Clinical Research & ICH GCP E6(R2) (Basic / Refresher Training):

*Principles of GCP, Investigator Responsibilities, Essential Documents*

v3 01-Feb-2017
Objectives

• To provide refresher training on ICH GCP to Cancer Trials Ireland members and those working on Cancer Trials Ireland studies (Background, Principles, Investigator responsibilities only)

(not to replace full mandatory ICH GCP training to new entrants to Clinical Research working on Cancer Trials Ireland studies)

(refresher training mandatory every 2 years per Cancer Trials Ireland requirements)
Expected outcome

- Consistent interpretation of ICH GCP
- Optimal quality data
- Optimal (increased) compliance with GCP
Agenda

• The Rules Governing Clinical Trials
• Principles of ICH GCP
• Investigator Responsibilities per ICH GCP
  – Resources / Training / Delegation
  – Medical Care
  – Protocol Compliance
  – Informed Consent
  – Management of Investigational Product
  – Safety reporting
  – Essential Documents
  – Reporting Responsibilities

(with Compliance Checkpoints throughout)
European Union / Commission

The Rules Governing *Medicinal Products* in the European Union

EUDRALEX

- Volume 10 Guidelines for Clinical Trials
- Volume 4 Annex 13 Good Manufacturing Practice (GMP) Guidelines
EU Directives / Statutory Instruments (SI) in Ireland - Summary

Clinical Trials Directive (2001/20/EC)
- SI 190 (2004)
- SI 878 (2004) (Amendment #1)
- SI 374 (2006) (Amendment #2)

- SI 374 (2006)

- SI 1 (2009)
EU Clinical Trials / GCP Directive: Scope and applicability

• Requirements regarding the conduct of clinical studies of interventional *Investigational Medicinal Products* in EU countries
  - commercial (industry sponsored)
  - non-commercial clinical trials (academic sponsored)

• Requirements described in the Directive itself & *associated guidance documents*
What is a clinical trial?

“clinical trial” means any investigation in human subjects, other than a non-interventional trial, intended ..... 

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal products, or 

(b) to identify any adverse reactions to one or more such investigational medicinal products, or 

(c) to study absorption, distribution, metabolism and excretion of one or more such investigational medicinal products, or 

(d) to discover, verify, identify or study any combination of the matters referred to at subparagraphs (a), (b), and (c), (SI 190 (2004))

........with the object of ascertaining the safety or efficacy of such products, or both; (ICH GCP E6/ DIRECTIVE 2001/20/EC)
What is an Investigational Medicinal Product (IMP)?

‘a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form’ - (DIRECTIVE 2001/20/EC)
EU Clinical Trials/ GCP Directive: Scope and applicability

non-interventional trials are outside of the scope, with a non-interventional trial defined as a study:

• where the medicinal product(s) is/are prescribed in the usual manner in accordance with the terms of the marketing authorisation;

• the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice, and the prescription of the medicine is clearly separated from the decision to include the patient in the study;

• no additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the data.
Future → EU Clinical Trial Regulation


- **14-Apr-2014**: Approved by Council of the European Union: Regulation is now adopted


- **May 2016**: Application of the new rules will start two years after.

  (Implementation date currently expected **2019**)

*Note: An EU Regulation does not require national legislation like the Directives*

US FDA Code of Federal Regulations (CFR)

Title 21 (food and drugs) CFR Part ...

- 50 Protection of human subjects
- 56 Institutional Review Boards
- 312 Investigational New Drug (IND) Application (NDA)
  - 50-70 Responsibilities of sponsors and investigators
  - 120 Foreign studies not conducted under an IND
- 314:106 Foreign data in an NDA
- 54 Financial Disclosure
- 11 Electronic records and Signatures
- 320 Bioavailability and Bioequivalence Requirements
- 601 General Biological Products Standards
- 610 Applications for FDA approval of a biologics license
ICH-GCP

ICH: International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)

GCP: Good Clinical Practice
ICH E6 (R2)- Addendum

- ICH GCP guideline E6 (R1) dated back to 1996.
- Since 1996, clinical trials have evolved substantially:
  - Increase in globalisation, scale, study complexity, cost.
  - Evolution in technology, risk management processes.
- Approach to GCP needed modernisation to keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology.

Integrated Addendum to ICH E6(R2) current Step 4 version dated 09-Nov-2016, published on ICH GCP website on 30-Nov-2016.

The EU has adopted (Step 5) of the ICH GCP E6 (R2) on 15th December 2016 and set a date for coming into effect of 14th June 2017.
Format of E6 (R2)- Addendum

- **Integrated Addendum** to parental guideline ICH E6 (R1):
  - Original wording of the guideline text has not been amended.
  - Changes are integrated directly into the parental guideline.
  - Sentences/ paragraphs are added in the context of the original text, new and old text will be read together and will allow to see the continuity of logic.
  - Addenda are identified by the word “Addendum” and vertical lines outlining the new text.
  - In the event of any conflict between the E6(R1) text and the E6(R2) addendum text, the E6(R2) addendum text should take priority.

(Addendum text highlighted in red throughout this presentation)
What is GCP?

Good Clinical Practice is an international ethical and scientific quality standard for the ........

• design,
• conduct,
• performance,
• monitoring,

• auditing,
• recording
• analyses and
• reporting

......... of clinical trials that involve the participation of human subjects that provides assurance that ....

• the data and reported results are credible and accurate,
• the rights, integrity, and confidentiality of trial subjects are protected.
When should ICH-GCP be followed?

- When generating clinical trial data intended to be submitted to regulatory authorities

- May also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects
Why do we work to GCP?

- A single standard of clinical research practice
- Provides universally accepted data
- Ensures patients are fully protected and fully informed
- Economics – ‘Do it right and do it once’
- Quality needs to be a continual developing process
- Quality cannot be built in at the end
Layout of ICH-GCP Guidelines

ICH topics: Quality (Q), Safety (S), Efficacy (E), Multi-disciplinary (M), Regulatory (R)

www.ich.org → E (Efficacy topic) → E6=GCP

1. Glossary

2. Principles of ICH GCP

3. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

4. Investigator (Responsibilities)

5. Sponsor (Responsibilities)

6. Clinical Trial Protocol and Protocol Amendments

7. Investigator's Brochure

8. Essential Documents for the conduct of a Clinical Trial
1. Glossary

- 65 definitions
- Terms associated with clinical trials
- Use as reference
- Bear in mind for definitions for IMP studies
  - EU directives and
  - Statutory Instruments in Ireland
2. Principles of ICH GCP

- Trial conducted in accordance with
  - Declaration of Helsinki (*see next slide*),
  - GCP, and
  - regulatory requirements (*i.e. the rules governing clinical trials*)
Declaration of Helsinki

• Ethical Principles for Medical Research involving Human Subjects

• It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research.

• It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

"The health of my patient will be my first consideration" (Declaration of Geneva, WMA)

"A physician shall act in the patient's best interest when providing medical care “ (International Code of Medical Ethics)
Principles of ICH GCP (continued)

• Benefit justifies Risks
• Rights, safety & well-being of subjects prevail over interests of science & society
• Non-clinical/ clinical data adequate to support trial
• Trial scientifically sound/ protocol clear, detailed
Principles of ICH GCP (continued)

• Trial in accordance with protocol approved by/has favourable opinion of IRB/IEC

• Medical care/ decisions responsibility of qualified physician *(or dentist if applicable)*

• Individuals involved qualified to perform tasks
  - Education
  - Training
  - Experience
Principles of ICH GCP (continued)

• Informed consent freely given before participation

• Information recorded, handled, stored to allow accurate reporting, interpretation and verification

This principle applies to all records, irrespective of the type of media used.
Principles of ICH GCP (continued)

- Confidentiality of records identifying subject in accordance with regulatory requirements

- Investigational Products used in accordance with protocol and manufactured, handled, stored in accordance with GMP

- Implement systems to assure quality

Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.
4. Investigator

1.34 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*. 
4. Investigator

1.56 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).
4. Investigator

1.54 Sponsor-Investigator

- An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.
Responsibilities:

1. Qualified by education, training, experience
   - evidence through up-to-date *curriculum vitae*
2. Familiar with Investigational Product
3. Comply with GCP/ Regulatory requirements
4. Permit monitoring, auditing, inspection (*next slides*)
5. Maintain list of appropriately qualified personnel
**1.38 Monitoring:** Oversight of the progress of the trial & ensuring that it is conducted, recorded, and reported ......

**1.6 Audit:** Systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported ......

..........*in accordance with the protocol, SOPs, GCP & applicable regulatory requirement(s).*
1.29 Inspection: Official review by a regulatory authority(ies) of documents, facilities, records, and any other resources related to the clinical trial and that may be located at the:

- trial site,
- Sponsor
- CRO
- other establishments deemed appropriate by the regulatory authority(ies).
Sponsor/ CRO

1.53 Sponsor

• An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.20 Contract Research Organization (CRO)

• A person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.
Investigator: Adequate Resources

Responsibilities:

1. Demonstrate potential to recruit required number of subjects
2. Sufficient time to properly conduct and complete the trial
3. Adequate no. appropriately qualified staff & adequate facilities
4. Staff adequately informed about protocol, IMP, duties/functions
5. Supervision of individual or party to whom duties/functions are delegated
6. Ensuring qualification of delegates and implement procedures to ensure integrity of duties/function performed and data generated
Checkpoint: Training

Training Requirements

- Legislation (regulatory requirements)
- GCP
- Study Protocol/Study Manuals
  - With particular focus on non-routine/non-standard elements
- CRF (data) completion
- Safety (adverse event) reporting
- Product information/IMP management
- Good documentation practices
Checkpoint: Training

Training Sources

By the Sponsor

• Investigator Meeting
• Initiation Meeting
• Ongoing (as necessary)

By the Investigator

• Staff/Departmental Meetings
• One to One
• Any training not provided by Sponsor
Checkpoint: **Training**

**Adequate & Effective Training**

- Training material content adequate and appropriate
- Relative to role of individual
- Training prior to carrying out activities
- Documentation of training
- Refresher training
- Amendment(s) training
- New staff training
[* Checkpoint: *Training*]

**Training Records**

- Should contain:
  - Copy of Agenda
  - Presentation slides
  - Attendance Record
  - Certificates of Attendance
  - “Read & Understood” records

- Training documents per Individual/ Team/ Study should include:
  - Training topic
  - Date of training
  - Trainer name
  - Trainee name
☑ Checkpoint: *Delegation*

- Careful consideration
- Only to trained & qualified individuals
- PI authorisation (*dated signature/ initials*)
- Prior to carrying out trial duties
- Include:
  - Start & stop dates
  - Signature & date of signature
  - List of duties
Checkpoint: **Training & Delegation**

- **Training**
  - (Complete Training Record)

- **Delegation**
  - (authorise on delegation log)

- **Study Activities**
  - (adequate supervision)

*Responsibility/Accountability resides with the Principal Investigator*
Checkpoint: Adequate Resources

- Computer equipment
- Office equipment and space
- Laboratory
- Research Team
- Procedures
- Patient facilities
- Pharmacy
- Money
- Stationery
- Time
Checkpoint: Recruitment potential

- Know the protocol, IMP/ intervention, GCP, regulations
- Hospital records/ electronic databases
- Talk to colleagues/ Consider referrals
- Previous trials in similar indications/ patient population
- Competing trials
- Patient’s willingness to enter trials
☑ Checkpoint: *Staff/Planning*

- Define roles and ensure all staff assisting clear on their trial related duties and functions
- Ensure staff know how to access study documents/materials
- Highlight any practical issues and changes from standard of care to minimise potential protocol violations
- Ensure contact information is easily accessible
- Restrict access to confidential information/materials to appropriate personnel
- Ensure a logical and secure filing system is set up
Investigator:
Medical Care of Trial Subjects

Responsibilities:

1. Qualified physician responsible for medical decisions

2. Adequate medical care for subjects
   – during and following participation
   – for any adverse events, including clinically significant laboratory values, related to the trial.
   – inform patient when medical care needed for intercurrent illness(es).
Responsibilities:

3. Inform primary physician (if agreed)

4. Make reasonable effort to ascertain why subject withdrew (not obligatory on part of subject)
☑ Checkpoint: **Principal Investigator Involvement in study conduct**

Common Audit finding: **Lack of PI involvement in study conduct**

- Evidence of supervision of delegated personnel (e.g. evidence of regular meetings or other communications with Study Team (document minutes/ decisions!))

- Evidence of supervision of medical care (review and document eligibility, consent, medical decisions, etc. in patient notes)

- Availability to meet with Study Monitor to discuss study issues
1.27 Independent Ethics Committee (IEC)

- An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

- The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.
1.31 Institutional Review Board (IRB)

- An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
Investigator: Communication with IRB/IEC

Responsibilities:

1. Before initiating a trial, written and dated approval/favourable opinion for the:
   - trial protocol,
   - written informed consent form,
   - consent form updates,
   - subject recruitment procedures (e.g., advertisements), and
   - any other written information to be provided to subjects.

2. Provide the current Investigator's Brochure (IB) as part of the written application – supply updated version during the trial if applicable

3. Before and during the trial provide all documents subject to review.
Investigator: Compliance with Protocol

Responsibilities:

1. Conduct study in compliance with protocol, GCP, regulatory requirements and confirm acceptance by signing protocol agreement

2. Not deviate from protocol without IEC/IRB agreement except where necessary to eliminate an immediate hazard(s) to trial subjects (should be submitted for review/approval by IEC/IRB)

3. Document & explain deviations
☑ Checkpoint: Protocol Compliance

• Documented evidence of authorisation (regulatory/ethics/sponsor)
  – Approval letters in place
  – Protocol Signature Pages signed/dated

• Timely implementation of amendments

• Training documented
 FontWeight: Checkpoint: *Protocol Compliance*

Strict adherence to protocol instructions - Remember the Protocol is NOT a guideline - instructions are mandatory

**Exceptions:**

- Eliminate immediate hazard/ Urgent Safety Measures *(Regulatory Authority and Ethics Committee notification within 3 days)*

- Protocol Instruction clearly stated as optional *(Investigator discretion can be applied)*
Checkpoint: *Protocol Compliance*

Assessment of Subject Eligibility

- All screening tests/procedures performed
- All eligibility criteria assessed
- Investigator decision documented
Checkpoint: Protocol Compliance

Compliance with Test/Procedure Methodology

• Required tests/procedures performed
• Timely manner (*required time points*)
• According to protocol methodology
• Using adequate facilities and qualified staff
• Awareness of changes from routine practice (*e.g. lab analyte not on routine panel*)
• Document
  – Result/clinical significance
  – Any required medical decision (*e.g. a dose modification*)
Checkpoint: Protocol Compliance

Subject Education

- Compliance with visit schedule
- Compliance with IMP administration (if applicable)
- Returning used/unused IMP (if applicable)
- Maintenance of diaries (if applicable)
- Questionnaire completion (if applicable)
- Question & document patients’ Adverse Event and Concomitant Medications details
✔ Checkpoint: Management of Deviations

- Document and explain any deviation
- Report to Sponsor
- Active Management
  - Establish root cause
  - Implement Corrective and Preventative Actions (CAPA)
    - Targeted training: How to Meet Requirements
    - Define roles: Investigator/Research Nurse, etc.
    - Communication between site staff
    - Due diligence vs. Formalised SOPs
Investigator: Investigational Product(s)

1.33 Investigational Product

- A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.14 Comparator (Product)

- An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.
Investigator: Investigational Product(s)

**Responsibilities:**

1. Investigator responsible for accountability
2. Appoint pharmacist (*supervision by inv.*)
3. Maintain records (*see next slide*)
4. Stored as specified (*sponsor/ regulatory*)
5. Correct Use
   - Per Protocol
   - Explained to subjects/ checked at intervals that instructions being followed
Responsibilities:

Records to be maintained

- product's delivery to the trial site,
- inventory at the site,
- use by each subject, and
- return to the sponsor or alternative disposition of unused product(s).
Investigator: Investigational Product(s) (continued)

• The records should include:
  – dates,
  – quantities,
  – batch/serial numbers,
  – expiration dates (if applicable), and the
  – unique code numbers assigned to the investigational product(s) and trial subjects.

• Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.
☐ Checkpoint: Investigational Product(s)

Storage of IMP

• Controlled access (*authorised personnel*) to IMP from receipt to destruction

• Sufficient storage space

• Segregation of stock

• Returns clearly identified and stored in separate area
Checkpoint: Investigational Product(s)

Storage conditions

• IMPs stored as specified by the sponsor

• Thermometers must be a continuous monitoring device (e.g. max/min thermometer, consider temperature mapping)

• Maintain signed/ dated records
  – daily temperature monitoring
  – print-outs from electronic temperature monitoring

• Evidence of:
  – calibration of temperature monitoring devices (at least annually or replaced by calibrated thermometers)
  – regular servicing of refrigerators
Checkpoint: Investigational Product(s)

Storage conditions

• Procedures in place to handle temperature excursions and to handle trial supplies following excursions
  – Back-up generator
  – Alarm system

• Document deviations
  – Reporting of and results of investigation
  – Evidence of corrective and preventive action in response
Subject Compliance

- Counsel subject on need to comply
- Document missed doses and reasons
- Consider subject diary (*needs EC approval*)
- Discuss subject diary entries and document on patient notes (as well as filing copy of diary)
- Evaluate subject compliance
- Ensure subject understanding of correct use/return requirements
- Every effort made to obtain unused IMP and reconcile returned IMP
- Document instructions and reminders to subjects
Checkpoint: Investigational Product(s)

IMP Preparation

• Awareness of protocol instructions/ procedures/ conditions different to commercial product

• Adequate facilities and equipment to prepare IMP
Checkpoint: Investigational Product(s)

Accountability records

- Timely and complete
- Complete IMP labels with subject number, date of dispensing, number of vials
- Retain packaging for accountability by monitor
- Destruction should occur after verification by monitor
- Records should include authorisation of destruction by sponsor
Investigator:
Randomization Procedures & Unblinding

Responsibilities:

• Follow the trial’s randomisation procedures

• Code break only according to protocol

• Promptly document & explain reason to sponsor
**Checkpoint: Randomization Procedures & Unblinding**

- Subject unblinding clearly documented in the source notes
- Timely *(prior)* reporting to sponsor
- Protect the blind/ prevent accidental unblinding
- Training/re-training re: study blind and importance of maintenance of the blind
1.28 Informed Consent

• A *process* by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. *Informed consent is documented by means of a written, signed and dated informed consent form.*
1.37 Legally Acceptable Representative

- An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
1.26 Impartial Witness

- A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.
Responsibilities:

• Comply with ICH GCP/ regulatory requirements/ Declaration of Helsinki

• Prior IEC/IRB approval

• Fully inform subject of all pertinent aspects prior to decision to participate

• Revise and inform in timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial.

• No coercion/ undue influence to participate

• Non-technical, understandable language (no waiver of rights, no release from liability for negligence)
Responsibilities (continued):

- Provide ample time; answer questions to satisfaction
- Prior to starting: personally signed/ dated
- Impartial witness if unable to read
- Contents of discussion & consent documents should contain all elements (*see later slides*)
- Provide copy (*signed/ dated*)
Responsibilities (continued):

Incapable of giving consent (*consent by legally acceptable representative*)

- should be to extent compatible with subject’s understanding and,
- if capable, subject to personally sign/ date
Responsibilities (continued):

Also described in ICH GCP:

• Vulnerable Subjects
• Emergency situations
• Non-therapeutic trials (i.e. no anticipated direct clinical benefit to the subject)
Refer also to:

- S.I No. 190 of 2004:
  - Schedule 1: Conditions and Principles for the Protection of Clinical trial Subjects.
    - Part 3: Able to give consent
    - Part 4: Minors
    - Part 5: Incapacitated Adult
Elements of Informed Consent:

a) That the trial involves research.

b) The purpose of the trial.

c) The trial treatment(s) and the probability for random assignment to each treatment.

d) The trial procedures to be followed, including all invasive procedures.

e) The subject's responsibilities.

f) Those aspects of the trial that are experimental.

g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
Elements of Informed Consent (continued):

h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

j) The compensation and/or treatment available to the subject in the event of trial-related injury.

k) The anticipated prorated payment, if any, to the subject for participating in the trial.

l) The anticipated expenses, if any, to the subject for participating in the trial.
Elements of Informed Consent (continued):

m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
Elements of Informed Consent (continued):

o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
Elements of Informed Consent (continued):

q) The **person(s) to contact** for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be **terminated**.

s) The expected **duration** of the subject's participation in the trial.

t) The approximate **number of subjects** involved in the trial.
✅ Checkpoint: *Informed Consent*

Roles:

• **Investigator & Research Nurse:** *Communicate and Explain*
  
  – Knowledge of required elements for informed consent discussion
  
  – Management of new important information

• **Subject/ legally acceptable representative (if applicable):** *Assess and make informed decision*
Checkpoint: *Informed Consent*

**Informed Consent Discussion:**

- *Interview with Investigator required*
- *Other staff may be involved*
- *Investigator:*
  - Assure Subject understood all information
  - Any questions have been answered
  - Obtain voluntary written informed consent
  - Form signed and dated *personally* by Subject and Investigator
  - Process *documented* in medical records
☒ Checkpoint: *Informed Consent*

- Current approved version used (*adequate version control*)
- Investigator: delegated and trained
- Consent obtained prior to any study specific procedures performed
- Provision of important new information, timely manner (*re-consent*)
- Consented Subjects:
  - Copy of Information Sheet/ Informed Consent Form
  - General Practitioner informed, if Subject agreed
Checkpoint: *Informed Consent*

Common Deficiencies:

- Subject or Investigator signed in the wrong place
- Subject didn’t initial boxes
- Subject didn’t indicate consent to all questions
- Subject printed name but didn’t sign
- Subject didn’t personally date his/her own signature
- Lack of version control – *cannot verify if approved form used*
Checkpoint: Informed Consent

Implement good documentation practices

- Version control
  - Check approval in place
  - Mark old version superseded
- Use tracking log for documentation of initial and re-consent
- Check form for deficiencies (previous slide) before copying for the subject and have corrected on the day with the subject/investigator as necessary before providing copy to subject
- Document remaining deficiencies (& reasons) as a result of poor documentation practices and implement corrective actions (training/checklist/procedure)
‘adverse event’: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;

(DIRECTIVE 2001/20/EC/ SI 190 (2004))
Investigator: Safety Reporting (continued)

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

• results in death,
• is life-threatening,
• requires inpatient hospitalization or prolongation of existing hospitalization,
• results in persistent or significant disability/incapacity, or
• is a congenital anomaly/birth defect

(also DIRECTIVE 2001/20/EC/ SI 190 (2004))
‘adverse reaction’: all untoward and unintended responses to an investigational medicinal product related to any dose administered;

(DIRECTIVE 2001/20/EC/ SI 190 (2004))
1.60 Unexpected Adverse Drug Reaction

- An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

(Also DIRECTIVE 2001/20/EC/ SI 190 (2004) = SUSAR: Suspected Unexpected Adverse Drug Reaction)
Responsibilities:

• Report SAEs **immediately** except for those SAEs that the protocol or other document (*e.g.*, Investigator's Brochure) identifies as not needing immediate reporting.

• Follow immediate report with detailed written report
  
  – **Identify subjects using Subject Identification Code (as with all trial-related data)**

• Comply with applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.
Responsibilities (continued):

- AE/ lab abnormalities identified in the protocol as critical to safety evaluations reported to Sponsor according to the reporting requirements and timeframes specified in the protocol.

- Supply the sponsor and IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports for reported deaths).
Checksum: Safety Reporting

Adverse Event Reporting

- As required by the protocol (*there may be protocol exceptions*)
- Complete and accurate source documentation (*CRF and SAE reports must be consistent with medical record*)
- Assessment of event documented in real time
- Assess and implement protocol requirements as a result of the AE

- **Routine reporting**: Know which AEs the required to be captured on the CRF (*all AEs or specific AEs*)
- ** Expedited reporting**: Know which events require immediate reporting (*SAEs*)
☑ Checkpoint: Safety Reporting

The medical notes should contain the following:

- description of the AE,
- date of onset,
- intensity (grade) as determined by AE grading scale in use for the study (e.g. mild/ moderate/ severe or Grade 1-5)
- whether or not it constitutes an SAE,
- investigator’s assessment of causality/ attribution (i.e., the prior experience/ expectedness of the AE),
Checkpoint: Safety Reporting

...continued:

• Treatment (*intervention, procedure, concomitant medication, etc.*) patient received specifically related to event

• Impact the AE has had on patient care, e.g., changes to study therapy (*including dose adjustment, cycle delay, and/or discontinuation*),

• Outcome (*e.g. resolved, resolved with sequelae, unresolved at final visit, death*) including dates if applicable

• Any other relevant information
✓ Checkpoint: *Safety Reporting*

**Attribution/ causality:**

- The attribution (relationship or causality) must be determined

- A determination made by an investigator (PI/sub-I) that describes the *relationship* of the IP with an AE

- This determination must be recorded both in the medical record as well as in the CRF (& SAE report if relevant)

- Consider:
  - Individual medical history
  - Known effects of concomitant medications.
Checkpoint: Safety Reporting

Attribution/causality:

- Definite – **Clearly related** to study agent
- Probable – **Likely related** to study agent
- Possible – **May be related** to study agent
- Unlikely – **Doubtfully related** to study agent
- Unrelated – **Clearly not related** to study agent
  - OR
- Related
- Not related
Checkpoint: **Safety Reporting**

- Minimum criteria for initial SAE Report:
  - Identifiable subject
  - Identifiable reporter
  - Event description
  - Product
  - *(Investigator assessment of causality/relationship)*
  - *(Investigator’s dated signature)*
  - *(Follow-up information as it becomes known)*

- Report within **24 hours of knowledge of AE**: Verbal/Written *(if verbal, immediate follow-up in writing)*
Checkpoint: **Safety Reporting**

- Monitor event until resolution
- Provide follow-up information to Sponsor as soon as it becomes available, e.g.
  - Discharge records
  - Laboratory reports/Other reports
  - Autopsy reports for deaths
- Don’t wait for Sponsor requests for FU
- Provide clear and accurate data
- Answer all queries from Sponsor in timely manner
Checkpoint: Safety Reporting

- Staff should be familiar with expected AEs
- Subjects should be instructed to report any AEs and staff should question subjects about clinical status/symptoms
- AEs should not be ignored even if minor as they may be a sign of a more significant or evolving clinical significant issue.
1.22 Documentation

• All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.
1.51 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).
1.52 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).
1.21 Direct Access

• Permission to examine, analyse, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor’s proprietary information.
1.11 Case Report Form (CRF)

• A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.
Investigator: Records and Reports (continued)

Responsibilities:

- Source data: **Attributable, Legible, Contemporaneous, Original, Accurate, Complete** (ALCOAC)

- Audit trail for changes (paper/electronic!)

- Data reported to Sponsor: Adequate, Accurate, complete, legible, timely

- CRF consistent with Source

- Changes/ Corrections (*audit trail: Documentation that allows reconstruction of the course of events*)
  - dated, initialled, and explained (if necessary)
  - not obscure the original entry
  - applies to both written and electronic changes or corrections
  - follow guidance from Sponsors on making such corrections
  - retain records of the changes and corrections
Responsibilities:

- Maintain/ Retain Essential Documents
- Financial Aspects documented in agreement
- Direct access
8. Essential Documents for the Conduct of a Clinical Trial

1.23 Essential Documents

- Documents which *individually and collectively permit* evaluation of the conduct of a study and the quality of the data produced.

- Demonstrate the *compliance* of the investigator, sponsor and monitor with the standards of GCP & all applicable regulatory requirements.
8. Essential Documents

- EDs serve a number of other important purposes.
  - timely filing at the investigator/sponsor sites assists the successful management of a trial by the investigator, sponsor and monitor.

  - Trial master files should be established at the beginning of the trial, both at the investigator/institution’s site and at the sponsor's office.

  - usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.
8. Essential Documents

Minimum list of EDs grouped in three sections

• **before** the clinical phase of the trial commences,
  – planning stage
  – generated and filed before the trial formally starts
• **during** the clinical conduct of the trial, and
  – added as evidence that all new relevant information is documented as it becomes available
• **after** completion or termination of the trial.
  – *A final close-out of a trial can only be done* when the monitor has reviewed both investigator/institution and sponsor files and *confirmed that all necessary documents are in the appropriate files.*
8. Essential Documents for the Conduct of a Clinical Trial

• Description
  – Title of Document
  – Purpose
  – Location (investigator/ sponsor files/ both)

• It is acceptable to combine some of the documents, provided the individual elements are readily identifiable
8. Essential Documents for the Conduct of a Clinical Trial

• Investigator/ sponsor should maintain record of location of essential documents including source documents

• Storage system should provide for document identification, version history, search, and retrieval

• Essential documents for the trial can be supplemented or reduced where justified

• Investigator should have control of and continuous access to CRF data

• Copy used to replace original document should be certified copy (see next slide)

• Investigator should have control of all essential documents generated by site before, during and after trial
8. Essential Documents for the Conduct of a Clinical Trial

• 1.63 **Certified copy**
  A copy (irrespective of the type of media used) of the original record that has been verified (e.g., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
**Responsibilities: Progress Reports**

- Submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

- Promptly provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.
Responsibilities: Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should

• inform the institution;
• provide the IRB/IEC with a summary of the trial’s outcome,
• provide the regulatory authority(ies) with any reports required.
Investigator: Premature Termination or Suspension of a Trial

Responsibilities:

• Promptly inform the trial subjects
• Assure appropriate therapy and follow-up for the subjects
• promptly inform the institution
• promptly inform the IRB/IEC (and Sponsor if applicable)
• provide the IRB/IEC (and Sponsor) a detailed written explanation of the termination or suspension.

Regardless of whether the premature termination or suspension was by the investigator/ Sponsor or IRB/IEC
GCP compliance

- Have a documented process for each trial related activity
- Follow it
- Document that you followed it (e.g. complete a form, make an entry in patient chart)

*If it’s not documented, it didn’t happen.*
GCP: Summary

- International minimum quality standard for the ethical and scientific conduct of clinical trials
- Based on the principles of the Declaration of Helsinki
- Concerns everyone working on any aspect of clinical research
- Ensures the rights and safety of clinical trial subjects
- Ensures the integrity and accuracy of clinical data