Planning of Clinical Trials

- Sample Size Estimation: number of patients/volunteers
- Clinical Trial Types and Designs:
  - controlled – uncontrolled trials
  - randomized – not randomized trials
  - parallelgroup design - cross-over design
  - monocentre – multicentre trials
  - cohort – case-control studies
  - prospective – retrospective studies
- Hierarchy of Evidence
  - metaanalysis of randomized controlled trials
  - randomized controlled trials
  - cohort studies
  - case-control studies
  - reports, opinions, experience of experts, consensus conferences

Data Management

- Data management plan: collection, administration, processing of data
  - creation of case report form
  - monitoring of data
    - quality control of study data and performance
  - programmation of database
  - programmation of plausibility check
  - data entry in data base, coding of data according to MedDRA
  - data verification:
    - completeness
    - consistency
    - plausibility
  - closure of data base
  - transfer of data to biometry

Data Analysis

- per protocol analysis
  - data only from patients who have completed study per protocol without major deviations
- intention to treat analysis
  - data of all patients randomized to treatment, i.e. intended to treat, whether they actually were treated per protocol or not

- exploratory analysis
  - phase I and II trials
  - descriptive statistics
- confirmatory analysis
  - phase III trials
  - statistical hypothesis testing
- descriptive statistics
  - e.g. arithmetic middle, median, standard deviation
- estimation of parameters
  - confidence intervals
  - correlation coefficients
- statistical tests / hypothesis testing
  - terms :
    - null hypothesis – alternative hypothesis
    - type I error, type II error
    - significance level , p-value
  - tests:
    - χ2-Tests, Fisher‘s Exact test, McNemar‘s Test
    - t-Tests, Wilcoxon-Test

III Law and Ethics (10 hours face-to-face, 2 hours E-learning)

International

- **Declaration of Helsinki of the World Medical Association**
  - animal tests before clinical trials,
  - risk-benefit-evaluation
  - independent ethics committee
  - informed consent, exceptions
- **ICH Guidelines of International Conferece on Harmonization**
  - Safety Topics (in vitro and in vivo pre-clinical studies)
  - e.g. toxicity testing in animals
  - Efficacy Topics (clinical studies in human subject)
  - e.g. Good Clinical Practice, e.g. geriatric, pediatric populations, e.g. statistical principles
  - Quality Topics (chemical and pharmaceutical quality assurance)
  - Stability testing, Impurity Testing
  - Multidisciplinary Topics (cross-cutting topics)
- **Guidance Documents of EMEA**
  - adopted ICH Guidelines (note for guidances)
  - note for guidances efficacy, safety ....
- **Directives of European Union**
  - *to be implemented in national law*
  - 2001/20/EG = GCP-Directive
  - GCP = international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials
  - 93/42/EWG = Medicinal Product-Directive
- **Bioethics Convention of European Council**
  - *not signed by all member states*

National

- Drug Law + GCP-Decree
- Medicinal Product Law
- Medical Association´s Professional Code of Conduct
- Data Protection Law
- Radiation Protection Law
- Responsibilities of
  - Sponsor
  - Investigator
  - Ethics committee
  - Competent Authority

IV Preclinical and Clinical Basics (10 hours face-to-face, 2 hours E-learning)

Preclinical topics

- characterization of properties of drug
- specific analytical method for determination of drug in body fluids
- pharmacological working profile in in-vitro and in-vivo tests
- dose / concentration – effect – relationship
- preclinical safety studies
  - safety pharmacological studies
  - single dose toxicity studies
  - multiple dose toxicity studies
  - local tolerance studies
  - genotoxicity studies
  - carcinogenicity studies
  - reproduction toxicity studies

Clinical topics

- phases of clinical trials
- pharmakokinetics
- pharmakodynamics
- safety and tolerability

Clinical Trials

- Clinical drug development: The four phases of clinical trials
  - phase I clinical trials
  - phase II clinical trials
  - phase III clinical trials
  - phase IV clinical trias

Pharmacokinetics

- pharmacokinetics:
  - drug absorption and systemic availability
  - drug distribution
  - drug metabolism
  - drug excretion
- pharmacokinetic terms and parameters
  - zero-order, first-order and non-linear kinetics
  - Cmax, tmax, AUC
  - half life (t1/2)
  - apparent volume of distribution V
  - Clearance (CL)
  - steady state - loading dose – maintenance dose

Pharmacodynamics

- pharmacodynamics:
  - drug action via direct effect on a receptor
  - drug action via indirect alteration of the effect of an endogenous agonist
  - drug action via inhibition of transport processes
  - drug action via enzyme inhibition / activation
  - phenomenon of stereoisomerism
  - dose / concentration – response - curves
- methods for measurement of pharmacodynamic effects e.g.:
  - cardiovascular drug effects
  - gastrointestinal drug effects
  - central nervous drug effects

Safety and Tolerability

- adverse events (AE)
  - definiftions: AE, AR, SAE, SAR, SUSAR
  - recording and evaluation
    - duration, course, intensity, outcome
    - seroiusness: non serious, serious
    - causality: none, unprobable, possible, probable, definitive
    - expectedness: expected, unexpected
  - reporting of SAE, SUSAR
  - responsibilities in recording and reporting of investigator, sponsor
- adverse reactions (AR)
  - incidence
    - hospital admissions, deaths due to AR, AR in in-patients
  - classification
    - dose-related AR
    - non-dose-related AR
    - long-term effects, withdrawal effects causing AR
    - delayd effects causing AR

Subgroups

- Clinical trials in
  - children and adolescents
  - in elderlies
  - in patients with renal failure
  - in patients with hepatic disease
  - in people with genetic polymorphisms