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Good Clinical Practice

Introduction to ICH-GCP E6(R2) and ISO 14155 (medical devices)

Danny G.P. Mathysen (MSc, PhD)

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Part 1. Introduction to ICH-GCP

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Introduction to ICH-GCP *Good Clinical Practice*

ICH = International Council for Harmonisation of technical requirements for pharmaceuticals for human use

- Regulatory authorities
- Pharmaceutical Industry

⇨ Discuss **scientific** and **technical aspects** of drug registration

GCP = Good Clinical Practice

Extrapolation of ICH-GCP

*Application of ICH-GCP guideline is possible to other clinical investigations that may have an impact on the **safety** and **(physical and mental) well-being** of human subjects*

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Objective of ICH-GCP *Good Clinical Practice*

- Unified **standard** for:
  - European Union (EU)
  - Japan
  - United States of America
  - Switzerland
  - Canada

  ICH-GCP E6(R1) (June 10th, 1996)

  ICH-GCP E6(R2) (November 9th, 2016)

- Facilitate **mutual acceptance** of clinical (experimental) data by the **regulatory authorities** in these jurisdictions

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Objective of ICH-GCP *Good Clinical Practice*

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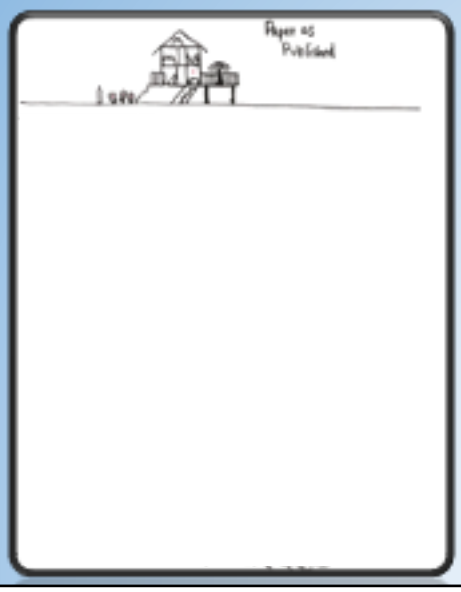
Need for harmonisation



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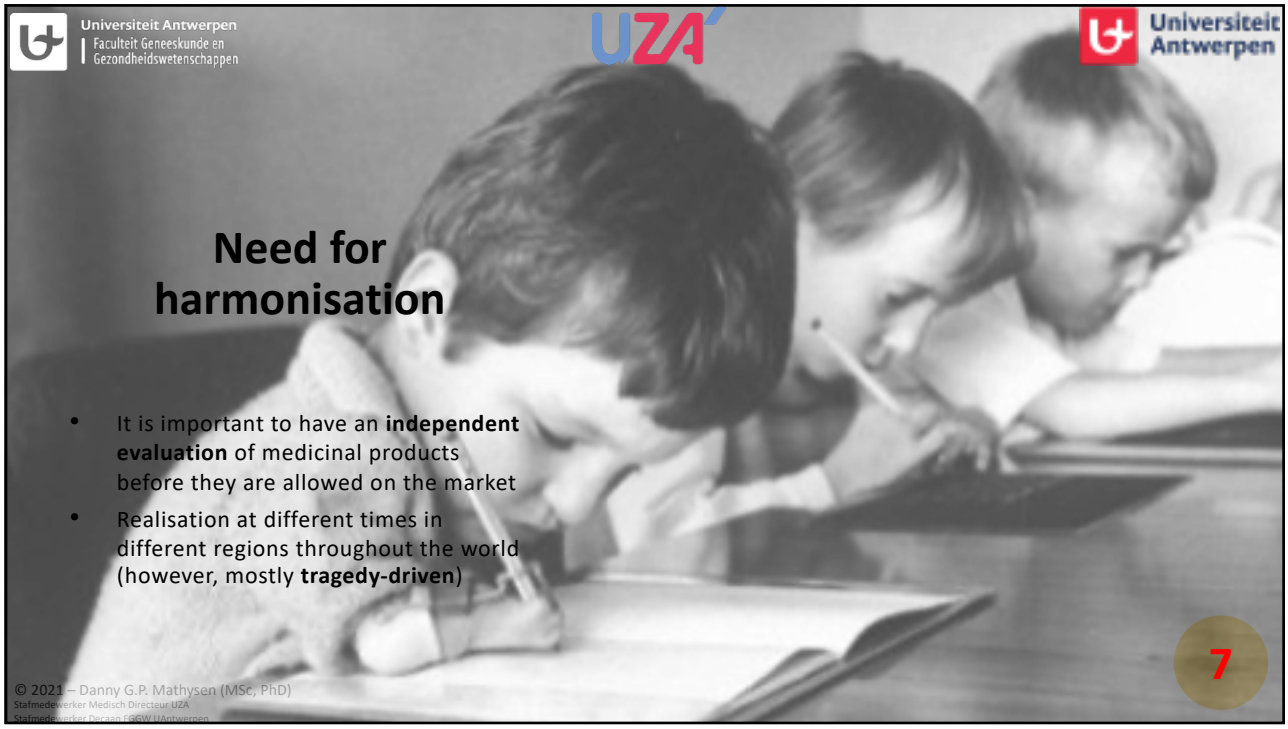
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Need for harmonisation
It is important to have an independent evaluation of medicinal products before they are allowed on the market
Realisation at different times in different regions throughout the world (however, mostly tragedy-driven)
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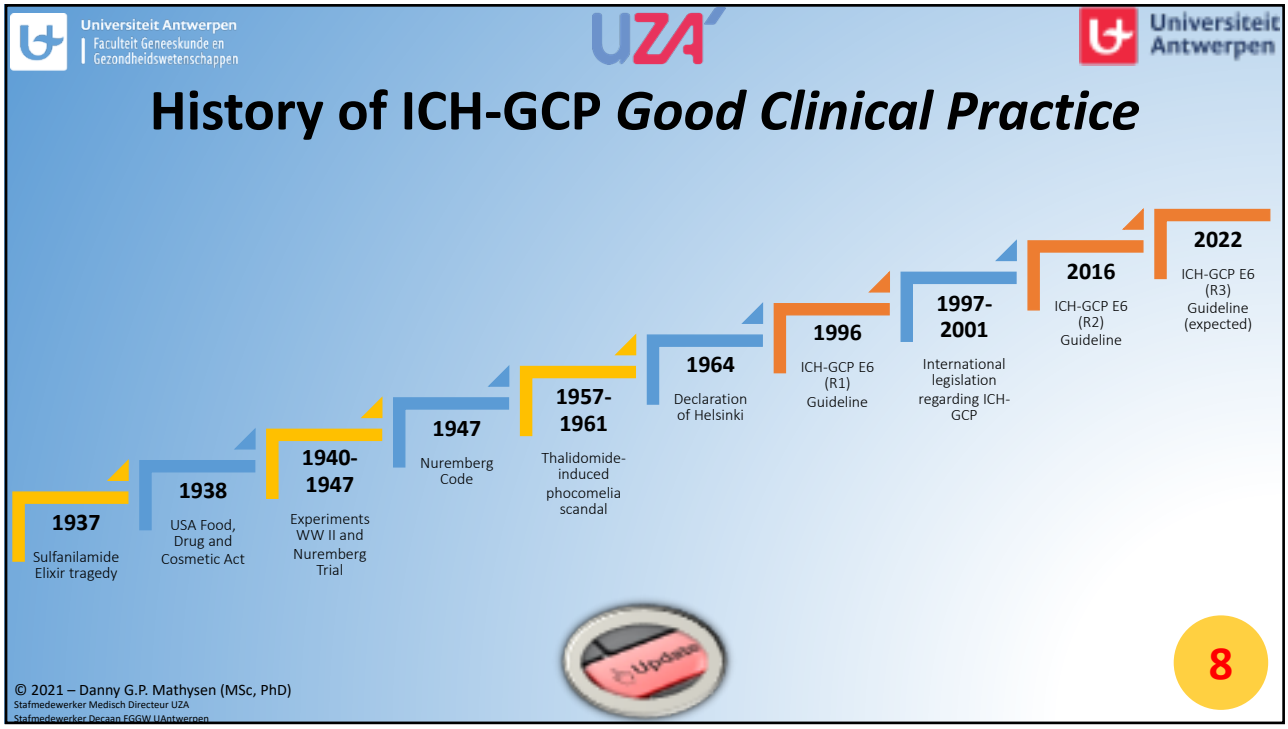
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History of ICH-GCP Good Clinical Practice
1937
Sulfanilamide Elixir tragedy
1938
USA Food, Drug and Cosmetic Act
1940-1947
Experiments WW II and Nuremberg Trial
1947
Nuremberg Code
1957-1961
Thalidomide-induced phocomelia scandal
1964
Declaration of Helsinki
1996
ICH-GCP E6 (R1) Guideline
1997-2001
International legislation regarding ICH-GCP
2016
ICH-GCP E6 (R2) Guideline
2022
ICH-GCP E6 (R3) Guideline (expected)
Update
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Motivation for harmonisation

- Concerns over **rising costs** of healthcare
- Escalation of costs for **research and development** (R&D)
- Need to meet public expectation that there should be a **minimum delay** in making safe and efficacious new treatments available to patients in need

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Why clinical research needs to be regulated?

- **To ensure**
  - Proper **protection** of study subjects
  - Studies to be based on **good scientific principles** including a well-designed study protocol and proper statistical analysis of data
  - Study **procedures** to be properly undertaken and documented

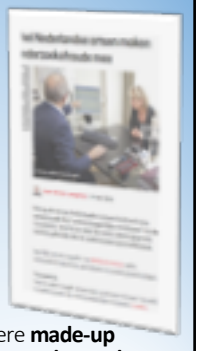
Nuremberg Code (1947): First international standard to protect patients

Declaration of Helsinki (1964, last revision 2013): Ethical Standard

Local initiatives to develop more detailed guidelines (1970-2000) within USA, Europe and Japan

ICH-GCP Guidelines (1996, addendum 2016): Worldwide harmonization

- Survey results (2012) *(The Netherlands)*
  - Organiser survery: Medisch Contact Magazine for Dutch MD's
  - 800 participants (general practicioners, medical specialists)



- Claims of experiences
  - 15 % scientific results were **made-up**
  - 22 % scientific results were **enhanced statistically** (significance)
  - 36 % **co-authors are added** without any contribution

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ICH-GCP *Good Clinical Practice*

- A **standard for all aspects** of clinical trials (design, conduct, performance, monitoring, auditing, recording, analyses, reporting) that provides **assurance** that the:
  - data and reported **results** are **credible** and **accurate**
  - **Rights, integrity and confidentiality** of clinical trial subjects are **protected**
- Origin of ICH-GCP *Good Clinical Practice* dates back to 1996 → clinical trials have evolved substantially, with increases in **globalisation**, **study complexity**, and **technological capabilities**

- ICH-GCP should be modernised to **enable implentation** of **innovative approaches** to clinical trial design, management, oversight, conduct, documentation, and reporting that will better ensure **human subject protection** and **data quality**
- Facilitation of broad and consistent international implementation of **new methodologies**

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Part 2. Thirteen principles of ICH-GCP

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13 principles of good clinical practice

- Principles related to **ethical issues**
  - Declaration of Helsinki (principle 1), estimation of risks involved in clinical research (principle 2), safeguarding patient rights (principle 3), review by an IRB/IEC (principle 6), informed consent (principle 9), assurance of confidentiality (principle 11)
- Principles related to **scientific aspects**
  - Based on adequate information (principle 4), described in a study protocol (principle 5), responsibility of a qualified physician (principle 7), performed by educated staff (principle 8)
- Principles related to **quality management**
  - Safeguarding of research data (principle 10), GMP manufacturing of investigational product (principle 12), implementation of a quality management system (principle 13)

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Principle 1

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the **Declaration of Helsinki**, and that are consistent with GCP and the applicable **regulatory requirement(s)**

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Principle 2

- Before a clinical trial is initiated, **foreseeable risks** and inconveniences should be **weighed against** the **anticipated benefit** for the individual trial subject and society (a clinical trial should be initiated and continued only if the anticipated benefits justify the risks)

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Principle 3

- The **rights**, **safety**, and **well-being** of the trial subjects are the most important considerations and should prevail over interests of science and society

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Principle 4

- The available non-clinical and clinical **information on an investigational product** should be adequate to **support** the proposed clinical trial

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Principle 5

- Clinical trials should be scientifically sound, and described in a **clear, detailed study protocol**

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Principle 6

- A trial should be conducted in compliance with the protocol that has received prior **institutional review board** (IRB) or **independent ethics committee** (IEC) **approval** or favourable opinion.

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Principle 7

- The medical care given to, and medical decisions made on behalf of, subjects should always be the **responsibility** of a **qualified physician** or, when appropriate, of a qualified dentist

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Principle 8

- Each individual involved in conducting a trial should be **qualified by education, training and experience** to perform his/her respective task(s)

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Principle 9

- Freely given **informed consent** should be obtained from every subject prior to clinical trial participation

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Principle 10

- All **clinical trial information** should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification

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Principle 11

- The **confidentiality** of records that could identify subjects should be **protected**, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)

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Principle 12

- Investigational products should be manufactured, handled, and stored in accordance with applicable **good manufacturing practice** (GMP) (they should be used in accordance with the approved protocol)

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Principle 13

- Systems with **procedures that assure quality** of every aspect of the trial should be implemented

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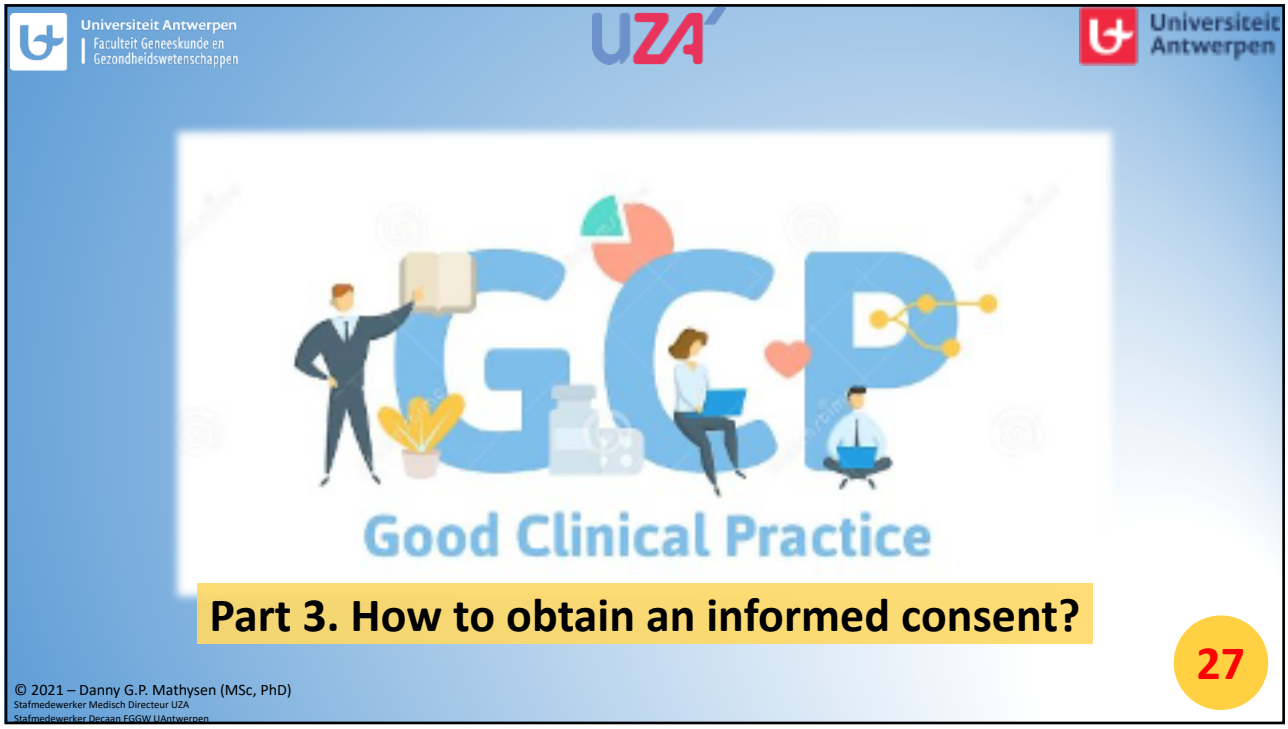
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Good Clinical Practice
Part 3. How to obtain an informed consent?
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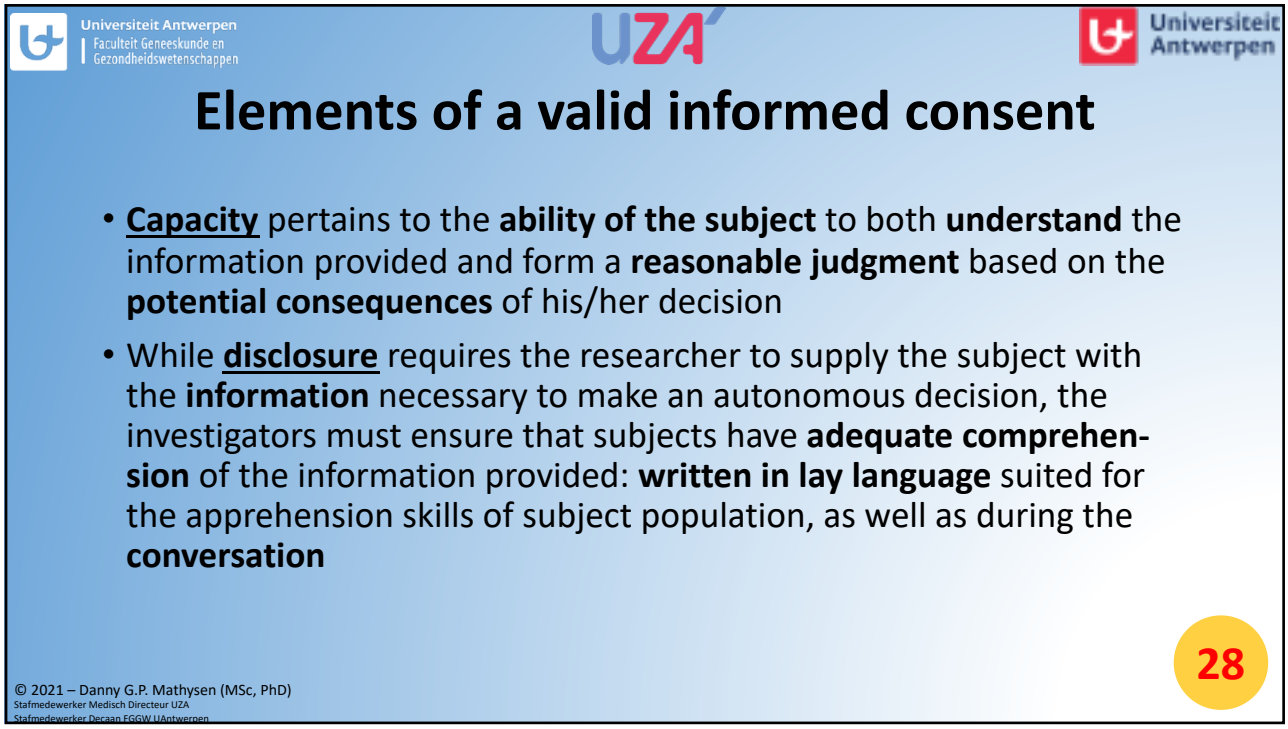
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Elements of a valid informed consent
• Capacity pertains to the ability of the subject to both understand the information provided and form a reasonable judgment based on the potential consequences of his/her decision
• While disclosure requires the researcher to supply the subject with the information necessary to make an autonomous decision, the investigators must ensure that subjects have adequate comprehension of the information provided: written in lay language suited for the apprehension skills of subject population, as well as during the conversation
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Elements of a valid informed consent

- **Voluntariness** refers to the **subject's right to freely exercise** his/her **decision making without** being subjected to **external pressure** such as coercion (compulsion), manipulation, or undue influence.

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Part 4. Quality management of clinical research

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Quality assurance versus quality control

- **Quality assurance (QA)**
  - All those **planned and systematic actions** that are established to **ensure** that the trial is performed and the data are generated, documented, and reported in **compliance** with *Good Clinical Practice* (ICH-GCP) and the applicable regulatory requirement(s)
- **Quality control (QC)**
  - The **operational techniques and activities** undertaken within the quality assurance system to **verify** that the **requirements** for quality of the trial-related activities have been **fulfilled**

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Monitoring of clinical research

- **Monitoring**
  - The act of overseeing the **progress** of a clinical trial, and of **ensuring** that it is conducted, recorded, and reported in **accordance** with the protocol, standard operating procedures (SOPs), *Good Clinical Practice* (ICH-GCP), and the applicable regulatory requirement(s)
- **Monitoring report**
  - A **written report** from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs
- **Monitoring plan**
  - A **description** of the methods, responsibilities and requirements

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Auditing of clinical research

- **Audit**
  - A **systematic and independent examination** of the trial-related activities and documents to determine whether the evaluated trial-related activities were **conducted**, and the **data** were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (ICH-GCP), and the applicable regulatory requirement(s)
- **Audit report**
  - A **written evaluation** by the sponsor's auditor of the results of the audit
- **Audit certificate**
  - A **declaration of conformity** by the auditor that an audit has taken place

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Validation of computerized systems

- A process of **establishing and documenting** that the specified **requirements** of a computerized system can be **consistently fulfilled**. Validation should ensure **accuracy**, **reliability** and consistent intended **performance**, from design until demissioning of the system or transition to a new system
- Data management plan

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Part 5. Responsibilities of the Sponsor

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Sponsor of clinical research

- An individual, company, institution or organization which takes responsibility for the **initiation**, **management**, and/or **financing** of a clinical trial

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Responsibilities of the sponsor

- Quality management
- Quality assurance and quality control
- Contract Research Organization (CRO)
- Medical expertise
- Trial design
- Trial management, data handling and record keeping
- Investigator selection
- Allocation of responsibilities

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Responsibilities of the sponsor

- Compensation to subjects and investigators
- Financing
- Notification/submission to regulatory authority (authorities)
- Confirmation of review by IRB/IEC
- Information on investigational product(s)
- Manufacturing, packaging, labelling and coding investigational product(s)
- Supplying and handling investigational product(s)

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Responsibilities of the sponsor

- Record access
- Safety information
- Adverse drug reaction reporting
- Monitoring / Audit
- Non-compliance
- Premature termination or suspension of a trial
- Clinical trial/study reports
- Multicentre trials

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Part 6. Responsibilities of the (Principal) Investigator

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Investigator according to ICH-GCP

- **Investigator**
  - A person responsible for the **conduct** of the **clinical trial** at a trial site; if a trial is conducted by a team of individuals at a trial site, the investigator is the **responsible leader** of the team and may be called the **principal investigator** (PI)
- **Subinvestigator**
  - Any individual **member of the clinical trial team** designated and supervised by the investigator at a trial site to perform **critical trial-related procedures** and/or to make important **trial-related decisions** (e.g. associates, residents, research fellows)

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(Principal) Investigator and his/her team

- Principal investigator (PI)
  - Single person: no possibility to assign co-PI's !!!
- Coordinating or Chief Investigator (CI)
- Subinvestigators
- Trial Coordinator / Study Coordinator / Study Nurse
- Pharmacy / Laboratory / Imaging Department / …

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Responsibilities of an investigator

- Investigator's qualifications and agreements
- Adequate resources
- Medical care of trial subjects
- Communication with IRB/IEC
- Compliance with protocol
- Investigational product(s)
- Randomization procedures and unblinding
- Informed consent of trial subjects

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Responsibilities of an investigator

- Records and reports
- Progress reports
- Safety reporting
- Premature termination or suspension of a trial
- Final report(s) by investigator

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Adequate resources

- Investigator is **responsible for supervising** any individual or party to whom the investigator delegates study tasks conducted at the clinical trial site
- If the investigator/institution retains the services of any party to perform study tasks they should **ensure** this party is **qualified** to perform those study tasks and should implement procedures to ensure the **integrity** of the study tasks performed and any data generated

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Records and reports

- Investigator should maintain **adequate and accurate source documents** and trial records that include all pertinent observations on each of the site's trial subjects
- Source data should be attributable, legible, contemporaneous, original, accurate and complete
- Changes to source data should be **traceable**
- Changes to source data should not obscure the original entry and should be **explained if necessary**

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Source data and source documents

- Source Data
  - All **information in original records and certified copies** of original records of clinical findings, observations, or other activities in a clinical trial **necessary** for the **reconstruction and evaluation of the trial**. Source data are contained in source documents (original records or certified copies)
- Source Documents
  - **Original documents, data, and records** (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)

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Part 7. Essential documents within Trial Master File (TMF) and Investigator Site File (ISF)

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Location of documents before start

Location of documents before start of a clinical trial	ISF (Investigator)	TMF (Sponsor)
Investigator's brochure	x	x
Signed protocol and amendments (if any)	x	x
Sample case report forms (CRF)	x	x
Informed consent form	x	x
Advertisement for subject recruitment	x	
Financial aspects of the clinical trial	x	x
Insurance statement	x	x
Signed agreement between investigator/institute and sponsor/CRO	x	x
Signed agreement between sponsor and CRO		x
Signed agreement between investigator/institute and authority(-ies)	x	x

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Location of documents before start

Location of documents before start of a clinical trial	ISF (Investigator)	TMF (Sponsor)
Dated, documented IRB/IEC approval/favourable opinion	x	x
IRB/IEC composition	x	x
Regulatory authority(-ies) authorisation	x	x
Regulatory authority(-ies) approval	x	x
Regulatory authority(-ies) protocol notification	x	x
Curriculum vitae of (sub)investigators	x	x
Technical procedures	x	x
Sample of investigational product(s) labelling		x
Instructions for handling of investigational product(s)	x	x
Shipping records for investigational product(s)	x	x

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Location of documents before start

Location of documents before start of a clinical trial	ISF (Investigator)	TMF (Sponsor)
Certificate(s) of analysis of investigational product(s)		x
Decoding procedures for blinded trials	x	x
Master randomisation list		x
Pre-trial monitoring report		x
Trial initiation monitoring report	x	x

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Location of documents during conduct

Location of documents during conduct of a clinical trial	ISF (Investigator)	TMF (Sponsor)
Investigator's brochure (updates)	x	x
Revised documents	x	x
Dated, documented IRB/IEC approval/favourable opinion	x	x
Regulatory authority(-ies) authorisation	x	x
Regulatory authority(-ies) approval	x	x
Regulatory authoirty(-ies) protocol notification	x	x
Curriculum vitae of (sub)investigators	x	x
Update of technical procedures	x	x
Documentation of investigational product(s)	x	x
Monitoring visit reports of clinical site	x	x

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Location of documents during conduct

Location of documents during conduct of a clinical trial	ISF (Investigator)	TMF (Sponsor)
Signed informed consent forms	x	
Source documents	x	
Signed, dated and completed case report forms (CRF)	x	x
Documentation of CRF corrections	x	x
Notification of serious adverse events	x	x
Notification of serious adverse event reporting	x	x
Notification by sponsor to investigators of safety info	x	x
Interim or annual reports to IRB/IEC and authority	x	x
Subject screening log	x	
Subject identification log	x	

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Location of documents during conduct

Location of documents during conduct of a clinical trial	ISF (Investigator)	TMF (Sponsor)
Subject enrolment log	x	
Investigational product(s) accountability at the site	x	x
Signature sheet	x	x
Record of retained body fluids or tissue samples (if any)	x	x

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Location of documents after completion

Location of documents after completion of a clinical trial	ISF (Investigator)	TMF (Sponsor)
Investigational product(s) accountability at site	x	x
Documentation of investigational product description	x	x
Completed subject identification code list	x	
Audit certificate of clinical site (if available)	x	x
Final trial close-out monitoring report of clinical site	x	x
Treatment allocation and decoding documentation		x
Final report by investigator to IRB/IEC and to authority(-ies)	x	
Clinical study report	x	x

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Part 8. ISO 14155 (update 2020) – Clinical investigation of medical devices for human subjects

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Medical device

- Medical device
  - Instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific purpose(s) of:
    - diagnosis, prevention, monitoring, treatment or alleviation of disease;
    - diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
    - investigation, replacement, modification, or support of the anatomy or of a physiological process;
    - supporting or sustaining life;
    - control of conception;
    - disinfection of medical devices;
    - providing information by means of in vitro examination of specimens derived from the human body;

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Medical device

- Medical device
  - Does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means
- Investigational medical device
  - Medical device being **assessed for clinical performance, effectiveness or safety** in a clinical investigation

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