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ICH GCP E6(R2): Revisão de Boas Práticas Clínicas

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CRO CETERA

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CONFLICT OF INTEREST

I have no actual or potential conflict of interest in relation to this program/presentation.

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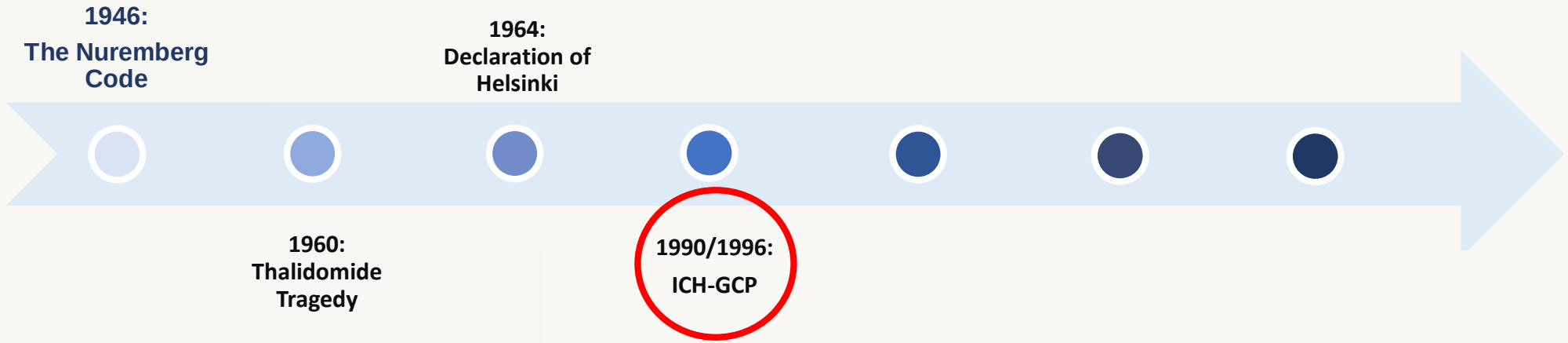
HISTORICAL PERSPECTIVE



INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH, 1996):

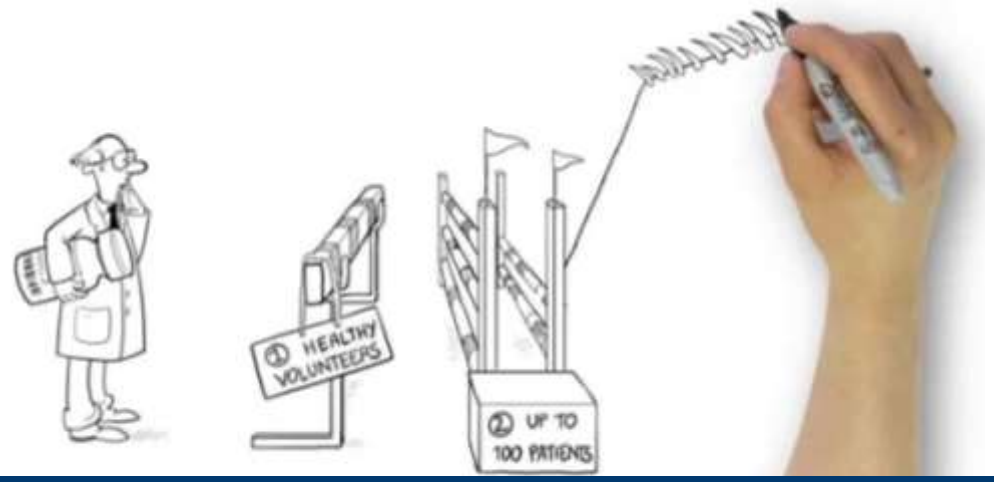
- A collaboration between the regulatory authorities of the European Union, United States and Japan.
- **Mission**: achieving greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner
- **AIM:** harmonization of the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby **reducing or obviating duplication of testing** carried out during the research and development of new human medicines.

GUIDELINE FOR GOOD CLINICAL PRACTICE

The **2 most important points** while conducting your research according to **GCP** are:

Protect participants involved in trials.

Ensure the credibility of the data generated in the trial.



QUIZZ Time

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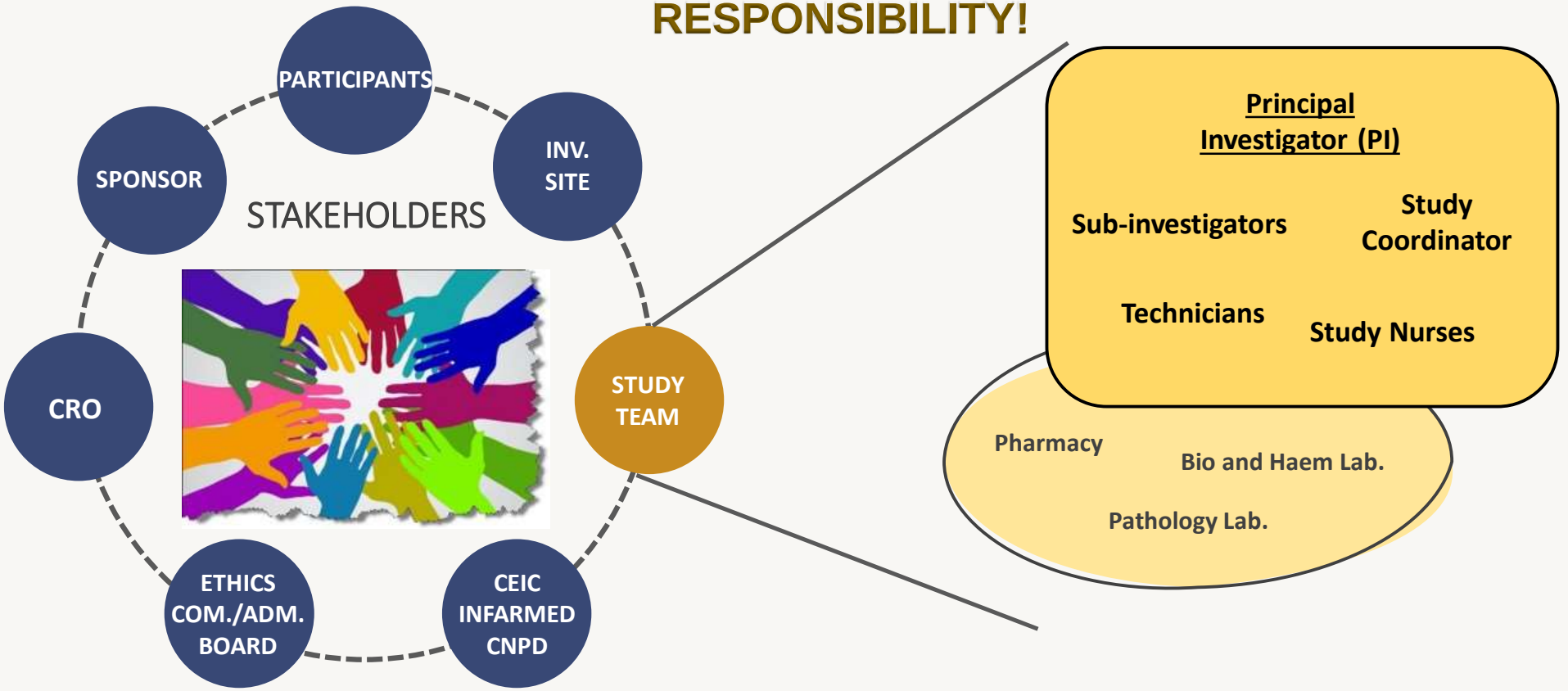
DEFINING THE RIGHT STUDY TEAM

RESPECT OF GCP IS A SHARED RESPONSIBILITY!

DEFINING THE RIGHT STUDY TEAM

RESPECT OF GCP IS A SHARED RESPONSIBILITY!



INTRODUCTION

Good Clinical Practices (GCP) are international ethical and scientific standards for the:

- >> Design
- >> Conduction
- >> Performance
- >> Monitoring
- >> Auditing
- >> Recording
- >> Analysis
- >> Reporting

… of clinical trials…

…that provide assurance that the data & reported results are credible and accurate & that the rights, integrity & confidentiality of trial subjects are protected.

Outlines the responsibilities of **Institutional Review Boards (IRBs), investigators, sponsors and monitors.**

Good Clinical Practice

GCP are widely accepted (at least 193 countries follow ICH-GCP Guidelines for Clinical Trials) and are expected to be followed in all research involving human participants. It is general and applicable to all protocols.

The ICH brought out a revised set of guidance - called E6(R2). The final version of this guidance was published on 17 November 2016.

Although many areas of GCP remain the same, there were some important changes especially in terms of risk management and data handling.

Reasons for R2 to ICH GCP:

>> To encourage the Sponsor to implement **improved and more efficient approaches (e.g. risk-based monitoring) to clinical trial design, conduction, oversight, recording and reporting;**

>> To **update standards regarding electronic records** and essential documents intended to increase trial quality and efficiency.

Format of the Addendum to GCP:

New text is inserted in the original text of the GCP guideline.

Effective from June 2017.

Main Differences in ICH GCP R3:

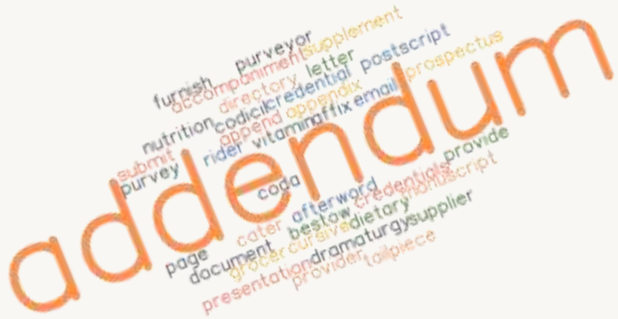
>> **Quality** **Eg: 6. Quality should be built into the scientific and operational design and conduct of clinical trials**

>> **Input from different stakeholders**

>> **Assent**

>> **Protocol Deviations**

>> **Confidentiality/Data Protection and Data Integrity**



Format of the Addendum to GCP:

Previous text of the GCP guideline (original + R2 addendum embedded in the text) is mostly **rewritten** – new text document is created.

Effective from <u>the end of 2023</u>

CORE GCP Principles

Ethics

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).
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 the trial subjects are the most important considerations and should prevail over interests of science and society.

Protocol & Science

4. The available nonclinical 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.

CORE GCP Principles

Responsibilities

6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable 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, of a qualified dentist.

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

Informed Consent

9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

CORE GCP Principles

Data Quality & Integrity

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

ADDENDUM: This principle applies to all records referenced in this guideline, irrespective of the type of media used.

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).

IMP

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.

Quality

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

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

OUR EXPERIENCE,

PRACTICAL EXAMPLES

AND TIPS

PRINCIPLE

5

Study Protocol

Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study title	**The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention.** **ATPCI study** **An international, multicentre, randomised, double-blind, placebo-controlled study in patients treated for 2 to 4 years.**
Test drug code	**S 06790 (Trimetazidine MR 35 mg)**
Indication	**Angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-06790-010**
EudraCT Number	**2010-022134-89**
Sponsor	**I.R.I.S.**
Date of the document	**14 April 2014**
Version of the document	**Final version**

Substantial Amendment integrated

No	Final version date	Countries concerned
1	26 February 2014	BGR
2	14 April 2014	ALL

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Name of the Sponsor: I.R.I.S. 50 rue Carnot 92284 Suresnes - France	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: NA	**Volume:**	
Name of Active Ingredient: Trimetazidine MR 35 mg (S 06790)	**Page:**	

Contractual signatories

I, the undersigned, have read the foregoing protocol and the "Participant information and consent form" document attached to the protocol and agree to conduct the study in compliance with such documents, GCP and the applicable regulatory requirements.

NAME DATE SIGNATURE

COORDINATOR / INVESTIGATOR: CENSORED 5/2014

CENTER NUMBER

DIRECTOR OF CARDIOVASCULAR INNOVATION THERAPEUTIC POLE: 16 April 2014 CENSORED

DIRECTOR OF CLINICAL DEVELOPMENT: CENSORED

PROJECT DIRECTOR: CENSORED

PRINCIPLE

7

Medical care of participants

Sub investigator:

"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)."

ICH GCP (R2)

An element of the Study medical team is essential to help the principal investigator in almost every aspect of the medical practice of the trial.

PRINCIPLE

8

Being Qualified

All individuals involved in implementing any aspect of a clinical research study must be suitably qualified to be able to perform their tasks in compliance with GCP requirements.

According to GCP, **being 'qualified'** means that each individual involved in implementing a part of the research study must be capable of doing their job through their:

- Education
- Training
- Experience

The investigator must be aware of, and comply with, GCP as it applies to their particular study and should be acquainted with all regulatory and ethics requirements, both nationally and locally.

PRINCIPLE

9

Informed Consent Process

Important:

The patient's participation in the Study needs to be registered in their medical notes:

- Informed Consent Process
- Participant's Study code/number

According to Good Clinical Practice!

Example:

Patient meets all inclusion criteria e none of the exclusion, having been invited to participate in the XXXX study. Patient was informed about the study and all their questions were clarified. They signed and dated two copies of the informed consent form version YY, dated DD of MM, YYYY. One original was given to the participant and another was archived in the Investigator Site File.
Participant was registered in the eCRF platform with the number NNNNN.

Informed Consent Process

PRINCIPLE

9

CONSENT

I have read the information in this consent form (or somebody read it to me). The Study Team answered all my questions about the study. I freely consent (agree) to participate in this research study.

I permit the release of my medical records for research or regulatory purposes to the sponsor, the FDA, DHHS agencies, governmental agencies in other countries, and Institutional Ethics Review Board of Jawaharlal Nehru University.

By signing this consent form I have not waived any of the legal rights which I otherwise would have as a subject in a research study.

_____
Subject Name

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

← Dated and signed by **patient**

← Dated and signed by the delegated **investigator**

PRINCIPLE

9

Common Pitfalls of the ICF!

1. Investigator **did not sign or signed before** the patient!
2. Patient **did not fill himself** all blank spaces.
3. An investigator signed the ICF, but he/she is **not included in the study team** – no evidence of training to obtain consent.
4. A patient does not write or read and is not able to understand what the investigator is explaining but signs the ICF and **no witness** is present.
5. ICF **not archived in the ISF/Patient File**– not possible to verify subject has given consent.
6. **Unapproved** consent form used.
7. Consent form used to reference **wrong patient information sheet**.

PRINCIPLE

9

What NOT to do:

Woo Meng Tat — Name of Patient — Signature — 06 JAN 2008 — Date

☐ NA — Name of Impartial Witness — Signature — Date

Witness Identification Number

Dr. Harry Ngan — Name of Person obtaining consent — Signature — 06 JAN 2008 — Date

Original consent form to be retained by the trial doctor. A copy should be given to the patient

Core Patient Information and Consent Form
Trial 1999.99, Version 1.0, 23 Oct 2007

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Essential Documents

PRINCIPLES

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11

ICH GCP 1.23, 2016

Prior to clinical phase → Clinical conduct → Following trial termination

Documents that individually and collectively allow evaluation of the conduct of a study and the quality of the data produced.

These documents are those usually **inspected by the regulatory authorities** and are part of the process to confirm the **validity of the trial conduct** and the **integrity of the data** collected.

These documents serve to demonstrate the **compliance** of the investigator, sponsor, and monitor **with the standards of GCP and all applicable regulatory requirements**.

Essential Documents

Investigator Site File (ISF)

PRINCIPLES

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- The ISF includes all **Essential Documents** to the Clinical Study conduct at the Study Site.
- ISF **maintenence** is the responsibility of the team at the **Study Site**.
- The ISF should be **regularly updated** – new versions of essential documents need to be included in a timely manner, **keeping the outdated versions** clearly identified as such.
- The ISF is **located at the Study Site**, and its archive should be ensured by the Study team.
- **Protocol** usually states the period in which the ISF needs to be archived.
- Archive can be outside of the Study Site, although it needs to be **clearly documented**, location needs to be **safe** and **easy access** in case of na audit or inspection guaranteed.

PRINCIPLE

12

Investigational product(s) managements

The investigator (or the assigned qualified pharmacist) is responsible for:

>> maintaining the investigational products records which include information on amounts delivered, dispensed, and returned/destroyed;

>> ensuring proper storage conditions are maintained and documented including details of temperatures, dates, quantities, batch numbers, expiry dates;

>> ensuring the investigational products are only used as specified by the approved protocol;

>> keeping a list of randomization code numbers assigned to participants;

>> reconciling all investigational products received.

Data Quality

PRINCIPLE

13

ICH GCP Section 5.5.1:

The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses and to prepare the trial reports.

The quality management system should use a risk-based approach based on:

>> Critical process and data identification;

>> Risk identification;

>> Risk evaluation;

>> Risk control;

>> Risk communication;

>> Risk review;

>> Risk reporting.

PRINCIPLE

13

Data Quality - Monitoring

Risk Based Monitoring (RBM) approach is part of the Risk Management

- **Source data verification (SDV) is only conducted on a sample of patients' data**
- **Not all patients are SDVed** (only in a % of the total patient's visits)
- **SDV will be increased only to address identified issues and risks**
- **Compliance checks are done remotely** (adherence to protocol and CRF completion rules)
- **Compliance checks** are performed **for all patients**

Data quality = Shared task

PRINCIPLE

13

Overseeing the progress of a clinical trial & ensuring that it is conducted, recorded & reported in accordance with the protocol, SOPs, GCP & the applicable regulatory requirement(s).

(1.38, ICH GCP 2016)

A systematic & independent examination of trial related activities & documents to determine whether the evaluated trial related activities were conducted, & the data were recorded, analyzed & accurately reported.

(1.6, ICH GCP 2016)

(1.29, ICH GCP 2016)

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.

PRINCIPLE

13

Data Quality

	AUDIT	INSPECTION
PERFORMED BY WHOM?	Sponsor or Contract Research Organization (CRO) **Internal Qualified Auditor**	**Qualified and Certified Inspectors** from Health Authorities (EMA, FDA, MHRA, INFARMED)
WHERE?	• **Investigational Sites** • **Sponsor** or **CRO** facilities • **IMP** production and/or storage facilities • **External vendors** (ex.: central clinical laboratory)	
HOW ARE THE INVESTIGATIONAL SITES CHOSEN?	**High patient enrolment and/or lack of retention** **High staff turnover** **Abnormal number of AEs** (high or low) **Fraud** suspicion	**High patient enrolment** **Fraud** suspicion
WHEN?	Before, during or after a Clinical Trial is concluded	

Audits and Inspections are part of the Quality Assurance (QA) activities and are undertaken by personnel independent of trial.

PRINCIPLE

13

Benefits of GC & QA in Clinical trials

Participants' Protection

Assist the Investigator:

- Maintain quality data and records
- Implement the protocol correctly
- Be ready for a possible regulatory inspection

Assist the Sponsor:

- Maintain awareness of trial progress/issues
- Adhere to GCP regulations and guidelines
- Submit data suitable for regulatory approval

CETERA

>>Investigator

INVESTIGATOR

Chapter 1.34, ICH GCP 2016

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.

Remember…

Sub investigator:

"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)."

ICH GCP (R2)

INVESTIGATOR

Chapter 4, ICH GCP 2016

>> Updated **CV**

>> **GCP** and regulations **compliance**

>> Study **protocol compliance**

>> Obtaining **informed consent** from study participants

>> **Randomization** procedures and **unblinding**, when needed

>> **Medical care** of study participants

>> **Investigational product(s)** handling and management at the site

>> Communication with the **IEC/IRB**

>> **Qualified staff** and agreements – **Delegation Log**

>> **Records** and **reports** management

>> **Safety reporting**

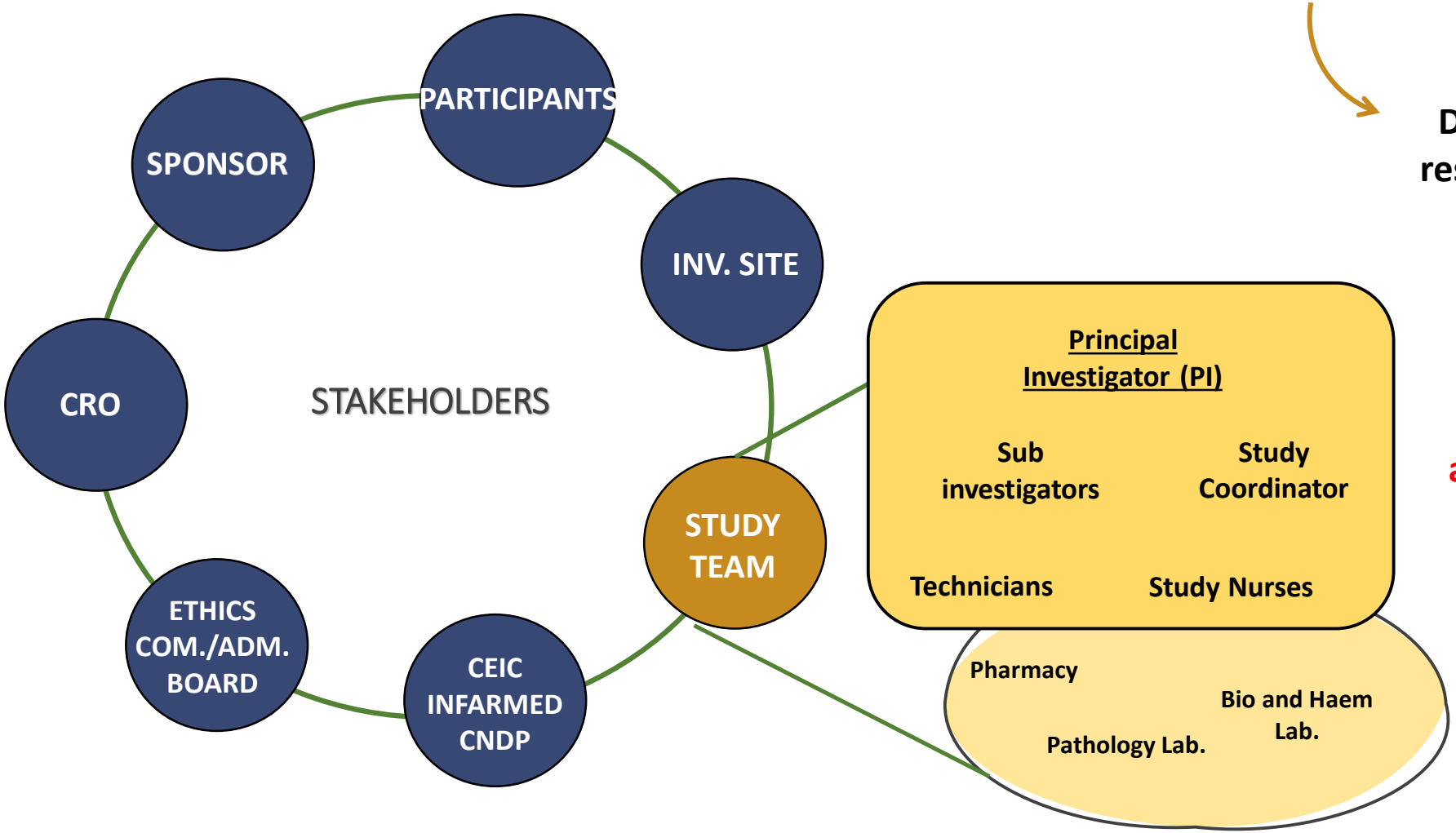
>> Ensuring **adequate resources**

>>Management of **premature termination or suspension** of a study

>> **Progress reporting** and **final reports**

Investigator

Study Team Coordinaton and Interaction



Delegation of responsabilities

Organization, Communication and Coordination are CRITICAL!

Investigator - Delegation Log

Protocol No.:	Centre No.:

- PRINCIPAL INVESTIGATOR -

Title, First Name and Surname:	Work address:	
Signature:	Telephone:	Initials:

- PERSONNEL [1] INVOLVED IN THE STUDY IN THIS CENTRE, UNDER PRINCIPAL INVESTIGATOR'S RESPONSIBILITY -

Function	Name	Tasks delegated by the principal investigator under his/her responsibility [2, 3]	Dates of participation in the study		Signature [4]	Initials	Certification by principal investigator / Signature
			Start	End			
Principal Investigator							

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[1] *Indicate the people to whom the principal investigator delegates under his/her responsibility a part of the study follow-up (study nurse, co-investigator…)*

[2] *See list attached*

[3] *For principal investigator, tasks actually performed by the principal investigator*

[4] *Signature means "I hereby certify that I have been informed of documents confidentiality as well as read and understood all study documentation that apply to my task(s) in the study"*

Investigator - Delegation Log

SITE SIGNATURE AND DELEGATION OF RESPONSIBILITIES LOG

Sponsor:	Montreal Heart Institute	Protocol Number:	
Investigator Name:	[redacted]	Site Number:	402

THIS FORM IS TO BE COMPLETED BY ALL PERSONNEL INVOLVED IN THE CLINICAL STUDY PRIOR TO TAKING PART IN ANY CLINICAL STUDY ACTIVITIES.

INVESTIGATOR
By signing, I acknowledge that the tasks listed below will only be delegated to appropriately skilled and qualified staff. I will remain responsible for the overall clinical study conduct and reported data and I will ensure clinical study oversight. All site staff assisting in the conduct of the clinical study are informed about their obligations, and have not performed any clinical study tasks prior to appropriate delegation and completion of appropriate training. Any changes in staff or delegation in staff will be recorded in a timely manner.

Investigator Name	Investigator Signature	Initials	Start Date (DD-MMM-YYYY)	End Date (DD-MMM-YYYY) COMPLETE ONLY IF PRIOR TO END OF CLINICAL STUDY
[redacted]	[redacted]	RG	10-08-2016 AVE	

***Task Codes (enter the number in the column)**

1. Obtain informed consent
2. Medical/ Surgery History assessments
3. Inclusion and exclusion assessments
4. Complete and sign ESF
5. Blood draw collection
6. Prepare, and ship laboratory samples
7. Assess concomitant medication
8. Report SAE and endpoint package for adjudication to MR
9. Complete and correct case report forms (CRFs)
10. Review and resolve queries
11. Sign CRFs
12. Submit, update, and maintain Ethics Committee documents
13. Document study visit and contacts
14. Provide subject education
15. Maintain subject screening and enrolment logs
16. Investigational product (IP) receipt, preparation dispensing and destruction
17. IP reconciliation
18. Maintain ISF binder throughout the study
19. Other, specify: 19. X Relabeling
20. UNBLINDED PROCEDURE
21. ASSESS EVENTS
22. REVIEW, EVALUATE AND SIGN LABORATORY RESULTS

**Tasks considered the sole responsibility of the Investigator or delegated Sub-Investigator.

Copy in ISF.

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Investigator – Safety Reporting

Important Concepts

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

Adverse Drug Reactions (ADRs): When there is a reasonable possibility that an AE has a causal relationship to the medicinal product being tested.

Serious Adverse Events (SAEs) or **Serious Adverse Drug Reactions (Serious ADRs)**: Any untoward medical occurrence that at any dose:

>> results in death
>> is life-threatening
>> requires patient hospitalization or prolongation of existing hospitalization
>> results in persistent or significant disability/incapacity
>> is a congenital anomaly/birth defect.

Suspected **U**nexpected **S**erious **A**dverse Drug **R**eaction **(SUSAR)** is when an adverse reaction is inconsistent with the characteristics of the medicinal product or its applicable product information.

1.1/1.2/1.50/1.60, ICH-GCP 2016

Investigator – Safety Reporting

The investigator should report AEs / laboratory abnormalities that are critical to safety evaluations as laid out in the protocol

Report all **SAEs immediately to the sponsor:**

- send promptly detailed written follow-up reports on SAEs
- supply additional information on reported deaths

The investigator must ensure that relevant site staff are aware of safety recording and reporting requirements.

Individual **safety reports should not identify the individual** but bear the subject code numbers for identification

Investigator Responsabilities

Key points:

>> An investigator should be **qualified by education, training and experience** and ensure their **study team** is also **sufficiently qualified**. Any delegated responsibility must be clearly recorded in the **study delegation log.**

>> Investigator should be thoroughly familiar with the **protocol** and investigational product as described in the **Investigator's Brochure**, the product information and any other literature on the product. They are **responsible for the IMP circuit**.

>> The investigator **must allow the study to be Monitored, Audited and Inspected** to enable oversight by the sponsor and regulatory authorities. **Records and reports** should be adequate.

>> Investigator is responsible for **Safety Reporting**, **Progress and Final Reports** and eventual Management of **premature termination or suspension.**

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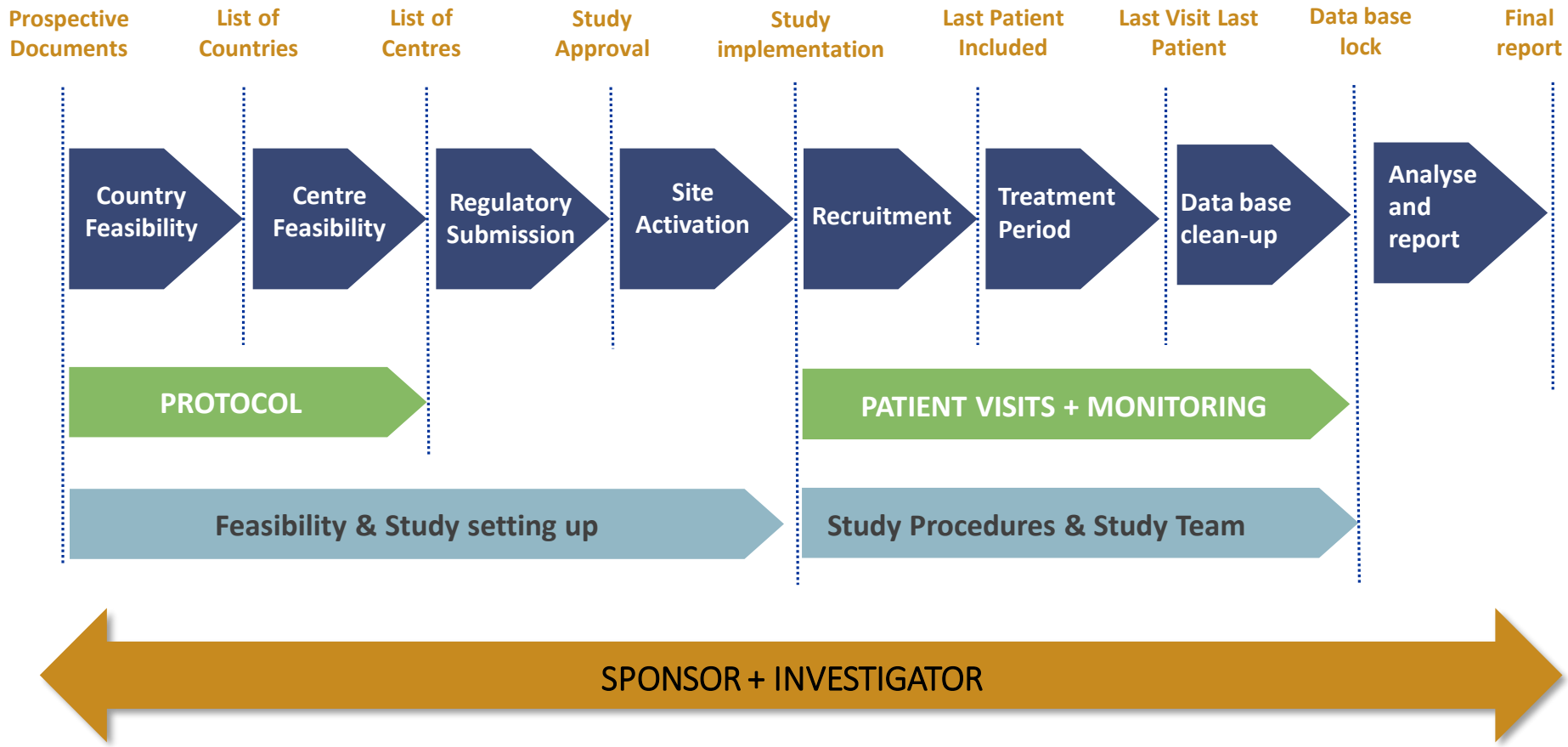
General Process



The PI's responsability exisits since the beggining, with the Feasibility Process.

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Obrigada pela atenção!

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Global Health Training Center
https://globalhealthtrainingcentre.tghn.org/login/

CETERA Training
training.cetera@medicina.ulisboa.pt

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