# Good Clinical Practice

# History

- Nuremberg Code
  - Ten point memorandum after the ‘Doctor’s Trial’ – 1947
- Helsinki Declaration
  - Ethical Principles for Medical Research Involving Human Subjects – 1964
- Belmont Report
  - Ethical Principles and Guidelines for the Protection of Human Subjects of Research – 1979

# Development

- WHO
  - Guidelines for good clinical practice for trials on pharmaceutical products – 1995
- ICH
  - E6(R1) Guideline for Good Clinical Practice – 1996
  - E6(R2) Integrated Addendum to ICH E6(R1) – 2016
- EU
  - Implementation of GCP in the Conduct of Clinical Trials on Medicinal Products for Human Use – 2001
- DGDA
  - Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products Bangladesh – 2015

# GCP = Ethical Standards + Quality Data

- Scope
  - Clinical trials (including multi-center) on human subjects
  - Not applicable to non-interventional trials (observational)
  - Ethical and scientific quality requirements
    - Design
    - Conduct
    - Recording
    - Reporting
  - Compliance provides assurance that
    - rights, safety, and well-being of trial subjects are protected
    - results are credible
  - All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of GCP

# Basic Principles

- Ethics
  - Ethical conduct
  - Benefit justifies risks
  - Rights, safety, and well-being of trial subjects prevail over interests of science and society
- Background and Protocol
  - Available information (nonclinical, clinical) supports the study
  - Compliance with a scientifically sound, detailed protocol
- Responsibilities
  - Protocol approved by ethics committee prior to study initiation
  - Medical care/decisions by qualified physician
  - Study personnel is qualified (education, training, experience) to perform required tasks

# Basic Principles

- Informed Consent
  - Freely given from every subject prior to participation
- Data Quality and Integrity
  - Accurate reporting, interpretation, and verification
  - Confidentiality of records guaranteed
- Investigational Products
  - Conform to cGMP and used according to protocol
- Quality Control / Quality Assurance
  - Systems with procedures to ensure quality of every aspect of the study

# Ethics

- Every interventional trial carries some risk
  - Adverse Drug Reactions (ADR)
    - Some drugs should not be administered to healthy subjects → study in patients
    - For some drugs in patients the standard treatment cannot be interrupted → multiple dose study only
  - Even phlebotomy…
- Sample size
  - ICH E9 (Statistical Principles for Clinical Trials)
    *"The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed."*
    - Sample size too small → Probability of success (power) not sufficient
    - Sample size too large → Risk for subjects in the study does not outweigh potential benefit for patients

# Background and Protocol

- Background supports the study
  - Literature
  - Information in the public domain, *e.g.*,
    - FDA's database of NDAs and ANDAs
    - European Public Assessment Reports (EPARs)
  - If available, nonclinical and clinical information
- Protocol
  - Scientifically sound
    *"Only if one asks the right question the answer can be useful."*
  - Detailed
    - Planned methods and procedures sufficiently described
    - Referring only to SOPs is not recommended
  - Procedure how to deal with deviations given

# Informed Consent

- Information about
  - Risks
    - All (!) potential ADRs (non-medical terms & language, likelihood)
    - Pertinent to the study's procedures
      - Number of blood samples & volume
      - Pre- and post-study lab exams, radiography, …
  - Study restrictions
    - Hospitalization
    - Physical activity
    - Standardized food / beverages
- Freely given from every subject prior to participation
  - If a subject is illiterate, an impartial witness is mandatory
    - A husband cannot act as an impartial witness for his wife

# Investigational Products

- Manufactured according to cGMP
  - If not established, the outcome of any BE study is of doubtful value
    - Patient's risk — If BE was demonstrated, batch-to-batch variability might lead to bioinequivalence in clinical practice
    - Producer's risk — If BE was not demonstrated, the risk of failure might have been higher than anticipated in study planning
- Used according to the protocol
  - Pranial state (fasting period, with / without food)
  - Oral administration (volume of water, temperature)
  - Intravenous administration (infusion rate)
  - Dermal application (area, occlusion)

# Data Quality and Integrity

- ALCOA
  - All data of a study has to be
    - Attributable
    - Legible
    - Contemporaneously recorded
    - Original or a true copy
    - Accurate
- Data capture / entry without substantial delay
  - What, when, and by whom?
    - If modification necessary (erroneous entry)
      - As above and
      - Why?
      - No overwriting – the original data has still to be legible

# Data Quality and Integrity

  - Recording on scrap paper for later transfer to a CRF / lab notebook is not acceptable
- Electronic data capture
  - Write-only access granted to authorized staff
  - Right to modifiy data as above; in a study with audit trail
  - Read-only access to QC/QA
- Audit trail in CDS, LIMS
  - Recommended in bioanalytical method development
  - Mandatorily activated
    - Bioanalytical method validation (BMV)
    - During the entire study (system suitability tests, analysis of calibrators, QC, and unknown samples)

# Data Quality and Integrity

- Compilation
  - If a paper-based system is used, double data entry to an electronic system with automatic comparison recommended
  - Software for automatic compilation has to be validated
- Data transfer (example BE)
  - Sponsor → Clinical site
    - Protocol
    - Randomization
  - Sponsor → Bioanalytical site
    - Protocol
    - Alternatively
      - Number of subjects
      - Number of periods
      - Scheduled sampling time points

# Data Quality and Integrity

- Data transfer (example BE) cont'd
  - Clinical site → Biostatistics
    - For each subject and period
      - Administered dose(s), actual date / time
      - Actual time points blood sampling
  - Bioanalytical site → Biostatistics
    - For each subject, period, and scheduled sampling time point
      - Measured concentrations (of parent and metabolite(s) if applicable)
  - After both data sets are joined in biostatistics, the study can be unblinded and the data base has to be locked
    - NCA to calculate PK metrics
    - Statistical evaluation and assessment for BE
  - Results → Medical Writing

# Data Quality and Integrity

- Transfer of data
  - Only if the final version of the respective report is approved by the QAU
  - Transfer of immediate results / draft reports is not acceptable
- Once a study is complete
  - In a paper-based system
    - All original data (CRFs, lab exams, chromatograms,…), draft and final report(s) have to be archived
  - In an electronic system
    - Print outs have to be archived
    - Electronic data have to locked
  - Access to the archive
    - Only by archivists and the QAU

# Quality Control / Quality Assurance

- QC guarantees data integrity
- QA supervises
  - The QRO's general procedures
    (SOPs, training of staff, maintenance of records,…)
  - The study's procedures
    (adherence to the protocol, record of deviations,…)
- The Quality Assurance Unit has to be *independent* from the CRO's general structure
  - Reports directly – and *only* – to the management
  - If a third-party is involved, audit by the QAU mandatory
  - If an electronic data system is established,
    read-only access to *all* files has to be granted

# Responsibilities

- Shared between
  - Sponsor
  - Independent Ethics Committee (IEC) / Institutional Review Board (IRB)
  - Contract Research Organization (CRO)
    - Principal Investigator (PI), Clinical Investigators (CI)
    - Clinical Research Coordinator (CRC) / Associate (CRA)
    - Research Nurses
    - Lab Technicians
    - Medical Monitors
    - Data Entry / IT Personnel
    - Biostatisticians
    - Medical Writers

Audited by QAU

Reports to management

# Responsibilities

- The CRO is responsible to have
  - a sufficient number of trained personell
  - an established system of SOPs
  - all equipment required for the study
  - an independent QAU
- But the sponsor is responsible to verify that
  - A fancy website and flowery promises of the CRO's business manager are not sufficient
  - At least before the first study the sponsor should perform an audit
  - Every study should be monitored by the sponsor (preferred) or an independent monitor

# Non-Compliance to GCP

- Informed consent procedure
  - Information not given by the PI but a study nurse
  - Language in subject information ‘too complicated’ and incomprehensible for laypersons
- SOP system
  - Data verification and traceability
    - For any given date it has to be possible to reconstruct why and how a certain result was obtained and considered valid
    - Required
      - Original data (and if modified access to the audit trail)
      - SOP which was current at the given date
  - Procedures followed in a study but not covered in an SOP
    - Have to be unambiguously described in the protocol

# Non-Compliance to GCP

- SOP system (cont'd)
  - SOPs should be written by the personell who will have to follow it, although support by a supervisor is acceptable
  - 'External' SOPs (bought from a third party) or ones written by the QC are discouraged
- Staff no sufficiently educated & trained
  - Data entry not in a timely manner
  - A study nurse might not be trained to add a very small volume of a stabilizer to whole blood
  - A biostatistican familiar with BE might not be qualified to evaluate a therapeutic equivalence study
- Software not validated
  - Difficult for off-the-shelf (commercial) software, almost impossible for spreadsheets

# Non-Compliance to GCP

- QAU
  - Not independent → reports to the PI
  - Write-access of data → (accidental) modification possible
- Corrective Action / Preventive Action (CAPA)
  - If anything happens in a study which was not anticipated, measures should be taken
    - Identify the source (‘root cause analysis’)
    - If possible, correct the error
    - Prevent its occurrence in the future
  - No room for creativity to ‘safe’ an undesired outcome!
- Useful Documents (EMA)
  - Q&A: Good clinical practice (GCP)
  - Inspections procedure