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ICH- GCP

Text

Release Date: DD-Mmm-YYYY

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Agenda

- ✓ ICH-GCP and its purpose
- ✓ Principles of ICH GCP
- ✓ Participants in a clinical trial and what are their responsibilities
- ✓ Audits and inspections
- ✓ Clinical trial protocol
- ✓ AE, SAE & ADR
- ✓ Essential documents required before, during and after the clinical trial

International Conference on Harmonization

ICH is the International Conference on Harmonisation of Technical requirements for Registration of Pharmaceuticals for Human Use.

A unique project that brought together the pharmaceutical industry and regulatory representatives of three regions:

- USA
- Japan
- European Union

Objectives:

- Discuss technical and scientific aspects of drug registration
- Avoid unnecessary delay in drug development
- Safeguard quality, safety and efficacy of drugs

Background of ICH

1) Sulfanilamide Tragedy (1937) – FDA Food, Drug, and Cosmetics Act (1938)

2) Inhuman medical experimentation on Nazi prisoners (WWII) - Nuremberg Code (August 1947)

3) Thalidomide Tragedy (1962) – Kefauver Harris Drug Amendment

4) Declaration of Helsinki (1964)

5) Tuskegee Syphilis Study (1932 – 1972) – Belmont Report

ICH-GCP is Good Clinical Practice guidelines agreed at the conference…..

Definition

"An international standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected“

Exactly what is GCP?

Ethical and scientific quality standards for designing, conducting, recording and reporting trials that involve participation of human subjects

Purpose of ICH GCP

- Patient safety
- Generation of credible and good quality clinical trial data

Advantages of Harmonisation

Regulatory harmonization offers many direct benefits to both regulatory authorities and the pharmaceutical industry:

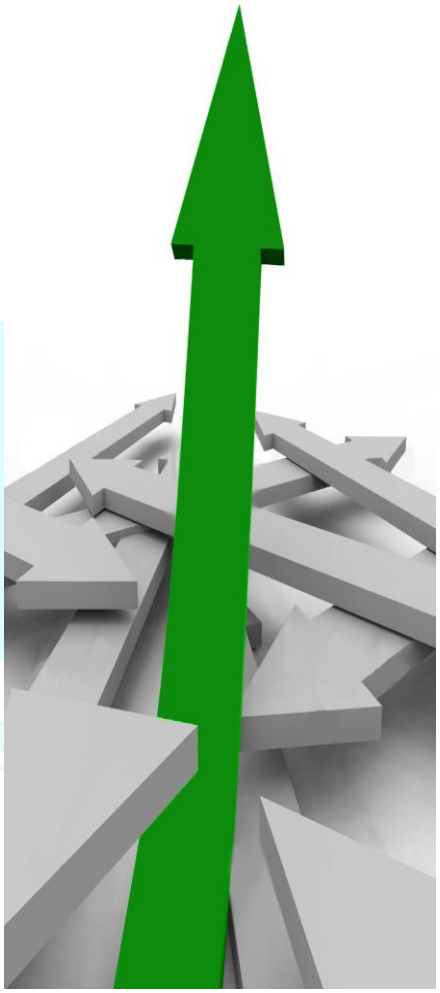
✓protection of public health

✓preventing duplication of clinical trials in humans

✓minimizing the use of animal testing without compromising safety and effectiveness

✓streamlining the regulatory assessment process for new drug applications

✓reducing the time and resources required for drug development



13 Principles of GCP

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 requirements.
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well being of trial subjects are the most important considerations.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

Continued…

6. A trial should be conducted in compliance with the protocol that has received prior IRB/ IEC approval/ favorable opinion.
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 a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his/ her tasks.
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Continued…

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

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).
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.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Participants in Clinical Trial

GCP makes various demands of each player and clearly defines the responsibilities of each!

Ethics Committee (EC): Responsibilities

Ethics Committee is an independent body of medical/scientific personnel and non-medical/non-scientific members

Ethical Responsibilities

- To ensure the protection of the rights, safety and well - being of human subjects involved in a trial
- To ensure unambiguous language in informed consent document
- Should pay special attention to trials that may include vulnerable subjects

Scientific Responsibilities

- Sound trial design
- Statistical validity

Ethics Committee: How to meet responsibilities?

By reviewing and approving/ providing opinion on:

- Trial protocol
- Suitability of the Investigator
- Facilities at sites and in trial
- Methods and materials to be used in the trial
- Methods for obtaining and documenting informed consent of the trial subjects

Ethics Committee: Composition

ICH GCP

- At least 5 members
- At least 1 member whose primary area of interest is a non-scientific area
- At least 1 member who is independent of the institution/ trial site
- Voting members to be independent of the investigator & sponsor of the trial

Schedule Y

- Minimum of 7 members (minimum of 5 to form a quorum)
- Chairperson not the head of institute/ affiliated to the institute
- Mix of medical and non-medical, scientific and non-scientific members
- Equal race and gender representation
- Include at least one lay person

Sponsor

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

The sponsor may be a pharmaceutical company, a private or academic organization, or an individual

Sponsor can outsource some or all of their responsibilities

Responsibilities of Sponsor/ CRO

- Trial design (Protocol & amendments)
- Information on IP (IB) & its management
- Investigator selection
- Notification/submission to RA
- Confirmation of review by IRB/IEC
- Financing of the clinical trial
- Monitoring, trial management, data handling & record keeping
- QA/QC, audits and managing non-compliance
- Clinical Study Report

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 (SOP), Good Clinical Practice (GCP) and the applicable regulatory requirements."

Responsibilities of Monitor

Monitor	Verifies if informed consent was taken and the process was documented per requirements
	Reviews if all procedures were conducted as per the protocol & regulatory guidelines
	Verifies compliance with the IRB/ IEC, regulatory bodies and the Sponsor requirements
	Checks if changes made to the CRF were made by authorized site staff and have been signed and dated
	Ensures all safety related data has been captured (SAEs, ADRs, IRAEs etc.)
	Completes a Site Visit Log

Responsibilities of Monitor

Monitor	Checks that the correct laboratory ranges are applicable to the trial subjects and that they are current
	Checks randomization & emergency procedures are appropriate and are documented correctly
	Answers any trial related or protocol related questions from site staff
	Discusses and documents any issues related to IP handling/ documentation, storage conditions, IP records, reconciliation, expiration date etc.
	Inspects storage conditions of laboratory kits, biological samples, expiration dates etc.

Investigator

Principal Investigator (PI):

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

Sub-Investigator/ Co-Investigator

Any individual member of the clinical trial team designated and supervised by the PI at a trial site to perform critical trial-related procedures and/or to make important decisions (e.g. associates, residents, research fellows).

Investigator's Qualification

- The investigator should be professionally qualified for the conduct of the trial (current, signed and dated CV)
- The investigator should be aware of and comply with GCP and applicable regulations
- The investigator should have adequate resources and must maintain a list of qualified individuals to whom trial related activities have been delegated
- The investigator should be familiar with the use of the IP
- The investigator/institution must permit monitoring/auditing by the Sponsor and inspections by regulatory authorities

Responsibilities of Principal Investigator

- Give medical care to trial subjects/patients
- Communicate with the IRB/IEC
- Comply with the protocol
- Maintain records of IP
- Follow randomization procedures and unblinding
- Completes proper informed consent process
- Submits timely progress report
- Ensures Investigational Product and clinical trial supplies
- Safety reporting
- Documents, records and reports properly including archival
- Sees if drug can causes premature termination/suspension of trial

The investigator is responsible for all medical decisions to be taken at the site!!

Knowledge Checks!

Tell 1 responsibility for each:

1) Investigator
2) Sponsor
3) Ethics Committee

Investigational Product (IP): Definition

"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 drug."

-**The term Investigational Product (IP) includes:**

-the drug under investigation as well as…..

- the comparator (placebo or active drug)

What is an Audit?

Independent examination of trial related activities and documents to determine whether the trial related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, sponsor SOPs, GCP & the applicable regulatory requirements.

Auditors are independent of the clinical trial.

Audit Types

- Routine surveillance
- For cause

What is an Inspection?

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Clinical Study Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

It should generally include the following topics:

General Information: Along with the protocol title and identifying number, it includes important contacts of Sponsor, its' medical expert, monitors, investigator, names and addresses of the clinical laboratories and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information: It includes name and description of the investigational product, with relevant information from the non-clinical studies, reference to literature and data that potentially have clinical significance to the trial. Summary of the known and potential risks and benefits, if any, to human subjects, and a statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

Trial Objectives and Purpose: A detailed description of the objectives and the purpose of the trial.

Trial Design : The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. It covers endpoints, randomisation and blinding information with a schematic diagram of trial design. It also includes, expected duration of subject participation, and a description of the sequence and duration of all trial periods , with "stopping rules" or "discontinuation criteria" . Accountability procedures for the investigational product(s), including the placebos and comparators.

Selection and Withdrawal of subjects: Subject inclusion and exclusion criteria , subject withdrawal criteria, with the details of when and how subjects to be withdrawn , type and timing of the data to be collected for withdrawn subjects. Whether and how subjects are to be replaced. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

Protocol Continued….

Treatment of Subjects: A detailed information regarding treatment plan including the route/modes of administration, and the treatment period, including the follow-up period for subjects for each investigational product treatment/trial treatment group/arm of the trial. Medication treatment permitted and not permitted before or during clinical trial. Procedures for monitoring subject compliance.

Assessment of Efficacy : Specification of the efficacy parameters and methods and timing for assessing, recording, and analyzing of efficacy parameters.

Assessment of Safety : Specification of safety parameters. The methods and timing for assessing, recording, and analyzing safety parameters. Procedures for eliciting reports of and for recording and reporting adverse event and inter-current illnesses. The type and duration of the follow-up of subjects after adverse events.

Statistics: A description of the statistical methods to be employed, including timing of any planned interim analysis. Reason for choice of sample size, including calculations of the power of the trial and clinical justification. Level of significance to be used , criteria for the termination of the trial. Procedure for accounting for missing, unused, and spurious data along with reporting procedure for any deviations from the original statistical plan , as any deviation from the original statistical plan should be described and justified in protocol , or in any other concerned document.

Direct Access to Source Data/Documents : The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator or institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection, providing direct access to source data/documents.

Quality Control and Quality Assurance: Elaborates the quality control and assurance plan s for all the protocol related procedures.

Ethics : Description of ethical considerations relating to the trial.

Data Handling and Record Keeping: Instructions for handling all the trial related data and record keeping procedures.

Financing and Insurance: Financing and insurance related details are documented, if not addressed in a separate agreement.

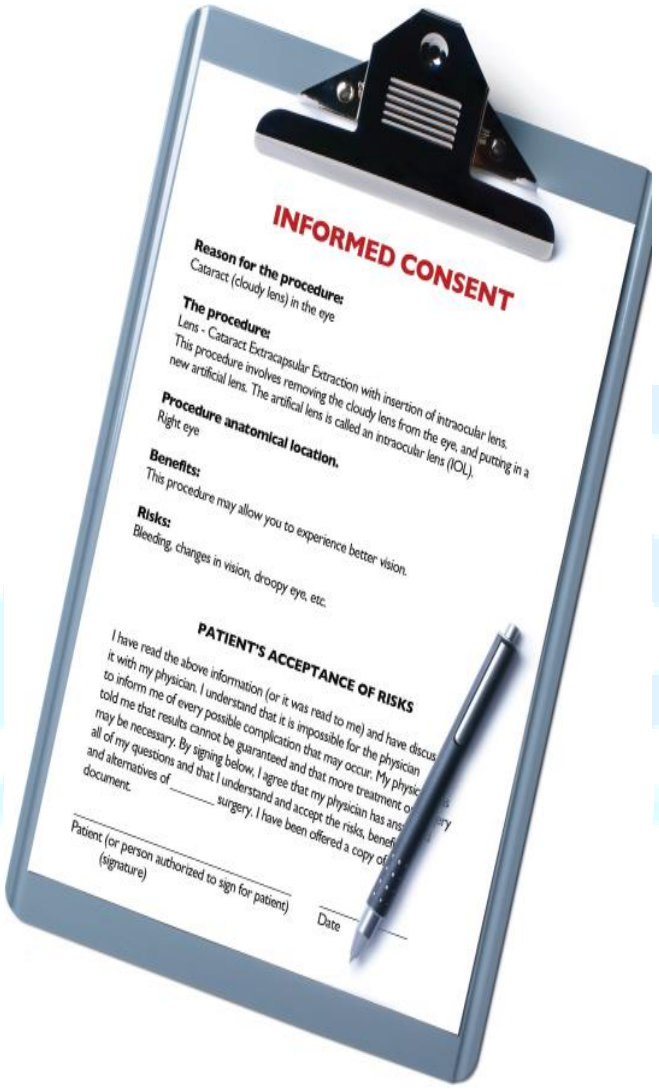
Publication Policy: Publication policy, if not addressed in a separate agreement, is detailed mainly describing the authority and discretion of publishing the trial generated information, through various publication channels.

Supplements : As required for a particular protocol ,depending on the study requirement as detailed in Structure and Content of Clinical Study Reports.

Informed Consent

A process by which a subject voluntarily confirms his/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.



Elements of Informed Consent

- Subject's responsibilities
- Aspects which are experimental
- Reasonably foreseeable risks/inconveniences
- Reasonably expected benefits
- Alternative procedure(s)/treatment(s)
- Compensation for trial related injury
- Anticipated payments
- Anticipated expenses

Elements of Informed Consent (cont.….)

- Voluntary participation/free to withdraw
- Direct access to medical records and by whom
- Confidentiality
- Make available information that may affect the subject's willingness to continue
- Contact number(s)
- Foreseeable circumstances under which participation may be terminated
- Duration of participation
- Approximate number of subjects involved

ICF: Signature Page

This page contains a place each for the subject, legally acceptable representative, impartial witness, and the person taking informed consent.

For each, the following has/ may have to be completed:

- the signature/ thumb impression of non-dominant hand
- the date and time
- the name
- for LAR, the relationship with the patient

Informed Consent Translation

- Translations in locally used language provided
- Back-translations in English always provided
- Translations and back translations submitted to the IRB/ IEC for review and approval of the translations
- Translations may be sent to sites for review of the correctness of the translated document

Special ICF Procedures

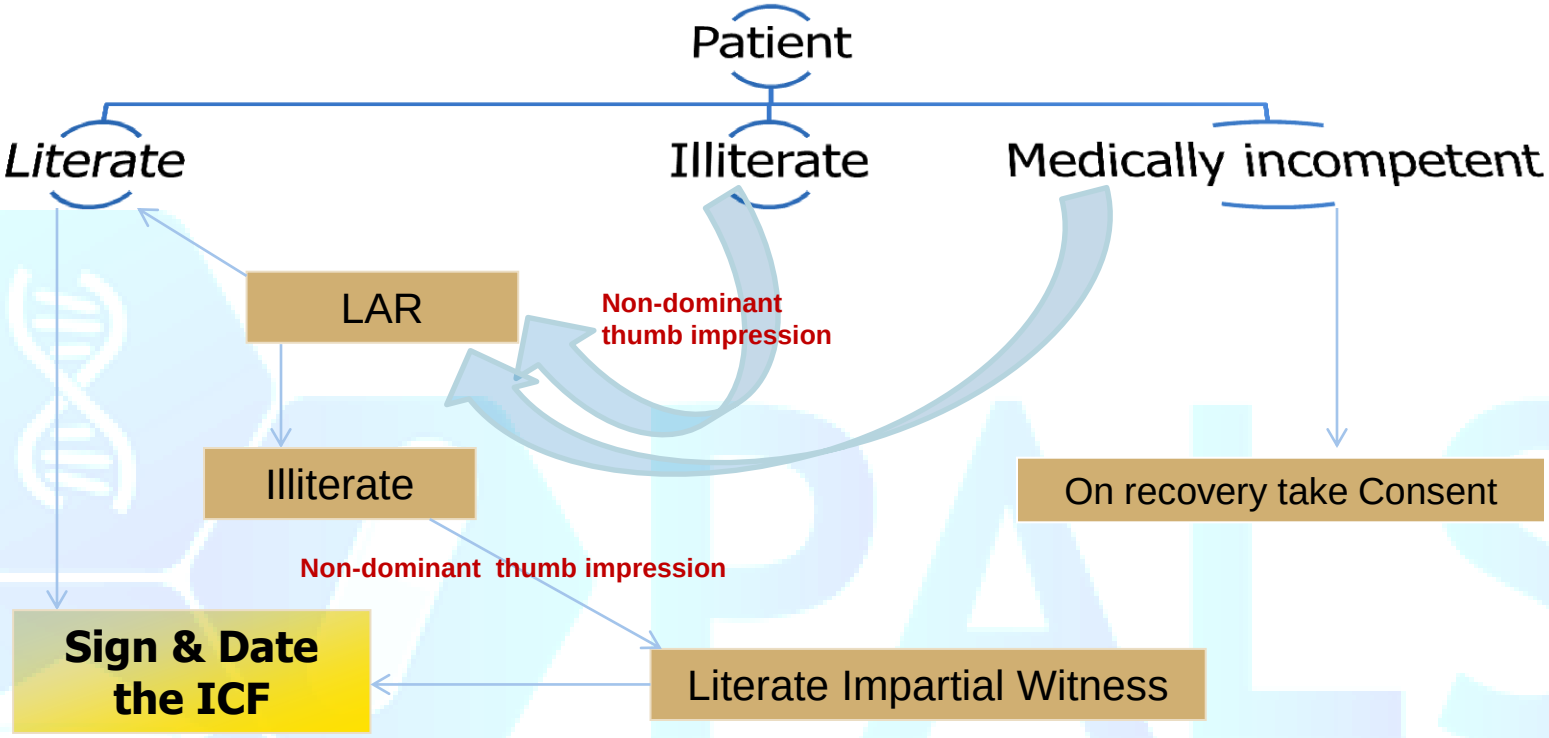
Witnessed consent by:-

Impartial witness, e.g., if subject is unable to read

Legally acceptable representative, e.g., pediatric trials, mentally ill subjects

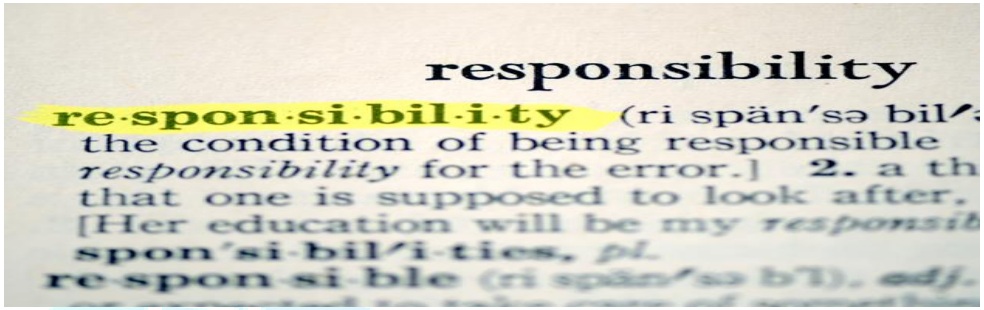
Emergency situations, e.g., unconscious subjects

All methods must be approved by IRB/IEC



ICF must be signed & dated by the Investigator

ICF: Investigator's responsibilities

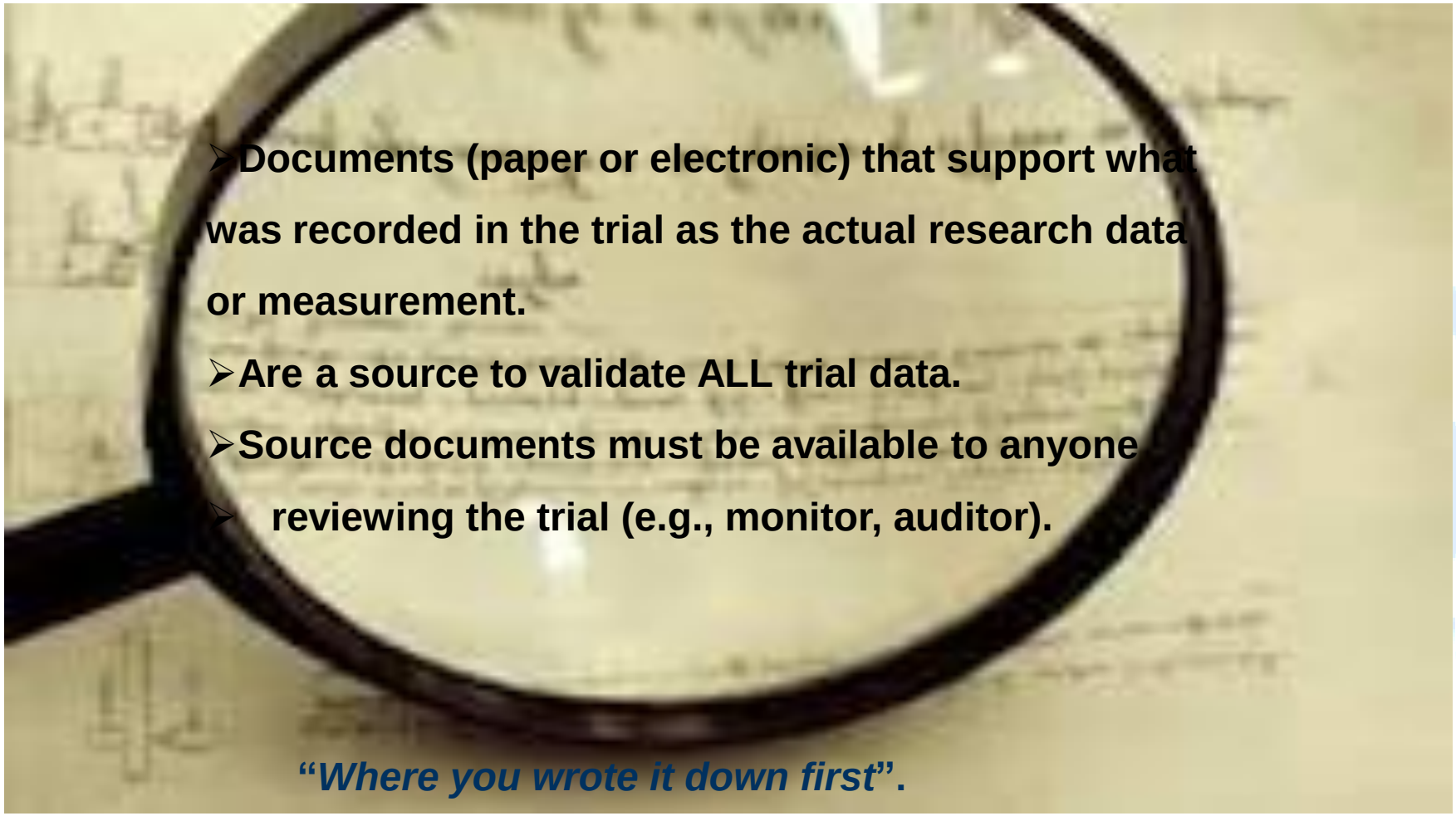


- Consent the subject prior to participation in a trial and before ANY trial procedure, including blood tests for screening unless it's part of normal clinical practice
- Ensure the subject is fully informed
- Give ample time and opportunity to the subject to ask questions
- Do not unduly influence a subject to participate
- Document the consent procedure
- Give the subject a copy of the signed and dated ICF
- Obtain written approval from IRB/IEC on ICF and all changes to ICF
- Ensure the language is understandable to the subjects

Knowledge Checks!

What is the difference between Audit and Inspection?

What are Source Documents?



- Documents (paper or electronic) that support what was recorded in the trial as the actual research data or measurement.
- Are a source to validate ALL trial data.
- Source documents must be available to anyone reviewing the trial (e.g., monitor, auditor).

"Where you wrote it down first".

Source Documents include...

Hospital records, clinical and office charts, lab. notes, memoranda, subject 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 labs and medico-technical departments.

Why is Source Data Verified?

- To ensure the quality and integrity of the trial data for the clinical trial
- To confirm that the patient exists and was eligible for the trial
- To ensure that the informed consent process was adequately conducted and documented
- To ensure there is adequate evidence of trial participation and exposure to investigational treatment
- To have documentation confirming the diagnosis of the disease/ medical condition

Case Report Forms (CRFs)

- These documents are used to record the information derived from trial activities that will be used as data
- Standardized format provided by the Sponsor
- May be paper based or electronic
- CRFs are NOT source documents unless stated as such in the trial protocol
- CRFs require a supporting source document to assure the validity of the data recorded
- CRFs must accurately match the source documentation.
- Any errors in entry should be queried, and must be corrected promptly with sign and date

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An AE can therefore also be :

- Any unfavorable and unintended sign (including abnormal laboratory findings)
- Symptom or disease temporally associated with the use of a medicinal (investigational) product
- Worsening of a pre-existing condition

Adverse Drug Reaction (ADR)

- All noxious and unintended responses to a medicinal product related to any dose should be considered as an ADR.
- Suggests a relationship to trial medication.

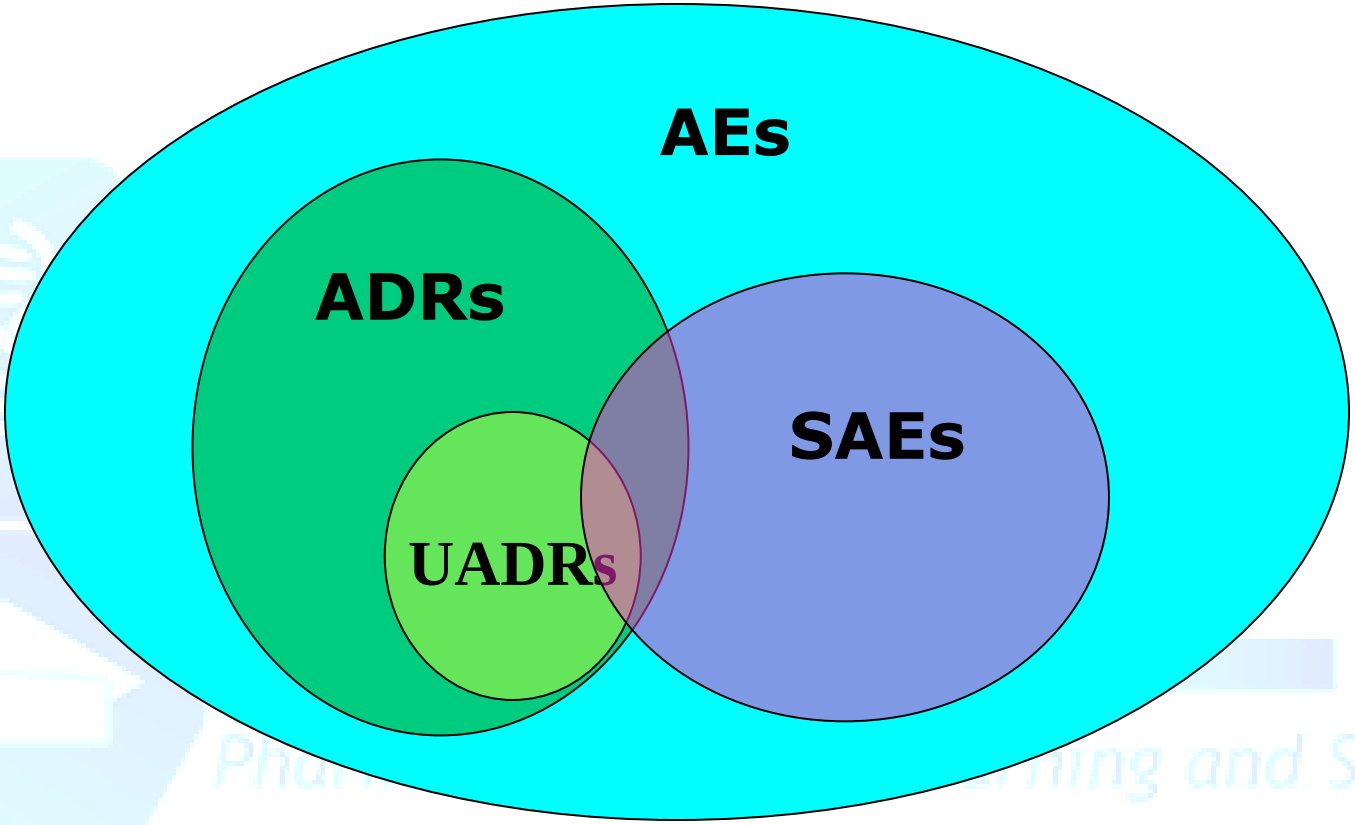
- **All AEs must be recorded irrespective of relationship to the study drug.**

- **All ADRs are AEs, but all AEs are not ADRs.**

Serious Adverse Event (SAE)

- Results in Death
- Is Life threatening
- Inpatient or Prolongation of Hospitalisation
- Persistent or Significant disability/Incapacity
- Congenital Anomaly/ Birth Defect
- Medically Significant

Definitions - Relationships



Reporting SAEs

- Reporting procedure will be fully explained in the protocol
- SAEs are reported IMMEDIATELY (within 24 hours) by the investigator to the sponsor/monitor, followed by written report
- SAEs are reported to the site's IRB/ IEC within 7 days of the occurrence of the event
- SAEs are reported within 7 or 15 days to regulatory authorities as per the seriousness

Pregnancy and Trial Subjects

- Most trials require that subjects are using 'adequate contraception methods' as part of the entry criteria
- Most sponsor companies will request that all pregnancies are reported in the same way as serious adverse events i.e. immediately and using the SAE report form
- Pregnancies are 'followed' to learn the outcome as 'congenital anomaly/birth defect' is a category of SAE

Knowledge Checks!

What is a SUSAR?

Essential Documents

DURING CONDUCT OF TRIAL:

- Investigator's Brochure updates
- Revisions to protocol, ICF, any other written information provided to subjects, advertisements for subject recruitment
- Dated, documented approval from IRB/ IEC for any such revisions
- Regulatory authorities notification/ approval for any such revisions
- CV of new investigators, sub investigators
- Updates to lab normal ranges
- Documentation of IP and trial material shipment
- Relevant communications other than site visits

Essential Documents (cont.…)

DURING CONDUCT OF TRIAL:

- Signed informed consent forms
- Source documents
- Signed, dated and completed CRFs
- Notification of SAEs and related reports
- Notification regarding serious, unexpected adverse drug reactions
- Interim or annual reports to IRB/ IEC and authorities
- Subject screening, identification, enrollment logs
- IP accountability at the site
- Signature sheet
- Records of retained body fluids and tissue samples, if any

AFTER COMPLETION/ TERMINATION OF TRIAL:

- Investigational product accountability at site
- Documentation of investigational product destruction
- Source documents
- Completed subject identification code list
- Final report by investigator to IRB/ IEC
- Clinical trial report

Which documents are submitted?

- Regulatory approval
- Available safety information, IB/ package insert and updates, report of prior investigations
- Protocol / Amendments
- Patient Information Sheet / Informed Consent Form and updates/ Translations/ Back translations
- Subject recruitment procedures (ads), patient instructions
- Insurance, Indemnity, Contract, compensation & payments to the patient
- Investigators' CV and Investigator's Undertaking
- Other project-specific documentation, e.g., diaries
- Any additional IRB/EC specific requirements (e.g. Questionnaire, CRF)
- Patient recruitment procedures/ advertisements, if any

What is archived: Essential Documents

ICH requires that all essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years after the formal discontinuation of the clinical development of the Investigational Product

Reference

- **Text**

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Thank You!

For any feedback/comment/clarification please contact us at PALS@tcs.com

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Change/Revision History

Revision No.	Revision Date	Revision Description	Slide No.	Rationale for the change	Change type (Add / Modify / Delete)
00.00	NA	Initial Release			

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