Quality Management Systems
Clinical Trial

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Rio de Janeiro - Brazil

Different types of Clinical Research

•**Treatment:** Also called “clinical trials” generally involves an intervention such as medication, psychotherapy, new devices, or new approaches to surgery or radiation therapy.

•**Prevention:** Also called “clinical trials” generally involves an intervention such as medication, psychotherapy, new devices, or new approaches to surgery or radiation therapy.

•**Diagnostic:** Refers to the practice of looking for better ways to identify a particular disorder or condition.

•**Screening:** Aims to find the best ways to detect certain disorders or health conditions.

•**Quality of Life:** Also known as “supportive care,” explores ways to improve comfort and the quality of life for individuals with a chronic illness.

•**Genetic Study:**

- Aim to improve the prediction of disorders by identifying and understanding how genes and illnesses may be related.
- May explore ways in which a person’s genes make him or her more or less likely to develop a disorder.
- This may lead to development of tailor-made treatments based on a patient’s genetic make-up.

•**Epidemiological Studies:** Seek to identify the patterns, causes, and control of disorders in groups of people.

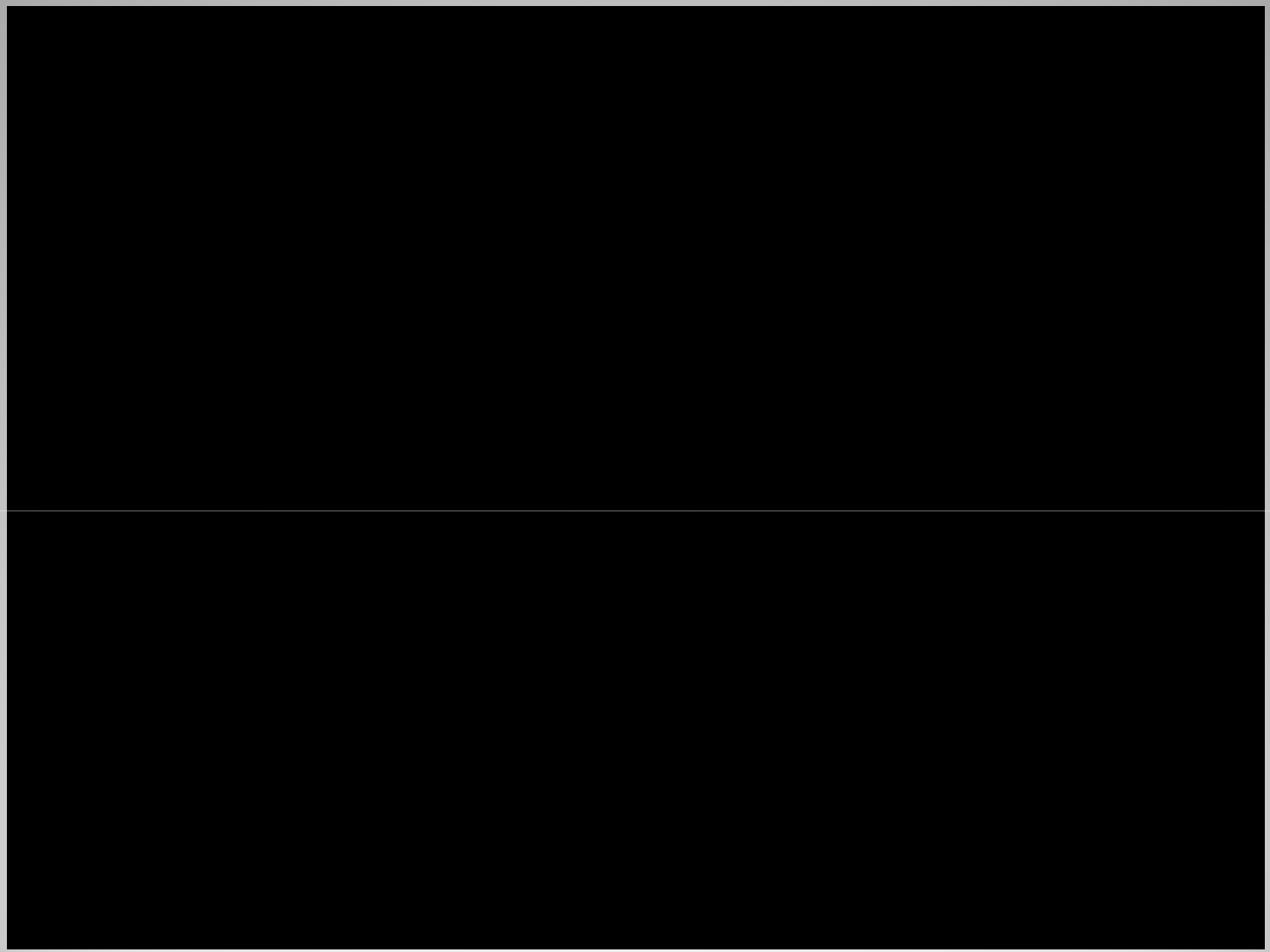
Observational Studies

• **Investigators assess:** Health outcomes in groups of participants according to a research plan or protocol.

• **Participants:** May receive interventions (which can include medical products: drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial).

i.e. Investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health.

VIDEO



https://www.youtube.com/watch?v=re5jy3fuOaw

Preclinical Tests (i.e)

Pharmacodynamic:

This is what the drug does in the body (mechanism of action, site of action, comparison with other drugs.

Pharmacikinetic:

It´s what the body does with the drug (absorption, distribution, biotransformation, excretion).

Clinical Trial: Study Phases (1-2)

Phase I

• Number of volunteers: 20 to 100 healthy or sick volunteers.
• Purpose: test new drug / treatment to evaluate drug safety, determine a safe dosage range.
• Length of Study: Several months.
• % of Drugs that move to the next Phase 70%.

Phase II

• Number of volunteers: 100 to 300 of healthy sick volunteers.
• Purpose: Efficacy and Safety.
• Lenght of Study: Several months to 2 years.
• % of Drugs that move to the next Phase 33%

May be divided into phases IIa and IIb:

➢IIa trial evaluates the short-term safety of drug.
➢IIb confirms clinical efficacy of a drug and determine the therapeutic dose range.

http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm#Clinical_Research_Phase_Studies

Clinical Trial: Study Phases (2-3)

Phase III

Number of volunteers: 1,000 to 3,000 (Except for Vaccine Trials) healthy or sick volunteers.

For Vaccines Phase III trials are often much bigger because you deal with a healthy population and you want to detect rare AEs.

i.e. Rota was 70.000.
A previous Cholera vaccine 160.000

- **Purpose:** Efficacy and monitoring adverse reactions.

- **Length of Study**: 1 to 4 years.

- **% of Drugs** that move to the Next Phase 25-30%.

-The phase III may be divided into IIIa and IIIb.

- **After this phase:** Internal Audits / Inspections, Definition of bull / leaflet, Final Regulatory of Study and Marketing Application.

Clinical Trial: Study Phases (3-3)

Phase IV

• **Post Marketing** studies delineate additional information including the drug´s risks, benefits, and optimal use.

• **Purpose:** Safety and Efficacy.

• **Patients:** Several thousand volunteers with the disease / condition.

Clinical Trial: Studies can be ...

Protocol

- **Multicentric (ICH 5.23):** Diferent Participants Sites in the trial.

  PI from all participant sites should conduct the trial according to protocol, share clinical and lab findings and the sponsor will facilitate the communications between them.

- **Multinational:** Participating Centers from different countries.

- **Different Phases, Pediatric or Adult.**

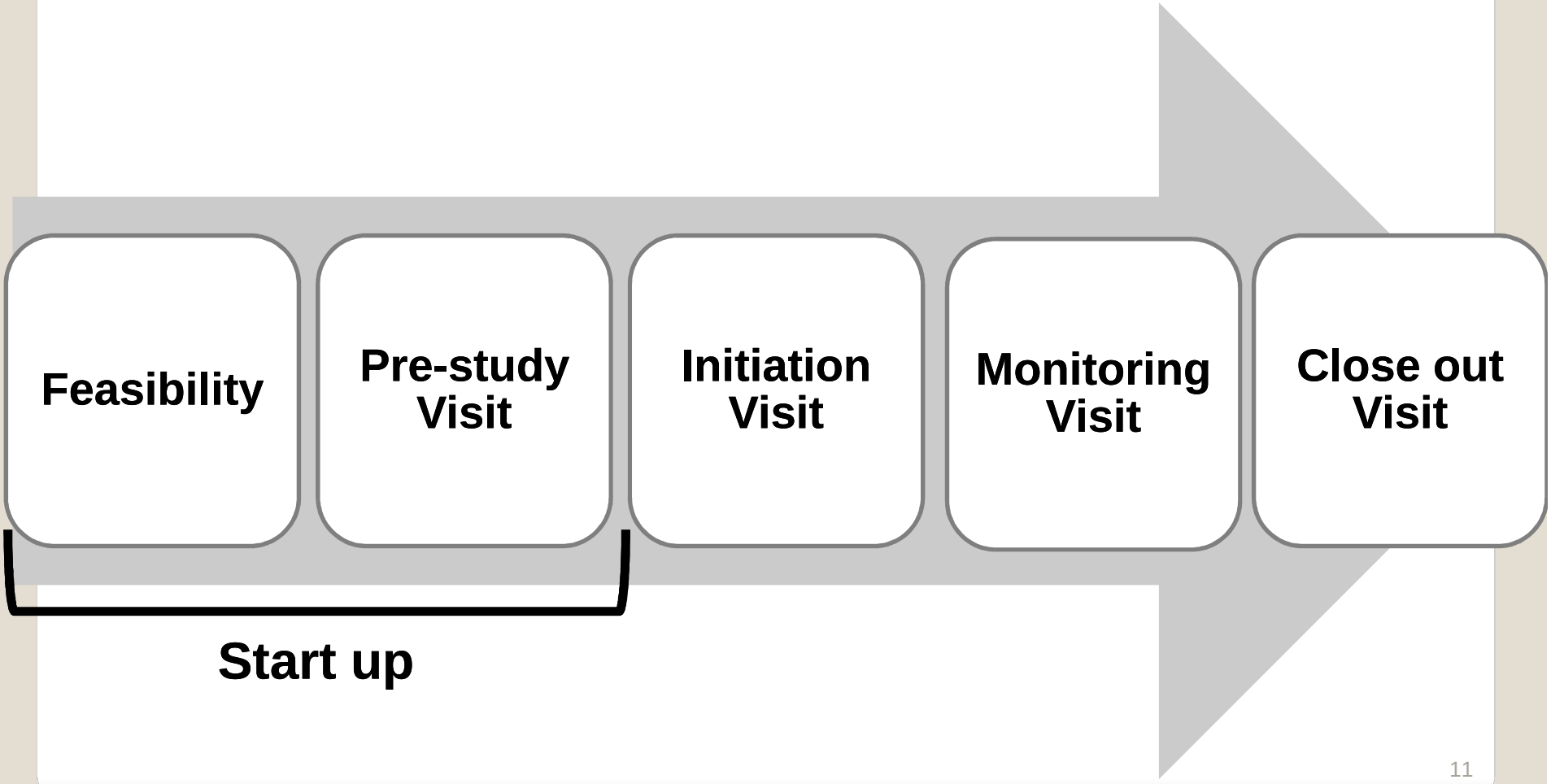
- **Randomized / Bliding (ICH 1.48):** Process of assigning trial subjects to reduce bias.

Project Management Plan

•Timeline	•Communication Plan
•Milestones	•Quality Control
•Hospital Grants	•Query
•Project Finance Cost	•Issues & Risks
•Budget	•Project Closure
•Site Selection Strategy	•Lessons Learned
•Project Goals	•Vendors
•Safety Management	•Site Selection Strategy
•Insurance	•Others

Clinical Trial: Working Process

Confidentiality Agreement: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.



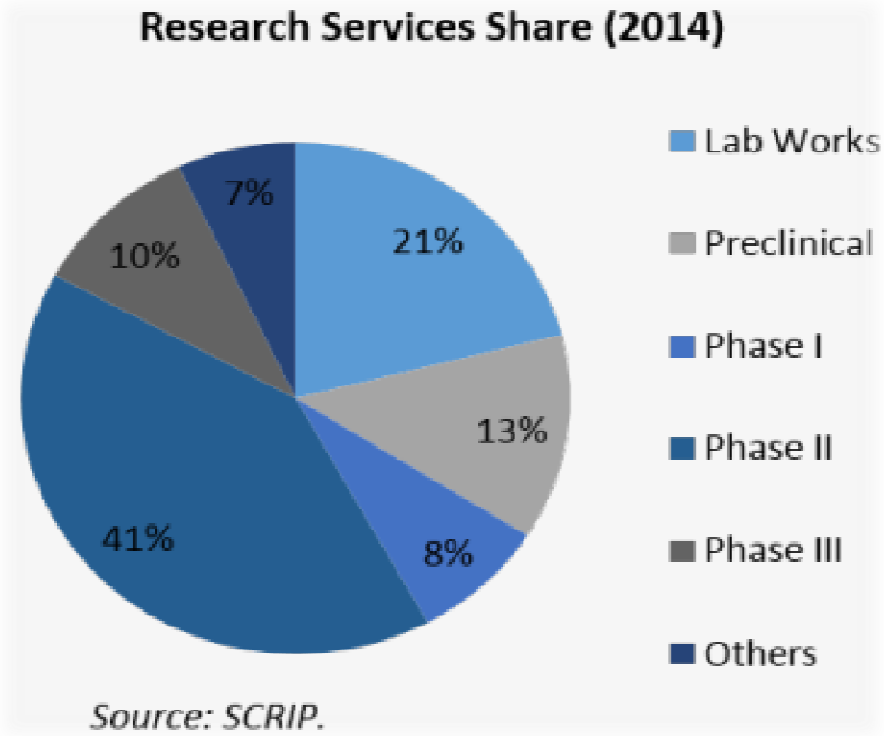
Define First Clinical Trial Services !

Sponsor

or

Contract Research Organizations (CRO)

Offer services across the entire pharmaceutical research spectrum.



https://igeahub.com/2016/04/14/top-10-global-cros-in-2016/

Working Process: CRO

ICH 5.2 Contract Research Organization (CRO)

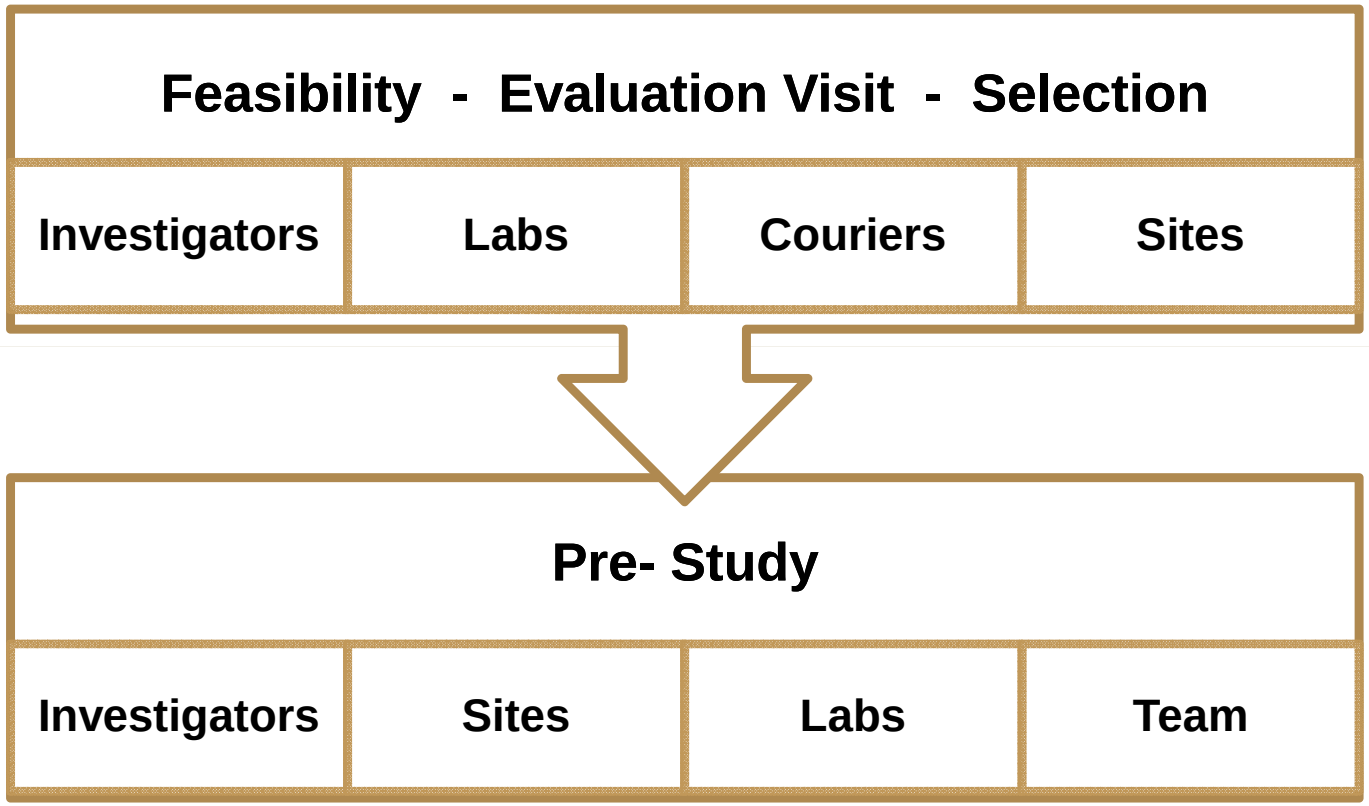
5.2.1 - **A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO,** but the **ultimate responsibility** for the quality and integrity of the trial data always resides with **the sponsor**.
The CRO should implement quality assurance and quality control.

5.2.2 - Any trial-related duty and function that is transferred to and assumed by a CRO **should be specified in writing.**

5.2.3 - Any trial-related duties and functions **not specifically transferred** to and assumed by a CRO are **retained by the sponsor.**

5.2.4 - All **references to a sponsor** in this guideline also **apply to a CRO** to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

Working Process: Start up



Why Feasibility ?

Evaluation of:

• Competitive environment for a study (PI / Site are conducting other studies).

• Possibility of conducting a clinical research in a **geographical region** according to timelines, targets and costs.

• **Available population** of patients likely to meet all major entry criteria of a trial.

• Current **patterns of care** in patients and the **acceptability of the protocol design.**

• **Availability to participate** in the study; **patient and physician.**

• Evaluation of **Regulatory timelines & challenges.**

Why Feasibility ?

Benefits:

- **Optimize performance:** Minimizing Risk and Maximizing Efficiencies.
- **Fast Process:** Site Identification, Selection and Contracting.
- Essential Document Collection, Management, Regulatory and Ethics Submission.
- Planning of Patient Recruitment.

How?

1. Visit
2. Telephone
3. Questionnaire (e-mail/mail)

Post Feasibility: Decision

- **PI / Site Selected:** Pre-study.
- **Not Selected:** Feasibility Database (if PI/Site accept).

➡ **Send a letter to all feasibility partipants informing about the decision.**

<u>Recommendation</u>

↓

Pre-study visit should be organized if potencial investigators
were not assessed within
the last 12 months
according to the SOP of each company.

Pre-study Visit

Purpose:

• **Suitability of PI** / Site to conduct the trial.

• **Qualifications of PI** to participate in the trial.

In some cases, you may even be able to perform this
via telephone, web-conference,
or it might be **waived** altogether.

"Conducting the trial: Sponsor/CRO should be present'

• **Review:** PI/Staff qualification, Protocol/Study Design, Regulatory requirements, Site procedures**,** Publication Policy, Translations, Insurance, Audit, Inspections, Miscellaneous Information.

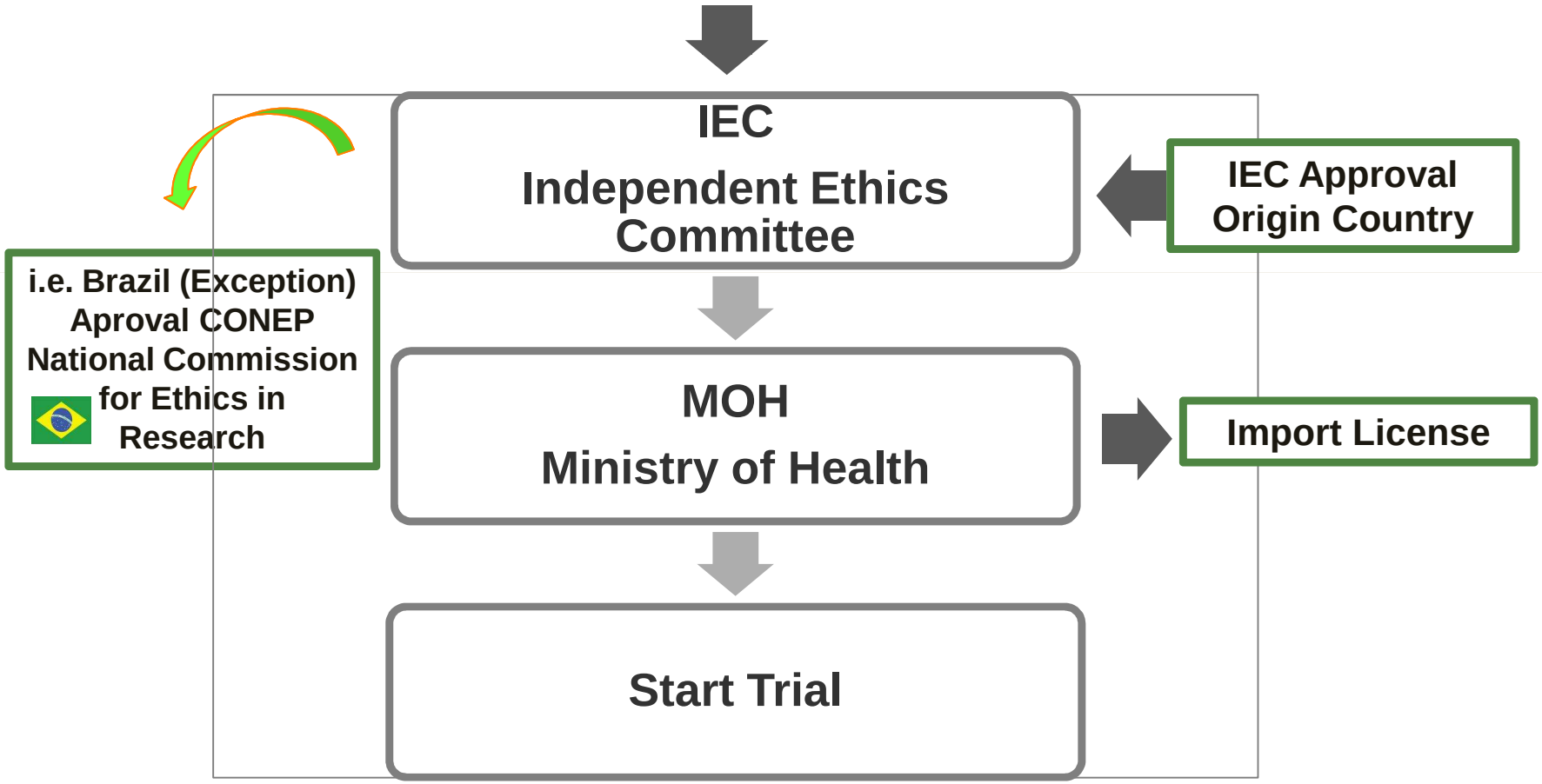
• **Assess:** Subject population / recruitment.

• **Evaluate:** Site Facilities and Equipments, Site motivation and if they are already participating in competitive trials (i.e. pool of patients).

• **Collect** Essential Documents and conclude the visit.

Pre-study: Approvals

Before study starts, it is mandatory to obtain all Ethic and Regulatory Approvals.



Pre-study: IEC

• An **independent body** (a review board or a committee, institutional, regional, national) constituted of medical professionals and non-medical members.

• **Objective** to **ensure the protection of the rights, safety and well-being** of human **subjects** involved in a **trial.**

• Provide public assurance of that protection, by among other things, reviewing and approving / providing favorable opinion (in writing) to the trial protocol.

• **Suitability of the investigator(s), facilities**, and the methods and material to be used in obtaining and documenting **ICF** to the trial subjects.

• Legal status, composition, function, operations and regulatory requirements may differ among countries, but should act in **agreement with GCP/ICH**.

Clinical Trial - Working Process: Investigator Meeting

SUGGESTED CONTENT	PARTICIPANTS
• Introduction Global and Local Study Team • Study Protocol. / Clinical Development Plan • Study Manuals (IP, Logistics, Exams, Study Operational) • Enrollment, ICF Process, Patient Tracking. • Safety: AE, SAE / Pregnancy /CIOMS / Local Regulations. • Study Logs. • E-CRF • GCP / ICH training / IND Rules, FDA 1572, Financial Disclosures, CVs. • Logistical Aspects • GCP/ICH • Monitoring Visits & Site Preparation. • Others	•Sponsor Study Team • PI and Site Staff • Contracted Lab • Contracted Couries • Experts • Others

Initiation Visit: Site Activation

Site Activation:

•The center is officially activated in this visit.
•All relevant study trainings should be performed to the PI & Site Staff to resolve all doubts!

Objective and Procedures:

• Prepare Study Team for conducting the study.

•The meeting includes (at a minimum) the PI, other investigators, coordinator, other staff assuming study responsibilities.

• If PI is not present organize a subsequent date to review the initiation procedures.

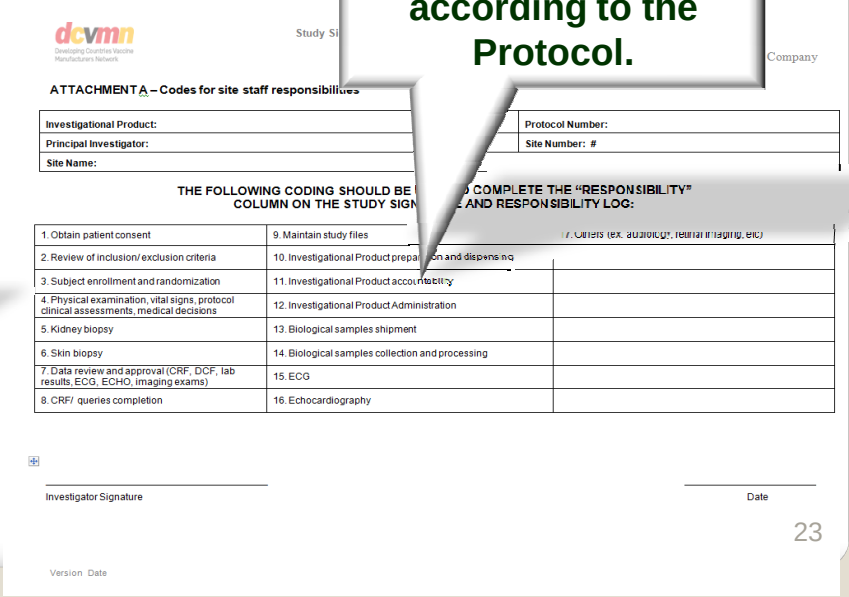
Initiation Visit: Site Activation

Objective and Procedures:

- **PI must sign the following documents** in this visit: Initiation checklist, Delegation of Responsibility Log (and team), Site Visit Log.
- Review **"Site Study File"** with PI / Site Staff.
- Review **any changes PI / Staff Qualifications.**
- **Time commitment** of PI and Key personnel for the study.

Include in this column Study Procedures according to the Protocol.

Immediately notify Project Manager / CTM designee in case of significant findings at the site!



dcvmn

Developing Countries Vaccine Manufacturers Network

Study Si

Company

ATTACHMENT A – Codes for site staff responsibilities

Investigational Product:	Protocol Number:
Principal Investigator:	Site Number: #
Site Name:	

THE FOLLOWING CODING SHOULD BE … O COMPLETE THE "RESPONSIBILITY" COLUMN ON THE STUDY SIGN… AND RESPONSIBILITY LOG:

1. Obtain patient consent	9. Maintain study files	17. Others (ex. audiology, retinal imaging, etc)
2. Review of inclusion/ exclusion criteria	10. Investigational Product prepa…on and dispensing	
3. Subject enrollment and randomization	11. Investigational Product accountability	
4. Physical examination, vital signs, protocol clinical assessments, medical decisions	12. Investigational Product Administration	
5. Kidney biopsy	13. Biological samples shipment	
6. Skin biopsy	14. Biological samples collection and processing	
7. Data review and approval (CRF, DCF, lab results, ECG, ECHO, imaging exams)	15. ECG	
8. CRF/ queries completion	16. Echocardiography	

Investigator Signature

Date

Version Date

Initiation Visit: Essential Documents

ICH - 1.23 Essential Documents:

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

• Serve to demonstrate compliance of the PI, Sponsor and Monitor with GCP and regulatory requirements.

• Should be filed at Site and Sponsor 's office in a timely manner with the objective to have a **successful management of Trial.**

• Usually **audited / inspected** as part of the process of confirmation of validity of the trial conduct and the integrity of the data collected.

• In the **ICH there is a list of the minimum documents** that should be obtained in a clinical trial. They are grouped in sections:

1) **Before the clinical phase of the trial commences**
2) **During the clinical conduct of the trial**
3) **After completion or termination of the trial**

They are also determined by the SOP of the Sponsor !

Initiation Visit: Essential Documents

- Protocol, Amendments
- Ethical Approvals, regulatory documents / submissions
- Contracts, Financial Agreements
- Insurance Declaration
- CV & Professional license
- Lab ranges (normal values), certifications
- Relevant communications
- Eletronic Case Report Form
- Documents of Investigational Product, Shipments, Destruction
- Financial Disclosure / FDA 1572
- Study Logs (screening log, delegation log, site visit log)
- Informed Consent Form & Others

After SIV
Send Fup Letter according to Sponsor / CRO timelines !

Monitoring Visit

Purpose:

ICH 5.18.1 - To verify that:

a) The rights and well-being of human subjects are protected.
b) The reported trial data are accurate, complete, and verifiable from source documents.
c) The conduct of the trial is in compliance with the currently approved protocol / amendment(s), with GCP, and with the applicable regulatory requirement(s).

How should be:

ICH - 5.18.3 - Extent and Nature of Monitoring

• **Sponsor should ensure that the trials are adequately monitored** and the appropriate extent and nature of monitoring.

• Extend based on considerations such as: objective, purpose, design, complexity, blinding, size, and endpoints of the trial.

• Statistically controlled **sampling** may be an acceptable method for selecting the **data to be verified.**

ICH - 5.18.5 - Monitoring Procedures

The **monitor(s) should follow the sponsors SOPs** and Procedures that are specified by the sponsor for monitoring a specific trial.

Monitoring Visit: Conducting the Visit

The CRA should:

- Sign "**Site Visit Log**" daily, obtain site signature (multiple locations)
- Review **Regulatory Submissions**
- Documents Accurate, Complete, Timely, Legible, Dated and Identify the Trial
- Review Subject **Recruitment**, **Source Documen**t
- **AE, SAEs**, Intercurrent illnesses, **Concomitant Medication** and reports
- **Essential Documents:** Ensure that the PI receives the **current version of all study documents**
- Protocol Aderence
- Review all **ICF** (Versions)
- **IP** & Study **Supplies**
- Lab Samples Storage & Shipping
- E-CRF
- Query & Others

Identify Deficiencies

&

Plan Corrective Actions

Monitoring Visit: Important !

eCRF and Source Documents have to be dated and signed by the PI

Corrections initialed in accordance with GCP/ICH

Medical Charts not secure = Confidentiality Compromise

Changes in the Facilities & Site Labs requires additional action

Communicate issues to the PI unless CRA suspects of altered / fabricated data

Copies of original documents have to be signed and dated by the person that has made the copy

Monitoring Visit: Important !

A Follow-up letter should be sent to site summarising the visit activities, after each monitoring visit

Study Monitoring must be conducted as soon as possible after 1st subject entry

New site staff has to be included in the Responsibility Log and a copy of his/her CV, Financial Disclosure Form should be obtained

Review issues from current and previous monitoring visit (s) and assist site personnel with plan for corrective actions

Check expiry date of IP and materials and collect the expired ones

Monitoring Visit: Safety “CRA must Review”!

Adverse Event (AE)	Serious Adverse Event (SAE)
Medical which does not necessarily have a causal relationship with the treatment	**Any medical occurrence that at any dose:** • Results in death.
AE can be unintentional sign (including abnormal lab finding), symptom or disease temporally associated with the study drug.	• Is life-threatening. • Requires subject hospitalization or prolongation of existing hospitalization. • Results in persistent or significant incapacity. • Congenital Anomaly / Birth Defect.

Monitoring Visit: Safety “CRA must review”!

1) **Adverse Events**

2) **Serious Adverse Events**

3) **SUSARs - Suspected Unexpected Serious Adverse Reactions**

- Serious Adverse Events
- Related
- Unexpected

Monitoring Visit: Safety

CRA should:

- Ensure SAE was informed by PI to the Sponsor / CRO Safety Department within 24 hours of becoming aware of the event.

- Ensure that all SAE / Pregnancy (if applicable) reports were signed by PI to acknowledge accuracy of report.

- Ensure that PI did follow-up for all AEs / SAEs (Pregnancy if app).

- Ensure that PI has submitted SAEs & SUSARs to IEC.

- Confirm that the PI has received the SUSARs in day 15th.

- Confirm that the PI review the updated Investigator Brochure with SUSARs.

SUSARs should be send to MoH.

Sponsor / CRO: Send safety information to DMC.

Monitoring Visit: “Safety Committee”

“Data Monitoring Committees (DMCs) also known as Data and Safety Monitoring Boards (DSMBs) or Data and Safety Monitoring Committees (DSMCs)”.

An independent data-monitoring committee that may be established

by the sponsor to

assess at intervals the progress of a clinical trial,

the **safety data, and the critical efficacy endpoints**, and to

recommend to the sponsor **whether to continue, modify, or stop a trial**

FDA Guidance for Clinical Trial Sponsors Establishment and Operational of

Clinical Data Monitoring Committees.

Exp. Date Dec 31 2018

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

Monitoring Visit: Study Drug

CRA should

Initial Shipment

Train the PI / Staff to **receive the study drug**, do the **accoutability**, check the **temperature** and general conditions of the drug / vaccine and complete / file all related documents.

During the Study

Train the PI / Staff to check the storage, to control the temperature, do the accountability, organize the documents and **report to Sponsor / CRO any issue of study drug / vaccine.**

End of Study

Train the PI / Staff to **return** the study drug / vaccine, do the accountability and retain a copy of all related documents.

Monitoring Visit: Study Drug & Specimens

Logs for Vaccines / Drugs:

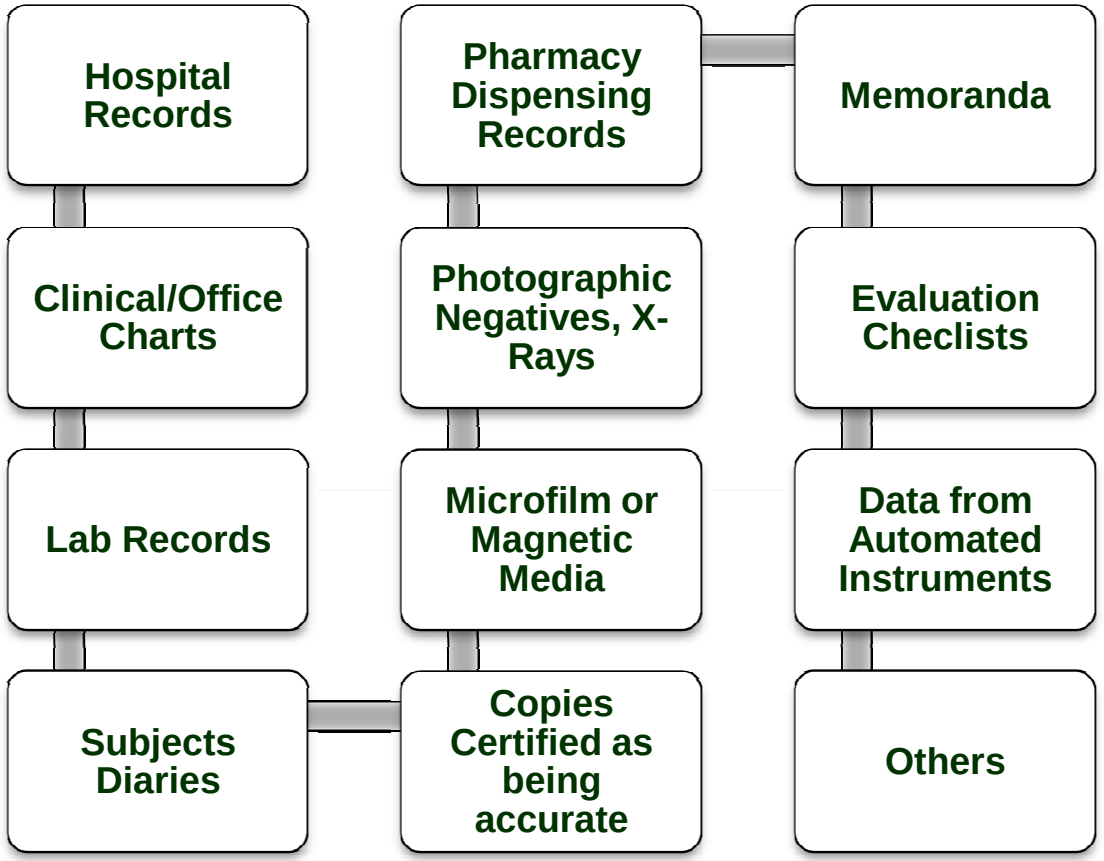
- Investigational Supply Receipt
- Notification of Vaccine Delivery / Temperature Control
- Vaccine / Drug Accountability Log (Replacement Vial)
- Temperature Log Sheet
- Clinical Supply Transfer Form
- Vaccine Return Form
- Complaints Form

Logs for Specimens

- Specimen Transfer Form
- Temperature Log
- Shipment
- Serum listing

Supplies issues have to be immediately notified to CRA !!!!!

Monitoring Visit: Examples of Source Documentation



The Original Source Document is the FIRST place where the information was registered !

Monitoring Visit: Source Documentation can be ...

- Paper & Subject Records
- Combination of Paper & Eletronic Records
- Electronic Records

Per FDA when original information are entered direct into computer system the “eletronic record” is the Source Data.

In this case the CRA needs to have access to “all” and the Auditor / Inspector needs to have access to the same content.

Eletronic Case Report Form or eCRF

A printed, or electronic document designed to record all protocol required information to be reported to the sponsor on each trial subject.

Automatic Query generated by the System

Query generated by Data Manager

Query generated by Study Monitor (CRA)

PI / Site Staff should answer as soon as possible all queries !!!!

Monitoring Visit: Why Review ICF ?

ICH - 1.28 Informed Consent :

A process by which a subject voluntarily confirms his or her willingness to participate in a 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.

A copy of ICF should be given to the trial participant and the original filed in the subject's records

ICF process should be registered in the Source Document

ICF / Amendments should be approved by IRB/IEC prior to subject´s signature

Subject is free to withdraw her/his consent anytime

Subjects under 18 years old need to sign ICF/ Legal Representative (≠ country)

ICH should be signed before any study procedures

The ICH language should be non-technical

Monitoring Visit: Suggestion for Efficient SDV

•The **CRA should always discuss SDV**, issues with PI / key site personnel at least at the end of each MV.

•Study Site should offer an **adequate place** to the CRA to perform the monitoring visit.

•Undertake SDV in **peace and quiet.**

•PI / Study Staff should maintain all **Study Documents organized** in the Study Investigator Files according to the Sponsor / CRO Table of Contents and **locked**

Monitoring Visit: Responsibility of PI

• **Follow up letter** is not a confirmation that the CRA was at site. It is an evaluation with suggested actions to the site.

• **Closing meeting after MV:** it is the time where relevant feedback about site status is given. **PI should take this moment to solve doubts and ask for solutions.**

• Maintain **Adequate Resources.**

• Provide adequate **Medical Care** to trial subjects.

• Inform & **Submit documents**, **Safety** & Progress Reports to IRB/IEC.

• Ensure **Compliance** with the Protocol & ICF Process.

• Maintain **IP and samples** according to the Protocol / Study Documents / Sponsor CRO SOPs.

• **Randomization Procedures & Documents** should be in compliance with Protocol.

Monitoring Visit: PI Responsibility

ICH - 4.2 Adequate Resources

4.2.4 - The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

Clinical Research Memmes Facebook

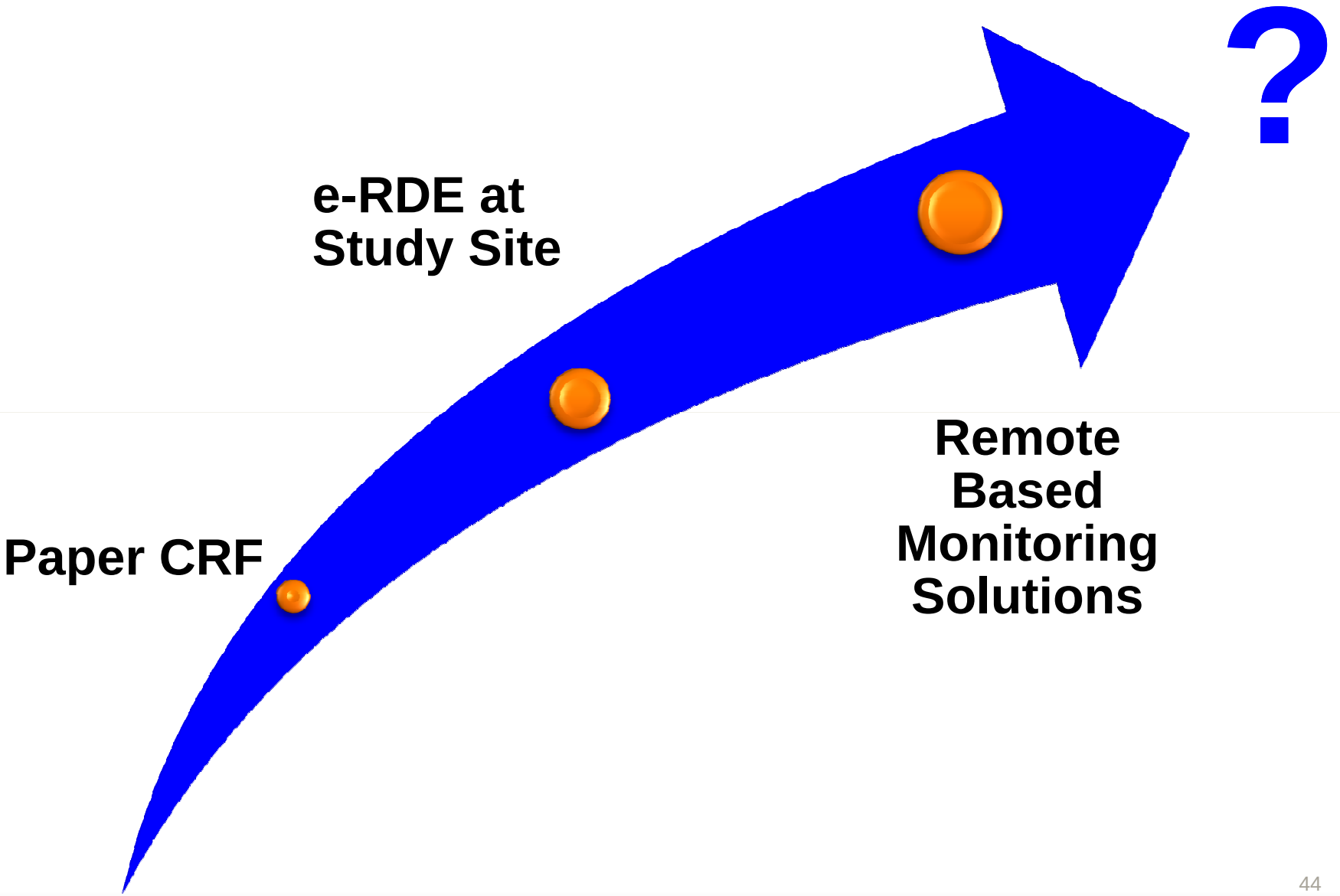
For over a year now I've been suspicious that the site wasn't providing me with all the subjects' medical records. For over a year the site has insisted I've seen everything. As we approach a soft DBL, I'm presented with this at the site this morning. I've never seen any of these records before. I'm feeling homicidal.

Dawn Arrington

Warrenton, Missouri

https://www.facebook.com/photo.php?fbid=10201598075870840&set=gm.1695655097357182&type=3&theater

Monitoring Visit: The Future ...



http://www.outsourcing-pharma.com/Clinical-Development/Pfizer-and-IBM-join-forces-to-develop-remote-monitoring-solutions

Site Close out Visit

Definition

Ensure that all required "**Study Documentation is present"** and will be available for an audit / inspection.

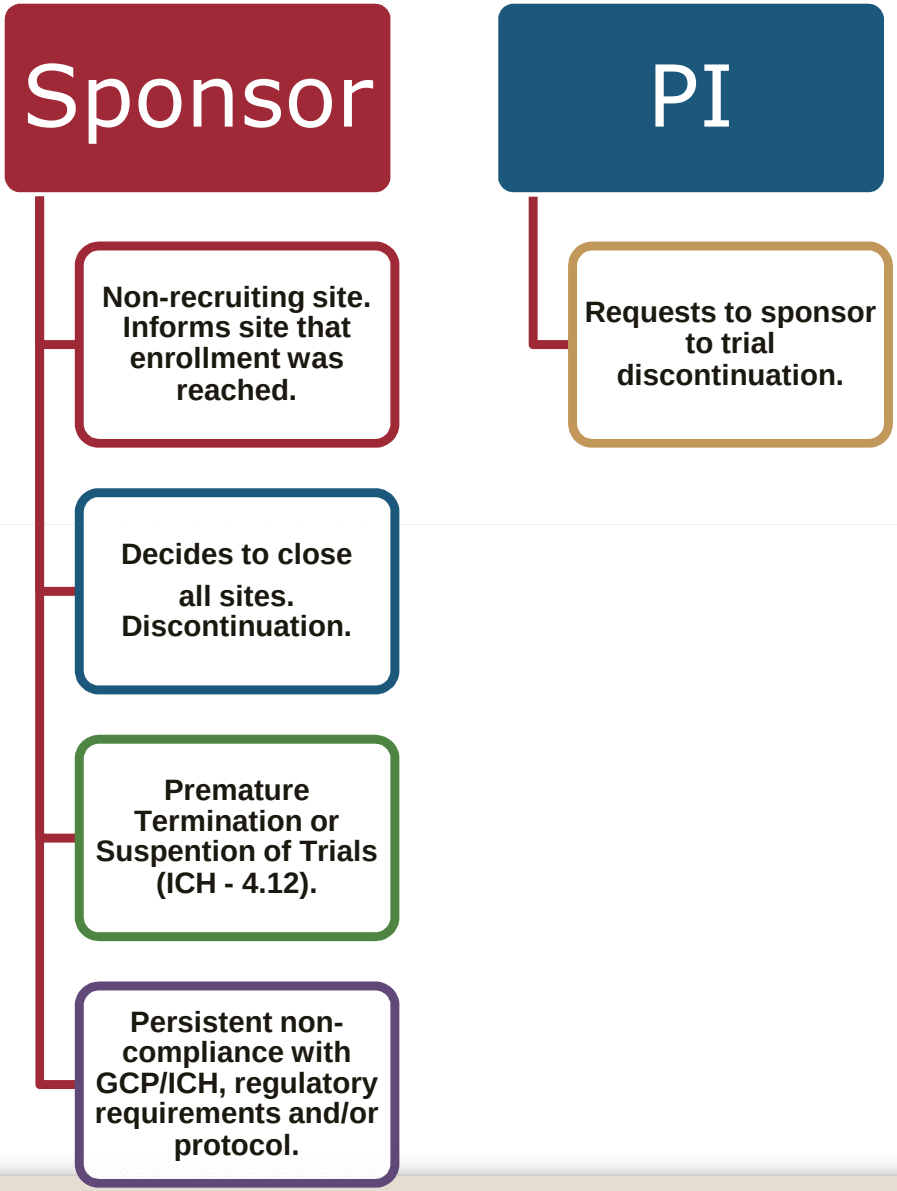
Normal reasons:

- When study completed (all eCRFs monitored & retrieved, ISF completed, PI obligations ok)
- If subject consented
- If Investigational Product at site

Remember !

COV should be conducted in all locations where Site Files & IP were stored (if multiple locations).

Close Out Visit: Exceptions



Close-out Visit

CRA	PI
•**Review eCRF** and inform PI that **passwords were disabled.** • **ISF**: Review all documents, collect originals from ISF to file in TMF. • **Records Retention:** Inform PI and timelines. • **Sign Monitoring Visit Log**	• **IEC Notification** about Study Closure and send them Summary of the trial's outcome. • Inform IEC /Sponsor where **study documents** will be filed and any change after agreement . **(Prevent accidental destruction)** • Inform **responsible person of Hospital labs** / facilities, Financial department about COV (if app).
• Do final **accountability and inventory of IP** and supplies • **Return IP / Supplies** for destruction (or instruct PI to return them) • Collect all **subject samples** (if applicable) • **After COV:** Inform in the Fup letter and Monitoring Report if any pending document. **Do the follow-up until resolution.**	• Notify Sponsor if any **changes in the Financial Disclosure** within 1 year after COV. • Inform Sponsor / CRO in case of **inspections.** • **Register in the Patient Medical Chart & Source Document that study was completed** according to Protocol or a different information in case of early study termination.

Close-out Visit

Non-Recruitment Site the procedures are exactly the same except:

- There will be no eCRF to review.
- All study supplies provided to sites should be removed / returned.

Without On-Site Visit

- No subjects have been enrolled.
- No IP was dispensed.
- All IP & Materials have been returned and properly accounted.
- Sponsor agrees that non-site visit is required.
- COV TC is one option.
- Final close-out letter should be sent to investigator.

Sponsor should ensure:

Study Report was provided to Regulatory Agencies as required by the applicable regulatory requirements.

Close-Out Visit- ICH Guidelines

Records Retention:

- Per GCP/ICH the **Essential Documents** should be retained **at least 2 years after the last approval of a marketing application.**

- Documents retained for a **longer period according to Regulations & Sponsor.**

- **Sponsor informs PI about Records Retention** and when the documents can be **discarded** (in writing).

Trial Registration and Results Submission

Some jurisdictions require that studies are registered

such as on **clintrials.gov** or even **WHO**,

and that results

MUST be shared depending on the jurisdiction within

6-12 months after study closure

(typically on the trial websites).

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

World Health Organization

QUESTIONS?

References

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf

video: https://www.youtube.com/watch?v=re5jy3fuOaw