CLINICAL TRIALS – GERMAN<>ENGLISH

AN INTRODUCTION TO PROCEDURES AND ENGLISH<>GERMAN TERMINOLOGY

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I. INTRODUCTION

- Clinical trials are conducted to test the **EFFICACY** and **SAFETY** of medications, medical devices, or other methods of treatment in humans who **VOLUNTARILY** participate in these studies.

- **The terms "clinical study" (klinische Studie) and "clinical trial" (klinische Prüfung) may be used interchangeably.**

- Clinical trials follow **preclinical investigations** that include:
  - in vitro studies (studies performed with cell cultures) and
  - **in vivo studies** (studies with animals).

- Preclinical studies are conducted over several years, and only a small percentage of these studies lead to clinical studies.

- Since results from animal studies cannot be extrapolated to the use in humans, **patients may or may not benefit from participating in a clinical study.**

FOUR MAJOR REQUIREMENTS FOR CLINICAL STUDIES FOR TESTING MEDICATIONS

1. Controlled
2. Randomized
3. Blinded
4. Ethical principles must be followed

1. CLINICAL TRIALS MUST BE CONTROLLED (KONTROLLIERT)

Treatment with study drug versus no treatment OR standard treatment

Study drug, Investigational product Studienpräparat, Prüfpräparat, Verum	Treatment group, Investigational group Behandlungsgruppe
Comparator, Comparator product Vergleichspräparat	Control group Kontrollgruppe

2. CLINICAL TRIALS MUST BE RANDOMIZED (RANDOMISIERT)

Random allocation to one or more treatment groups and at least one control group

3. CLINICAL TRIALS MUST BE BLINDED (VERBLINDET)

Double-blind trial Doppelblindstudie	Patient AND physician are “blind”
Single-blind trial Einfachblindstudie	Patient OR physician are “blind”

Placebo:
- Pill or liquid without active substances
- looks exactly the same as the study drug
- used as comparator

4. CURRENT ETHICAL PRINCIPLES MUST BE FOLLOWED

- Study participation must be voluntary
- Unnecessary suffering must be avoided
- Informed Consent must be signed by the study participant

II. LANDMARKS IN THE HISTORY OF CLINICAL TRIALS

(in relation to current requirements)

- **FIRST CONTROLLED TRIAL**

  1747 by James Lind on board of a ship

  Treated disease: scurvy

  Study drug: 2 oranges and 1 lemon/day

  Comparators: cider, vinegar, nutmeg, seawater and others

  Results: Citrus fruits were effective, none of the comparators were effective

- **FIRST RANDOMIZED TRIAL**

  1896/97 by Johannes Fibiger in Denmark

  Treated disease: diphtheria

  Study group: antiserum + standard therapy

  Control group: standard therapy only

  Randomization: allocation of newly admitted patients to the hospital on alternating days to treatment group or control group

  Outcome measure: mortality

  Results: 8 of 239 patients in the treatment group and 30 of 245 patients in the control group died

HISTORY (cont.)

- **FIRST BLINDED TRIAL**

  1948 by the Medical Research Council in London
  Treated disease: Pulmonary tuberculosis
  Study group: Streptomycin + bed-rest
  Control group: Bed-rest only
  Blinding: Radiologists who compared the x-rays before and after treatment were blinded
  Outcome measures: Radiological improvement, mortality
  Results:

	Study Group	Control Group
Radiological Improvement	27 of 55 (51%)	4 of 52 (8%)
Death within 6 months	4 of 55 (7%)	14 of 52 (27%)

HISTORY (cont.)

- **ETHICAL PRINCIPLES**

  First introduced in 1949 by the Nuremberg Code, written after the Nuremberg trials

  Major principles of the Nuremberg Code:

- The voluntary consent of the subject is essential
- Unnecessary suffering and injury should be avoided
- The subject must be free to withdraw from the study at any time and for any reason

  Declaration of Helsinki 1964

  Issued by the World Medical Assembly and amended several times (last time 2002)

- Ethical principles of the Nuremberg Code were adopted
- Informed Consent was declared a “major requirement for ethical research”

HISTORY (cont.)

- **Belmont Report**

  - Issued in 1979 in response to the **Tuskegee Syphilis Study** (1932-1972) by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

  - Tuskegee Study: 399 African American men with syphilis were monitored but did not receive treatment, in particular no penicillin when it became available in the late 1940s.

  - The report includes three principles: **Respect for persons**, **beneficence**, **justice**

  - The report led to the **establishment of Institutional Review Boards (Ethics committees)**

III. PREPARATION OF A CLINICAL TRIAL

- STUDY PROTOCOL – PRÜFPLAN, STUDIENPROTOKOLL
- PATIENT INFORMATION AND INFORMED CONSENT – PATIENTENINFORMATION UND EINWILLIGUNGSERKLÄRUNG
- INVESTIGATOR'S BROCHURE – PRÜFARZTBROSCHÜRE
- CASE REPORT FORM (CRF) – PRÜFBOGEN (CRF)
- ADDITIONAL DOCUMENTS

STUDY PROTOCOL - PRÜFPLAN

1. Study title
2. Sponsor's name and contact information
3. Investigator's/principal investigator's name and contact information
4. Description of the background and objectives of the study
5. Study design
   - Experimental design
   - Study population
   - Inclusion and exclusion criteria
   - Sample size
   - Recruitment procedures
   - Screening procedures
   - Randomization
   - Blinding method
   - Drug administration schedule
   - Study procedures
   - Endpoints
   - Safety monitoring
   - Unblinding
   - Statistical methods

1. Studientitel
2. Name und Kontaktinformation des Sponsors
3. Name und Kontaktinformation des Prüfers/Hauptprüfers
4. Beschreibung des Hintergrunds und der Ziele der Studie
5. Studiendesign
   - Experimentelles Design
   - Studienpopulation
   - Einschluss- und Ausschlusskriterien
   - Fallzahl, Stichprobengröße
   - Rekrutierung
   - Screening
   - Randomisierung
   - Verblindungsmethode
   - Medikamentenverabreichung
   - Studienablauf und Untersuchungsmethoden
   - Endpunkte
   - Erfassung der Sicherheit
   - Entblindung
   - Statistische Methoden

STUDY PROTOCOL (cont.)

Detailed plan of a clinical study and the most important document for conducting a clinical study.

1. STUDY TITLE — **STUDIENTITEL**

[for example: A randomized, double-blind, placebo-controlled, multicenter study on the treatment of stage III melanoma with XXX]

2. SPONSOR'S NAME AND CONTACT INFORMATION — **NAME UND KONTAKTINFORMATION DES SPONSORS**

A <u>sponsor</u> is an individual, company (e.g., pharmaceutical company) or institution that takes the responsibility to initiate, manage, and finance a clinical study

STUDY PROTOCOL (cont.)

3. INVESTIGATOR'S NAME AND CONTACT INFORMATION / NAME UND KONTAKTINFORMATION DES PRÜFARZTES (PRÜFERS)

The investigator
- must have appropriate qualifications und prove them
- is responsible for writing the protocol
- is responsible for preparing the trial
- is responsible for conducting the trial including medical management of study participants (subjects) / Studienteilnehmer (Probanden)

If there is more than one investigator, one of them is the leader and is called principal investigator / Hauptprüfer (Leiter der klinischen Prüfung, LKP)

Investigator Sponsored Trial (IST): Sponsor = Investigator

STUDY PROTOCOL (cont.)

4. DESCRIPTION OF THE BACKGROUND AND OBJECTIVES OF THE STUDY

BESCHREIBUNG DES HINTERGRUNDS UND DER ZIELE DER STUDIE

including

- **a literature overview of the symptoms and course of the treated disease**
- **currently available treatment**
- **measurements of outcome, i.e., efficacy and toxicity**

STUDY PROTOCOL (cont.)

STUDY DESIGN

5. STUDY DESIGN **STUDIENDESIGN**

Plan for procedures before, during and after the study

- **Experimental design** **Experimentelles Design**

Monocenter or multicenter	monozentrisch oder multizentrisch
placebo-controlled	placebokontrolliert
active controlled	aktiv kontrolliert
randomized	randomisiert
double-blind or single-blind	doppleblind oder einfachblind

STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

- **Study population** **Studienpopulation**
  Defined by inclusion and exclusion criteria

- **Inclusion and exclusion critieria** **Einschluss- und Ausschlusskriterien**
  Determine eligibility of a patient. Criteria include among others:
  - Age range
  - Gender
  - Stage of disease
  - Concomitant diseases
  - Previous treatments

STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

- **Sample size** — **Fallzahl, Stichprobengröße**

  Number of participating subjects calculated with statistical methods taking expected results into account

- **Recruitment procedures** — **Rekrutierung**

  - Public listings (e.g., Internet)
  - Public notices in newspapers and journals,
  - Announcements on radio and TV
  - Through information from the patient's physician or other health care providers

  Potential patients receive a
  Patient Brochure — **Patientenbroschüre**
  (= Patient Information Sheet)
  The broschure includes:
  - investigator's name and contact information
  - information about the tested drug and the conduct of the study

STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

- **Screening procedures** **Screening**

  Determination of eligibility of a potential subject for a specific study using inclusion and exclusion criteria.

  Procedures include but are not limited to:

  - History and physical examination

  - Laboratory tests

  - Imaging procedures

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STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

- **Randomization method**
  Randomisierungsmethode

Most common methods include:

- **<u>Simple randomization:</u> Equivalent to tossing coins for each subject**
- **<u>Block randomization:</u> Patients are divided into two or more blocks of equal size and the blocks are randomized to treatments.**
- **<u>Stratified randomization:</u> Patients are divided into blocks according to certain characteristics such as age range or gender, and the blocks are randomized to treatments**

STUDY PROTOCOL(cont.)

STUDY DESIGN (cont.)

- **Blinding method** **Verblindungsmethode**

- **Single-blind**
- **Double-blind**
- **Triple-blind** **Dreifachblind**

  Double blind study, in which data management staff and/or physicians (e.g., radiologists) and/or statisticians interpreting and analyzing results are also blinded

STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

- **Dosages, administration schedule, and route of administration** **Dosierung, Applikationsart**
  of the investigational product and comparator(s)

- **Study Procedures (Study activities)** **Studienablauf und Untersuchungsmethoden**

  For example:
  - **Method of dispensing medications to the patient**
  - **Schedule of baseline and follow-up visits and procedures at each visit (e.g., physical examination, laboratory tests, imaging procedures, ECG)**
  - **Methods for evaluation of results:**
    a. Data acquisition and collection methods
    b. Statistical methods

STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

- **Endpoints:** **Endpunkte:**

  Outcome measures (Zielkriterien) related to EFFICACY and SAFETY

  Primary endpoints (Primäre Endpunkte): **direct measures of the response to treatment (e.g., remission) or lack of response (e.g., tumor progression).**

  Secondary endpoints (Sekundäre Endpunkte): **measures related to primary endpoints such as quality of life, duration of remission, survival, or laboratory values.**

STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

• Safety Monitoring Adverse events (AE) Adverse drug reactions (ADR)	• Erfassung der Sicherheit Unerwünschte Ereignisse (UE) Unerwünschte Arzneimittelwirkungen (UAW)
1. Adverse Events (AE) Any medical event (including intercurrent diseases and accidents) - that occurs under treatment with a medicinal product and - does not necessarily have a causal relationship with the treatment.	1. Unerwünschte Ereignisse (UE) Jedes unerwünschte medizinische Ereignis (einschließlich interkurrenter Erkrankungen und Unfälle), - das unter Behandlung mit einem Arzneimittels auftritt und - nicht unbedingt in ursächlichem Zusammenhang mit dieser Behandlung steht.

STUDY PROTOCOL(cont.)

STUDY DESIGN (cont.)

Safety Monitoring (cont.)	Erfassung der Sicherheit (Forts.)
2. Adverse Drug Reactions (ADR) Any unintended, harmful or unpleasant response to a medicinal product that occurs under treatment with a medicinal product at any dose used for ▪ diagnosis, prophylaxis or treatment of diseases or ▪ modification of physiological functions The response is such that there is a reasonable possibility that the adverse reaction was caused by the medicinal product.	**2. Unerwünschte Arzneimittelwirkungen (UAW)** Alle unbeabsichtigten, schädlichen bzw. unangenehmen Arzneimittelwirkungen unabhängig von der Dosis bei Anwendung des Arzneimittels zur ▪ Diagnose, Prophylaxe oder Behandlung einer Krankheit oder ▪ zur Modifikation physiologischer Funktionen, wobei ein kausaler Zusammenhang mit dem Arzneimittel angenommen werden kann.

STUDY PROTOCOL (cont.) STUDY DESIGN (CONT.)

Safety Monitoring (cont.)	**Erfassung der Sicherheit**
3. Serious Adverse Events (sAE) and Serious Adverse Drug Reactions (sADR) **Any adverse experience at any dose that** ▪ **is fatal or life threatening,** ▪ **is permanently disabling,** ▪ **results in hospitalization or prolongation of hospitalization** ▪ **results in a persistent or significant disability/incapacity, or a congenital anomaly/birth defect (ICH).**	**3. Schwerwiegende unerwünschte Ereignisse (SUE) und schwerwiegende unerwünschte Arzneimittelwirkungen (schwerwiedende UAW)** **Jedes unerwünschte Ereignis, das unabhängig von der Dosis** ▪ **tödlich oder lebensbedrohlich ist** ▪ **eine stationäre Behandlung oder deren Verlängerung erforderlich macht,** ▪ **zu einer bleibenden oder schwerwiegenden Behinderung oder Invalidität führt oder eine angeborene Missbildung bzw. eine angeborene Anomalie darstellt (ICH).**

STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

Safety Monitoring **Erfassung der Sicherheit**

THE FOLLOWING MUST BE DETERMINED:

- **Methods for monitoring safety**
- **Person who is responsible for identifying, recording, and reporting AEs, ADRs, sAEs, and sADRs**
- **Frequency of reporting ADR and AE**
- **Criteria for discontinuing a patient due to an ADR**
- **Criteria for terminating a study due to an ADR**

STUDY PROTOCOL (cont.)

STUDY DESIGN (cont.)

- **Unblinding**
- **Entblindung**

a. Unblinding after completion of the study

Identification of the treatment code and revealing the treatment to the subject, the investigator, and the study staff.

b. Unblinding before completion of the study

not allowed unless knowledge of the administered drug is absolutely necessary for treatment of adverse reactions or intercurrent diseases.

- **Analysis and assessment of study results**
- **Analyse und Beurteilung der Studienergebnisse**

including methods of statistical analysis

INFORMED CONSENT – EINWILLIGUNGSERKLÄRUNG

Presented and explained to the patient during the screening or a separate visit. Verification of the patient's voluntary participation in the study after receiving information about the trial including:

• Purpose of the study	• Zweck der Studie
• Description of the study	• Beschreibung (Ablauf) der Studie
• Potential risks and discomforts	• Potenzielle Risiken und Beschwerden
• Potential benefits	• Potenzielle Nutzen
• Alternative treatments	• Alternative Behandlungen
• Right to withdraw from the study at any time	• Recht aus der Studie jederzeit auszuscheiden
• Costs, reimbursement, compensation	• Kosten, Kostenersatz, Vergütung
• Confidentiality agreement	• Wahrung der Vertraulichkeit (Schweigepflicht)
• Signature of the study participant or his legal guardian and the investigator	• Unterschrift des Studienteilnehmers oder seine gesetzlichen Vormundes und des Prüfers

INVESTIGATOR'S BROCHURE - PRÜFARZTBROSCHÜRE

The brochure is provided to the Investigator before initiation of the study and must contain the following:

Description of the study drug and its formulation	**Beschreibung des Studienpräparates und seiner Formulierung**
Pharmacological and toxic effects of the study drug in animal experiments	**Pharmakologische und toxische Wirkungen des Studienpräparates in Tierexperimenten**
Anticipated possible risks and adverse reactions	**Erwartete Risiken und unerwünschte Arzneimittelwirkungen**

As soon as **clinical data** on risks, safety, and efficacy are available, they must be **included** in the Investigator's Brochure **before** further clinical investigations are conducted.

CASE REPORT FORM (CRF) - PRÜFBOGEN

- A printed or electronic questionnaire
- Designed by the sponsor
- Purpose: To report to the sponsor all information on each subject as outlined in the protocol

The CRF contains but is not limited to:

Contact information of the investigator	**Kontaktinformation des Prüfers**
Contact information of the subject (patient)	**Kontaktinformation des Probanden (Patienten)**
History of the subject	**Anamnese (Krankengeschichte)**
Physical examination at baseline and follow-up visits	**Körperliche Untersuchung bei der Baseline- und weiteren Klinikbesuchen (Visiten)**
Laboratory values at baseline and follow-up visits	**Laborwerte bei der Baseline- und weiteren Klinikbesuchen**
Results of imaging procedures at baseline and follow-up visits	**Ergebnisse bildgebender Verfahren bei der Baseline- und weiteren Klinikbesuchen**
Adverse events and adverse reactions	**Unerwünschte Ereignisse und unerwünschte Arzneimittelreaktionen**

ADDITIONAL DOCUMENTS
(Examples)

- Data acquisition, collection and management procedures
- Manual of study activities (procedures)
- Guidelines for collaborating with the laboratory, radiology department and other involved departments
- Guidelines for collaborating with the pharmacy, including distribution and dispensing of medications
- Guidelines for interactions between the participating centers
- Computer programs for scheduling appointments for follow-up visits
- Training material for clinic staff and other staff involved in the study

IV. ETHICAL ASPECTS

INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH)	**INTERNATIONALE HARMONISIERUNGSKONFERENZ**
GOOD CLINICAL PRACTICE (GCP)	**GUTE KLINISCHE PRAXIS**
STANDARD OPERATING PROCEDURES (GCP)	**STANDARDARBEITSANWEISUNGEN**

The **ICH** is an International body that

- Issues **GOOD CLINICAL PRACTICE (GCP)** RECOMMENDATIONS. The ICH GCP recommendations are defined in the **ICH Guidelines for the EU, Japan and the US**
- Defines **STANDARD OPERATING PROCEDURES (SOPs).**

- In Germany, compliance with GCP is regulated by the drug law (**Arzneimittelgesetz**, AMG)
- American GCP is codified in the **Code of Federal Regulations**

ETHICAL ASPECTS (cont.)

GOOD CLINICAL PRACTICE (GCP):
International standard for ethical and scientific quality of clinical trials
Includes standards for:

- Design
- Conduct
- Monitoring
- Recording
- Analysis of results

STANDARD OPERATING PROCEDURES (SOPs):
"Detailed written instructions to achieve uniformity of the performance of a specific function" (ICH definition)

SOPs must be prepared for each individual or group of individuals with the same function, including (but not limited to):

- Sponsor
- Monitor
- Investigator
- Clinic staff
- Institutional Review Board (Ethics Committee)

ETHICAL ASPECTS (cont.)

STANDARD OPERATING PROCEDURES (SOPs) (cont.)

- SOPs must be prepared by the institution that conducts the trial, in cooperation with the sponsor
- SOPs must be prepared **according to GCP recommendations**

EXAMPLE: The **SOPs for the Investigator** include (but are not limited to):

- Review the investigator's brochure and the literature on the investigational product
- Ensure that there is enough staff available for study procedures and emergencies
- Ensure safety conditions for subjects
- Ensure availability of needed equipment

ETHICAL ASPECTS (cont.)

INSTITUTIONAL REVIEW BOARDS (IRBs) = INDEPENDENT ETHICS COMMITTEES (IECs)	INSTITUTIONELLE PRÜFUNGSKOMMISSIONEN = UNABHÄNGIGE ETHIKKOMMISSIONEN (EK)
FOOD AND DRUG ADMINISTRATION (FDA)	AMERIKANISCHE ZULASSUNGSBEHÖRDE FÜR LEBENSMITTEL UND ARZNEIMITTEL
GERMAN FEDERAL INSTITUTE FOR DRUGS AND MEDICAL DEVICES	BUNDESINSTITUT FÜR ARZNEIMITTEL UND MEDIZINPRODUKTE (BfArM)
EUORPEAN MEDICINES AGENCY (EMEA)	EUROPÄISCHE ARZNEIMITTELAGENTUR

ETHICAL ASPECTS (cont.)

INSTITUTIONAL REVIEW BOARDS (IRBs)/INDEPENDEN ETHICS COMMITTEES

IRBs are responsible for the **ETHICAL CONDUCT OF CLINICAL TRIALS ACCORDING TO GOOD CLINICAL PRACTICE (GCP)**

IRBs consist of:

- Physicians
- Researchers
- Statisticians
- Community advocates

In the **US**, IRBs are regulated by the **Office for Human Research Protection** which is part of the **Department of Health and Human Services (DHHS)**

In **Germany**, IRBSs are accredited and registered by the **Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)**

ETHICAL ASPECTS (cont.)

FOOD AND DRUG ADMINISTRATION (FDA)

- An agency of the Department of Health and Human Services (DHHS)
- Responsible for regulating foods, drugs, and other dietary and medicinal products, including monitoring the safety of drugs, and their approval

BUNDESINSTITUT FÜR ARZNEIMITTEL UND MEDIZINPRODUKTE (BfArM)

- Ein Bundeinstitut (eine selbständige Bundesoberbehörde) im Geschäftsbereich des Bundesministeriums für Gesundheit mit Sitz in Bonn
- Responsible for approval of drugs, improving the safety of drugs, monitoring and reducing risks of medicinal products

ETHICAL ASPECTS (cont.)

EUROPEAN MEDICINES AGENCY (EMEA)

- A decentralized body of the European Union
- Responsible for monitoring the safety of drugs and approval of drugs
- If a drug receives approval from a country-specific agency before it is approved by EMEA, the drug can be marketed in this specific country.
- Drugs for treatment of AIDS, cancer, diabetes, and neurodegenerative diseases must be approved by the EMEA

ETHICAL ASPECTS (cont.)

The **Institutional Review Board (IRB)/**the **Independent Ethics Committee (IEC)** **AND** the **Food and Drug Administration (FDA)/**the **Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)**

- Review and approve or disapprove:
  - All documents written before the initiation of the study
  - Investigator's curriculum vitae
- Evaluate the conduct of the study

The major objectives of reviews and evaluations include:

- To assess the scientific merit of the study
- To promote fully informed and voluntary participation of subjects
- To optimize the safety of subjects
- To assure compliance with the study protocol

Both the IRB/IEC and the FDA/BfArM may request modifications before the clinical trial can be initiated.

V. PHASES OF CLINICAL TRIALS

PHASE I

- Not controlled
- Small number of subjects (20-80), most often healthy volunteers
- Duration: several weeks
- Objectives:
  - Pharmacokinetics (distribution, metabolization, elimination of the drug)
  - Tolerability and safety (side effects)
  - Best route of administration
  - Dose range with acceptable tolerability

PHASES OF CLINICAL TRIALS (cont.)

PHASE II

- Controlled or not controlled, randomized or not randomized
- Several hundred subjects with a specific disease
- Duration: Several weeks to months
- Objectives:
  - Efficacy
  - Safety
  - Best dosage

Phase IIa: Proof-of-concept studies – Überprüfung des Therapiekonzepts
Phase IIb: Dose-finding studies - Dosisfindungsstudien

PHASES OF CLINICAL TRIALS (cont.)

PHASE III

- Double-blind, controlled, randomized
- Several hundred to several thousand subjects
- Duration: Months to years
- Objectives:
  - Further investigation of efficacy and safety
  - Dose adjustments
- After completion, the sponsor applies to the Food and Drug administration (FDA) or the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) for approval to market the drug

PHASES OF CLINICAL TRIALS (cont.)

PHASE IV

- Double-blind, controlled, randomized
- Large number (several thousand)
- Duration: Years
- Objectives:
  - Rare and long-term side effects
  - Drug interactions
- May result in drug withdrawal or restrictions (example: Vioxx)

VI. CONDUCT OF THE CLINICAL STUDY ACCORDING TO THE PROTOCOL

WHAT IS INVOLVED FOR THE **PARTICIPATING SUBJECT (TEILNEHMER)**?

- **BASELINE VISIT (BASELINE-VISITE, AUSGANGSUNTERSUCHUNG)**:
  Visit before treatment (combined with or after the screening visit)
  - History
  - Physical examination
  - Laboratory tests
  - Imaging tests
  - Subject receives medication (if taken or administered at home) for a certain period of time
  - Subject receives information about dosage and administration schedule
  - Subject receives schedule of follow-up visits
  - Subject receives additional information if needed, for example, on diet, exercise, keeping a diary

CONDUCT OF THE CLINICAL STUDY ACCORDING TO THE PROTOCOL (cont.)

- FOLLOW-UP VISITS (FOLLOW-UP-VISITEN, KLINIKBESUCHE [VISITEN] IM VERLAUF DER STUDIE)

  - Some or all examinations as at the baseline visit
  - Additional examinations and/or tests
  - Subject receives medication
  - Subject delivers his/her diary

CONDUCT OF THE CLINICAL STUDY ACCORDING TO THE PROTOCOL (cont.)

RESPONSIBILITIES OF THE **INVESTIGATOR (PRÜFER, PRÜFARZT)**

- Ensures that all study procedures are performed according the protocol
- Completes the Case Report Forms (CRF) at each patient visit
- Meets with the **monitor** at regular intervals. The **monitor** is a person who is employed by the sponsor and reviews study records to determine whether a study is being conducted in accordance with the protocol.
- Reports adverse events (AEs) to

  - the Investigational Review Board (IRB)/Independent Ethics Committee (IEC)

  - the FDA/BfArM

  - the sponsor.

Specific forms for AEs (part of the CRF) must be completed.

VII. QUALITY MANAGEMENT

The QUALITY of

- **study related documents**
- **the conduct of the study**
- **the evaluation of results**

must be monitored using STANDARD PROCEDURES

QUALITY MANAGEMENT (cont.)

QUALITY ASSURANCE (QA) **QUALITÄTSSICHERUNG (QS)**

<u>Regulations and requirements</u> established to ensure that

- **the trial is conducted in compliance with Good Clinical Practice (GCP)**
- **data are generated, documented and reported in compliance with Good Clinical Practice (GCP)**

QUALITY CONTROL (QC) **QUALITÄTSKONTROLLE (QK)**

<u>Techniques and activities</u> undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities are fulfilled.

QUALITY MANAGEMENT (cont.)

AUDITS

AUDITS

Who performs an audit?

- an employee (who is not involved in the study) or a hired consultant of the Sponsor
- Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs)
- the Food and Drug Administration (FDA)

The person performing the audit is the AUDITOR.

The FDA uses INSPECTION for audit and INSPECTOR for auditor.

QUALITY MANAGEMENT (cont.)

What is an audit?

A systematic and independent examination of

- **trial-related activities**
- **trial-related documents**

What is the purpose of the audit?

TO DETERMINE WHETHER the trial-related activities are/were conducted and the trial-related documents are/were recorded, analyzed and reported in accordance with

- **the study protocol**
- **Standard Operating Procedures (SOPs)**
- **Good Clinical Practice (GCP)**
- **federal regulations**

QUALITY MANAGEMENT (cont.)

When is an audit performed?

- as a routine (routine audit)
- if there is reason for potential fraud or misinterpretation of data (for cause audit)
- after a marketing application has been filed by the sponsor

QUALITY MANAGEMENT (cont.)

MONITORING

MONITORING

Who performs the monitoring?

- An employee of the Sponsor or
- An Independent Clinical Research Associate (CRA)

The person or institution performing the monitoring is the MONITOR.

What is monitoring?

- Overseeing the progress of a clinical trial
- Assisting the investigator and his staff in performing their activities

QUALITY MANAGEMENT (cont.)

What is the purpose of monitoring?

TO ENSURE THAT the trial-related activities are conducted and the trial-related documents are recorded, analyzed and reported in accordance with

- **the study protocol**
- **Standard Operating Procedures (SOPs)**
- **Good Clinical Practice (GCP)**
- **federal regulations**

When is the monitoring performed?

- **In regular intervals during the course of the study**

VIII. DATA ACQUISITION, COLLECTION AND ANALYSIS

Study procedures, data, and results are electronically collected, processed, and analyzed by various systems and computer programs.

EXAMPLES:

INTERACTIVE VOICE RESPONSE SYSTEMS (IVRS)

- Data are entered into a database using a touchtone phone
- The **investigator** may enter, for example
  - patient demographics
  - randomization of individual patients
  - dosing
  - dispensing medications (date and amount) to individual patients
- The **subject** may enter, for example:
  - symptoms during a certain period of time
  - effects of the study drug
  - side effects of the study drug

DATA ACQUISITION, COLLECTION AND ANALYSIS (cont.)

ELECTRONIC DATA CAPTURE (EDC)

- Systems for collecting patient data electronically and transmitting the data over the Internet
- The data are automatically checked against predefined rules and corrected if necessary

IX. GENERAL ASPECTS OF CLINICAL TRIAL DOCUMENT TRANSLATION

- **Translations from English into German become more and more literal and contain an increasing number of Anglicisms**

- **In German clinical trial documents and translations into German, many English terms are used, sometimes with the German translation in parentheses**

GENERAL ASPECTS OF CLINICAL TRIAL DOCUMENT TRANSLATION (cont.)

Examples:

- **Prüfplan → Studienprotokoll, Protokoll**
- **Doppelblindstudie → doppelblinde (doppelmaskierte) Studie**
- **Prüfbogen → Case Report Form (CRF)**
- **Klinik- oder Arztbesuch → Visite**
- **Ausgangsuntersuchung → Baseline-Visite**
- **Nachuntersuchung → Follow-up-Visite**

IX. PUBLISHING AN ARTICLE

- **Introduction**: Description of the treated disease and its current standard treatment
- **Material and Methods:**

  - Patients: Demographics, pretreatment, treated disease and stage of disease

  - Methods: Dosage, administration schedule, examinations and tests, statistical analysis and other methods of evaluation
- **Results**: Response rate, types of responses (complete, incomplete), test results, adverse events, statistical analysis
- **Discussion**: Interpretation of results and comparison with conventional treatment, influence of the investigational product on prognosis of treated disease, and recommendations