Trial Conduct & Monitoring of a Clinical Trial: From A to Z

Georges Labaki, Pharm D, MSc, MBA

F-MRI

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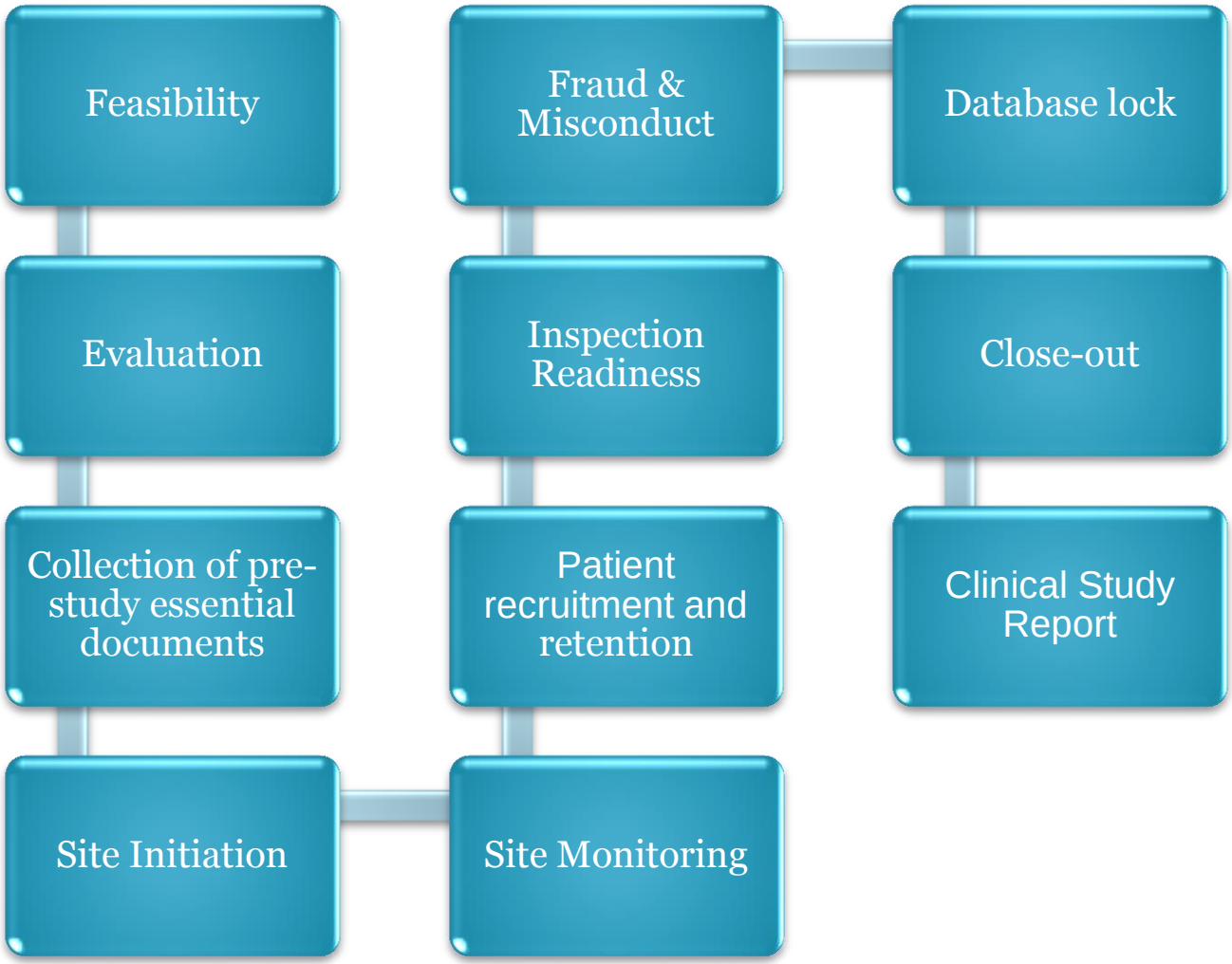
Agenda

- Feasibility
- Evaluation
  - Objectives
  - Prior to SEV
  - During SEV
  - After the SEV
  - Start –up activities
- Initiation
  - Objectives
  - ISF
  - FDF
  - FDA 1572
- Monitoring
  - Objectives
  - Preparation
  - Conduct
  - Post MV
  - MVR Review
- Close-out
  - Reason
  - Procedures
- Fraud & Misconduct
  - Difference between Fraud & Misconduct
  - CRA Responsibilities
  - Prevention
- CRA Communication Skills
  - Training
  - Qualifications


Feasibility
Evaluation
Collection of pre-study essential documents
Site Initiation
Site Monitoring
Patient recruitment and retention
Inspection Readiness
Fraud & Misconduct
Database lock
Close-out
Clinical Study Report

Clinical Trial Feasibility

Evaluation visit

Study Initiation

Study Monitoring

Study Close-out

Clinical Trial Conduct

Clinical trial feasibility

- **Why do Sponsors conduct study feasibility?**

Clinical trial feasibility

Phoenix Clinical Research

Objectives

- **Identify potential investigators:**
  - **Pubmed**
  - **www.clinicaltrials.gov**
  - **WHO website**
  - **Physicians databases**
  - **Physicians associations / Societies**
  - **Networking**
- **Review clinical trial synopsis, protocol & study design**
- **Early identification of issues that may affect patient's recruitment & retention**

Clinical trial feasibility

Objectives

- Identification of competing trials
- From theory to clinical practice
- Good feasibilities can Save sponsors Millions $$$$
- Can either be done remotely or face to face
- Duration: < 30 minutes on average

Clinical trial feasibility

Examples of wrong study design

A Multi-Centre, Phase II, Randomized, Double-Blind, Placebo-Controlled Study to Explore Efficacy and Safety of XXX for the Management of XXX in Subjects with XXXX

Design: When infusion of study drug is terminated, PK samples will be drawn 5, 15, 30 min, 1, 2, 4 and 12 hours after termination of infusion.

Clinical Trial Feasibility

Evaluation visit

Study Initiation

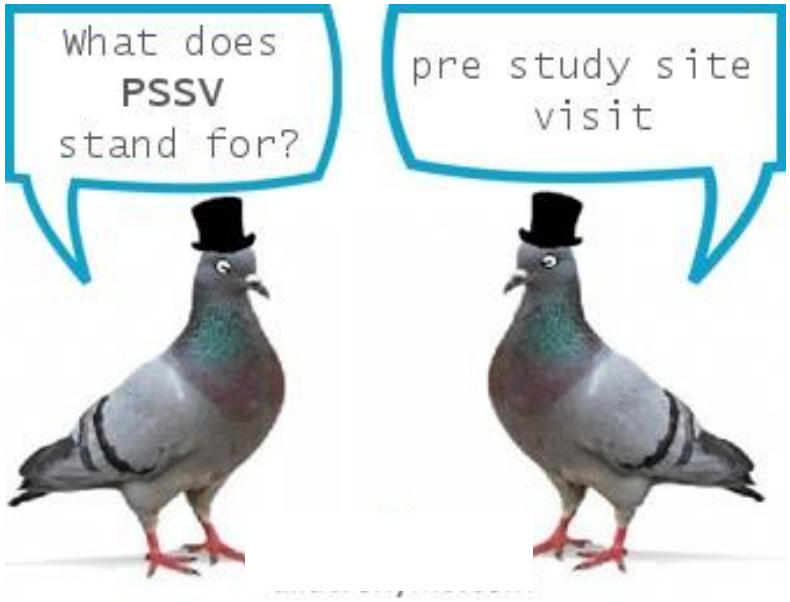
Study Monitoring

Study Close-out

Clinical Trial Conduct

Site Evaluation Visit (EV)

Also named as Site Selection Visits (SSV) or Site Qualification Visits (SQV)



Objectives?

SEV objectives

- Qualifications of the investigator
- Qualifications of the site:
  - University Hospital
  - IEC/IRB availability and requirements
  - Proper set-up, equipment…
  - 24/7…
- Availability of site staff
- Motivation of PI and site staff
- Start-up timelines
- Contracts process

SEV objectives

- Recruitment potential
- Competing trials
- AE reporting
- Source documentation & record retention
- Space requirements (Place for monitoring, ISF storage…)
- Proper IMP storage
- Archival process

Prior to SEV

- Contact the site to schedule the SEV
- Send confirmation email and mention the amount of time required
- Mention documents needed to be collected during PSV (CVs, Lab normal ranges, FDF, signed CDAs, Prot sign page…)
- Prepare the CDA if not done already
- Review the study protocol and study related documents
- Prepare documents to be delivered during PSV
- Prepare checklist of items that need to be discussed during PSV

During the SEV

- Collected signed and dated CDA from the PI
- Collect other required essential documents (CVs, completed FDFs…)
- Review the trial organization and management
- Review the protocol and trial presentation
- Check patients recruitment and follow-up
- Explain trial monitoring & coordination
- Review Investigator's qualifications & responsibilities
- Meet other trial team members
- Tour of facilities

Evaluation Visit Checklist

Investigator

- Qualifications
- Licensure
- Specialty
- CT experience:
- N previous trials
- N similar trials
- Enrollment in previous trials (numbers, time to enroll)
- Previous audits/inspections

Staff

- Study Coordinator
- Other specialized personnel
- Training and licensure
- Experience
- Turnover
- General interest and attitude

Facility

- Appropriate for trials
- Ample storage for study supplies
- Appropriate IMP storage
- Special storage equipment available (-80 freezer…)
- Special equipment available
- Active practice
- Tour offered, taken

IEC / IRB

- Local IRB available:
- Frequency & timing of meetings
- Average time to approvals
- Responsiveness

Laboratory

- Local Lab available
- Necessary tests can be done
- Certification
- Experience with central labs

Protocol feasibility

- Experience with similar studies
- Interest level
- Availability of potential subjects
- Competing studies
- Timing appropriate
- Can attend Inv Meeting

Estimation of patient recruitment

The "Halving Technique"

The Investigator says, "I have 500 patients with the disease of interest in my protocol." your protocol has 5 major exclusion criteria. Cut the 500 in half for each one.

- **For which type of diseases it is easier to assess enrolment potential: chronic diseases or acute diseases?**

After the SEV

- Completion of the SEV Report by the CRA and transmit for review to the Sponsor
- CRA informs the site by email about Sponsor's decision (Go or No Go):
  - If it's a No Go, rationale behind the decision should be provided
- CRA performs and check prerequisites to the sites initiation visit
- CRA sends to TMF the collected documents (electronically or by courier depending on Sponsor's requirements)

Questions about SEV

1. Can SEV be conducted remotely?
2. Can SEV be conducted without prior study feasibility?
3. How long should be the duration of a SEV?

What needs to be done before Site Initiation Visit

1. Submissions for IEC/ IRB/ Competent Authorities

2. Approvals obtained:
   - ✓ IEC/ IRB approval
   - ✓ MOH Approval if applicable
   - ✓ Import License / Export License approval
   - ✓ Other approvals if required

3. Collection of all required essential documents prior to SIV

4. Pre-study visit in case of huge delay between the Evaluation visit and SIV

What needs to be done before Site Initiation Visit

Phoenix Clinical Research

1. **IEC / IRB Submissions package required documents:**

- ✓ Submission Form
- ✓ Study Protocol
- ✓ Informed Consent Forms (Master and site specific)
- ✓ Summary of Consent Form
- ✓ Investigator's Brochure
- ✓ CV of PI
- ✓ GCP certificate
- ✓ Insurance Certificate
- ✓ Patient related documents (diary cards, questionnaires, Emergency card…)
- ✓ Sample CRF
- ✓ Draft contract and budget sheet

What needs to be done before Site Initiation Visit

2. IMP Import License approval

- An approval issued by the MoH authorizing the importation of IMP into its territory.

The required documents for Import License are:

- ✓ Copy of Study Protocol
- ✓ Copy of IRB/IEC approval for each participating site
- ✓ Letter from the PI to the MoH informing them that the study will be conducted under his/her responsibility
- ✓ Order Request from the Hospital Pharmacist stating the product name and quantity needed
- ✓ Original signed proforma invoice for the goods
- ✓ Technical information on IMP

Non-University hospitals in Lebanon need special authorization from the MoH to take part in interventional clinical trials

What needs to be done before Site Initiation Visit

3. Export License

- A permit issued from the authorities to export human biological material for research

The required documents for Export License are:

- ✓ Export request addressed to MoH to be completed per test, site, PI & study; to be signed and dated by the PI and the Hospital Director
- ✓ Copy of IRB/IEC approval per site
- ✓ Copy of the protocol
- ✓ Information required on the request (Template issued by the MoH):
  - ➢ Clinical trial name and reference
  - ➢ Quantity, nature and life period of the samples
  - ➢ Storage conditions for transportation
  - ➢ Consignee name and full address
- ✓ Customs invoice

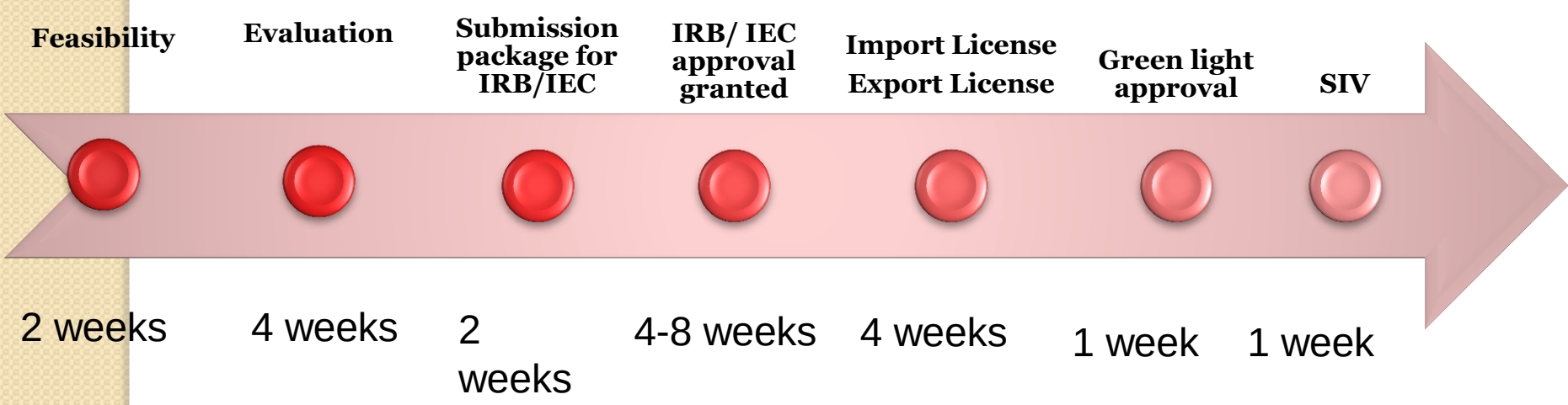
What needs to be done before Site Initiation Visit

Phoenix Clinical Research

4. Greenlight for SIV

- Written IRB/IEC approval
- Insurance Certificate issued
- List of lab normal ranges obtained
- Lab accreditation records obtained
- Import License granted and IMP delivered to the site
- Export license granted
- Protocol/ amendments signature page of PI
- IB AOR signed and dated by the PI
- Signed CTA/ Investigator's Contract
- CV of PI/ site staff
- Signed Financial Disclosure Forms by PI/ Sub-I
- Evaluation Visit Report completed
- FDA 1572 Form completed

In Summary


Feasibility
Evaluation
Submission package for IRB/IEC
IRB/ IEC approval granted
Import License
Export License
Green light approval
SIV
2 weeks
4 weeks
2 weeks
4-8 weeks
4 weeks
1 week
1 week

Investigator's Meeting

- **Why Investigator's Meetings are held?**
- **When is the best timing to organize an Investigator's Meeting?**

Investigator's Meeting

- Although not required by regulation, IM is one of the most important activities pertaining to the conduct of a good trial
- Participants: PI – Sub-I – Study Coordinators – Sponsor Personnel
- Objectives:
  - ✓ Allow participants to get to know each other
  - ✓ Facilitates communication amongst stakeholders
  - ✓ Review the entire study and its conduct
  - ✓ Everyone hears the same thing at the same time
  - ✓ Powerful motivational and training tool

Investigator's Meeting

Timing and Location

- Ideally IM should be held when as many sites as possible are ready to start
- Location: Balance between business and pleasure & centrally located
- Duration: 1 day IM & 1 day CRA training in general

Hints

- Plan a social event
- As a CRA, spend time with your hosts and establish good relationships with your site personnel
- Don't forget Evaluation Form at the end of the meeting

Investigator's Meeting Agenda template

- Welcome
  - Introductions
    - The company (very brief promotion)
    - Individuals and their roles
- Overview of drug development program
- Discussion of the Protocol
- Administration
  - Responsibilities and obligations of the investigator
  - Informed Consent
  - Study documents
- IMP
- Laboratory
- Special Procedures and Forms
- eCRF training
- Closing remarks and questions


KEEP
CALM
AND
TAKE
A
BREAK

Clinical Trial Feasibility

Evaluation visit

Study Initiation

Study Monitoring

Study Close-out

Clinical Trial Conduct

Study Initiation Visit (SIV)

Objectives

- Review the study protocol, processes and procedures
- Ensure all site personnel understand what is necessary to perform the study
- Prepare the site for the screening of the first patient and the official launch of the study at the site

Study Initiation Visit (SIV)

Hints

- Confirmation email needs to be sent by the CRA prior to SIV
- Mainly conducted by the CRA
- SIV may take half-day or even longer for complicated studies
- SIVs can be split into more than one day
- All site personnel who will be involved in the study must attend the Meeting
- SIVs might need to be organized during week-ends
- Make sure all required material & ISF available before the SIV

Study Initiation Visit (SIV)

Hints

- Be well prepared before the meeting
- Plan to arrive to the site in advance
- Arrange for refreshments, coffee and snacks
- Start the Meeting by saying how pleased you are to be there…
- Attendees should know they can ask questions as you go along
- Don’t forget to sign and date the Monitoring Log

Study Initiation Visit (SIV)

Items that need to be covered

- **Detailed discussion of the Protocol including:**
  - Inc / Exc criteria
  - Study Procedures
  - Administration of study Drug
  - IVRS; unblinding…
  - Primary outcome measures, other pertinent details…

- **Drug accountability**
- **AE reporting**
- **(e)CRF completion** (Queries, eCRF against Source Data…)
- **Monitoring Visits** (Frequency, duration, access to medical records…)
- **Regulatory requirements** (Reporting, study update…)
- **Archival**
- **Proper delegation of activities**
- **Investigator's Site File**
- **Audits & Inspections**

Study Initiation Visit (SIV)

What needs to be done after SIV?

- Send an email to the Sponsor informing them about the outcome of the SIV and raised questions that need an answer
- Send a SIV Follow-up Letter about the items discussed during the meeting and answers to the raised queries
- Don't forget to ask the site when they are planning to screen their first patient
- Complete your SIV Report

Investigator Study File (ISF)

- **The Investigator Site File contains the essential documents necessary for the investigator and the research team**

- **Essential documents (ICH/GCP section 8) are those, which individually and collectively:**

  - Permit the evaluation of the conduct of a trial & the quality of the data produced
  - Serve to demonstrate the compliance of the PI, research team and sponsor with the standards of GCP and regulatory requirements
  - When filed in an appropriate and timely manner greatly assist in the successful management of a trial by the investigator
  - Are usually audited by the sponsors independent audit function and inspected by regulatory authorities as part of the process to confirm the validity of the trial conduct and data collection.

ISF Checklist

To be used as a guide only
All documents listed below may not necessarily be applicable to all studies
Where documents are missing, File Note should be included documenting the reason

Section	Details
1	**Protocol and Patient Information** • Current protocol • Previous protocol amendments • Current Patient Information Leaflet (PIL) and consent form • Previous amended PIL and consent forms • Examples of any other written information provided to patients • Copy of advertisement for patient recruitment
2	**Approvals** • Ethics approval for current protocol and any amendments • And any other applicable approvals
3	**Agreements/funding** • Copy of any signed agreements between involved parties • Sponsorship agreement/sponsorship letter • Completed Financial Disclosure Forms • Insurance statement • FDA 172 Form

ISF Checklist

4	Safety • Unblinding procedure for blinded trials • Blank SAE/ Pregnancy forms • Reporting arrangements for SAEs (if not already in the protocol) • Copies of completed SAE forms • Copies of correspondence re SAE from Investigator to Sponsor and/or Ethics • Copy of safety information from Sponsor to Investigator
5	Consent forms • Original consent patient consent forms (or a statement documenting the location if not stored in the ISF)
6	Logs • Patient ID log • Screening log • Signature log

ISF Checklist

7	Research Team – Staff and Training • Signed/dated CV of Investigators, research team, Pharmacy staff… • Delegation log • Evidence of GCP training (if not stated in researchers CVs)
8	Monitoring and Audit • Monitoring log • Monitoring Confirmation / Follow-up letters • Monitoring correspondence
9	Laboratories • Accreditation of all labs used (and updates) • Lab normal values
10	Case Report Forms • Sample copy of eCRF • CRF completion guidelines • 21 CFR Part 11 signed and dated documents
11	Reports • Annual progress reports • Final study report (after completion of trial)
12	General correspondence

Financial Disclosure Form (FDF)

Objectives?

- Identify any potential conflict of interest that could bias a clinical trial
- FDF must be completed for all people listed on the FDA 1572 Form, and their immediate family members
- Collected for the time period of the study and one year following
- FDF to be reported to FDA when the NDA is filed

FDA Form 1572

Definition

The Statement of Investigator, Form FDA 1572 (1572), is an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic.

It should be sign whenever a sponsor selects a new investigator to participate in a clinical investigation that is being conducted under an investigational new drug application (IND) in USA.

Clinical Trial Feasibility

Evaluation visit

Study Initiation

Study Monitoring

Study Close-out

Clinical Trial Conduct

Study Monitoring

Objectives

- Ensure quality and integrity of the data
- To ensure that critical elements, such as written Informed Consents, IMP, ISF are reviewed for accuracy and compliance
- To train (or re-train) personnel

Poor study monitoring is probably the largest single contributor to inferior study quality

Study Monitoring

Monitoring Strategy

- Good communication (Written and Verbal) (Avoid typo mistakes)
- Monitoring Frequency
  - ✓ Complexity of the protocol
  - ✓ Disease being evaluated
  - ✓ Experience of Investigator/ staff and site performance
  - ✓ Number/ rate of enrolled subjects
  - ✓ Sponsor monitoring SOPs
  - ✓ CRA experience and effectiveness
- MV be done ASAP after 1st Pt screened **and** 1st Pt treated
- Regular visits to the site even if no patients enrolled
- Spend minimum of 4 hours at site for each MV

Study Monitoring

Preparation for a MV

5Ps: Proper Preparation Prevents Poor Performance

- Send Confirmation Letter or email
- Review your previous report/ SIV Report and check ongoing items
- **Prepare checklist**
- Review the MV Report template
- CRA Travel kit: Post-It®, pens, note pad, USB, snacks, water…
- Internet USB key
- Turn on your Out Of Office autoreply the evening before

Study Monitoring

Preparation for a MV

- CRA Travel File Content:
  - Personal notes
  - Copies of last MV Reports
  - Study progress/enrollment logs
  - Key study documents:
    - ✓ Protocol
    - ✓ Monitoring Plan
    - ✓ CRF completion Guidelines
    - ✓ Latest drug shipment Forms
    - ✓ Blank copies of ICFs, diary cards….
  - Pertinent correspondence
  - Latest released SUSARs

- Wear appropriate business attire and always arrive on site at time or bit earlier

Study Monitoring

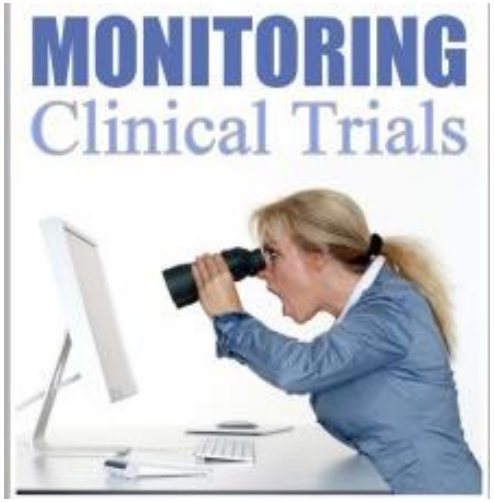
MV conduct at the site

- Avoid checking your emails when at site and focus on your monitoring tasks
- If possible, spend few minutes with the PI at start of the visit; give him latest study update and what you will do at the site today
- Good collaboration & relationship with Study Coordinator
- No site politics
- Exit visit with the PI

Study Monitoring

Recommended tasks to be done by order of priority

1. Serious Adverse Event review
2. ICF review
3. Checking protocol adherence
4. eCRF review and Source Document Verification (SDV)
5. Queries and error correction
6. IMP review and accountability
7. Review of lab samples
8. ISF review



Study Monitoring

Recommended tasks to be done by order of priority

1. Serious Adverse Event review

- Ask the PI, Sub-I & SC if there has been any SAE from last visit
- If yes, make sure the SAE was reported to Sponsor within 24 h
- In both cases, you should examine the information available about the events by reviewing medical charts and supporting documents

Study Monitoring

Recommended tasks to be done by order of priority

2. Informed Consent review

- Check new written ICFs from last visit
- Make sure the correct ICFs & versions are signed & dated
- Check date/time against date/time subject started the study
- Pay attention about the hand-written and pencil used
- Site personnel must never date subject's signature
- Site personnel must never complete witness section or Legally Authorized Representative section
- If the ICF has changed (e.g. Prot Amdt), make sure all new and ongoing subjects will sign it and date it
- Periodically, go back and check all ICFs at the same time

Study Monitoring

Recommended tasks to be done by order of priority

3. Checking protocol adherence

- Subject Eligibility: Did he/she met all Inc/Exc criteria?
- Randomization: randomized to the correct subject number and did he or she received the appropriate IMP package(s)?
- Procedures: have they been followed?
- Visit schedule and windows: Were they respected?
- Drug dispensing:
  - ✓ Was the subject given the appropriate drug and amount at each visit?
  - ✓ Did the subject return any unused drug?
  - ✓ Was the subject drug compliant?

Study Monitoring

Recommended tasks to be done by order of priority

4. eCRF review and Source Document Verification (SDV)

SDV involves checking data recorded in (e)CRF against data found in available SD, including patient charts, lab reports & other supporting docs

- Take most of your time
- It's always recommended to start with the new enrolled subjects since last MV
- Check thoroughly the whole medical chart of the subject before doing SDV
- Finish one subject at a time
- Check one page after the other
- Get used to PI hand-written style

Study Monitoring

Recommended tasks to be done by order of priority

4. eCRF review and Source Document Verification (SDV) Objectives (Contd)

- Verify that the patient exists
- Data entered in (e)CRF is consistent with information found in SD, which verifies integrity of data

✓Any data entered on (e)CRF should be mentioned in the SD

✓Occasionally, printed CRF can be considered as SD in some cases (scales…)

✓When it's not documented, it's not done

✓What happens when there's discrepancy between CRF & SD?

✓What amount of data need to be SDV?

Study Monitoring

Recommended tasks to be done by order of priority

5. Queries & error correction

- **No Overwriting**
- Corrections need to be done according to **ALCOA** guidelines
- Corrections are made by drawing a line through incorrect entry, making correct entry, dating and initialing it:

  Date 14/Jan/~~2013~~ 2014 GL 10/Jan/2015
- If CRA can't sort out discrepancies & errors during his MV, queries need to be generated
- In general, errors have the tendency to decrease during the study conduct

ALCOA Guidelines

Attributable

It should be clear who documented the data

Legible

Readable and signatures identifiable

Contemporaneous

The information should be documented in the correct time frame along with the flow of events

Original

Earliest record

Changes and / or corrections should not obscure prior entries.

Accurate

eCRF should be a valid representation of the source data.

Study Monitoring

Recommended tasks to be done by order of priority

6. IMP review and accountability

- IMP accountability need to be done at least every other MV
- Temp Logs need to be checked at every MV
- If possible, provide the site with USB thermometer
- IMP always needs to be stored properly (secured area with limited access, refrigerated conditions…)
- Do return used IMP to local Depot/Sponsor whenever possible
- Destruction of used/unused is usually done at the end of study
- Transfer of IMP from a site to another follow very strict guidelines and depends on Sponsor's SOPs

Study Monitoring

Recommended tasks to be done by order of priority

7. Review of lab samples

- Ensure all human samples collected during the study are being done properly
- Avoid delays in shipment of human samples to central lab
- Collect temp logs of the freezers where samples are stored
- Collect maintenance documents and calibration certificates of freezers, centrifuges, ECGs……
- Inform local courier in advance about samples shipment and order of dry ice
- Some Sponsors require lab personnel to be IATA certified

Study Monitoring

Recommended tasks to be done by order of priority

8. ISF review

- Don’t forget to sign & date the Monitoring Log at every site visit
- ISF to be reviewed at every other MV at least
- Make sure the ISF is stored in secured conditions
- Use a proper checklist
- Make sure all approvals and updated documents are correctly filed
- Don’t forget to file your Conf Letter and FU letter and any relevant communication with the site

- As CRA, you should be very attentive to confidentiality
- No study record, other than ICF should identify the subject
- As a CRA, you have the obligation to help protect the confidentiality of all study subjects
- Once you're done with your MV, make sure all study documents are properly filed and no document kept at PI desk

Study Monitoring

Tasks to be done at then end of the visit and after

- Plan ahead for the next MV
- Write ASAP your MV Report
- Debrief the PI about your findings
- Resolve as many queries as possible
- Thank the site staff for their help, support and time during the visit
- Send a MV FU Letter

Study Monitoring

Phoenix Clinical Research

Quizzes

Monitoring Visit Report Review

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The purpose of this session is:

- To reach a consensus on what should be contained in a monitoring visit report
- Give general guidelines while still allowing for individual style
- Give examples of what to do (or not to do…)

Monitoring Visit Report Review

Informed Consent:

1. **Are Informed Consent procedures satisfactory?** [Help] *Please comment on the adequacy of informed consent administration procedures (proper documentation, version used, location, pt given copy, etc)*	Yes	No	Not done	Not applicable
	X			

A cumulative log is attached.

Comments: All iCF's have been appropriately signed.

Monitoring Visit Report Review

Informed Consent:

1. **Are Informed Consent procedures satisfactory?** [Help] *Please comment on the adequacy of informed consent administration procedures (proper documentation, version used, location, pt given copy, etc)*	Yes	No	Not done	Not applicable
	X			

Comments:

During the monitoring visit after the request of study management to perform a Quality Check Confirmation at the site the informed consent of all patients were checked. Please see cumulative log attached to the end of this report.

All ICFs are adequate. The correct versions were used:

- version 1 dated 07/FEB/2005, reviewed 23/Aug/05 approved by the EC on 18/May/05
- version 2 dated 23/SEP/2005, reviewed 15/Dec/05 approved by the EC on 16/Jun/06

Amendment 3 was approved by the local EC of the site on the 16th of June and the new ICFs were couriered to the site on the 3rd of July.

The checked ICFs were completed correctly, the patients have signed and dated the document, and a copy was given to them. Minor error that patient 065-0001 put her signature on version 1 and only her initials on version 2. The investigator was requested to ask the patient during the next visit to sign version 2 with the signature.

All 9 signed ICFs are attached to the appropriate section of the Investigator File, except version 2 for patient 069-0001.

Please see cumulative log attached at the end of this report.

Monitoring Visit Report Review

Informed Consent:

1. **Are Informed Consent procedures satisfactory?** [Help] *Please comment on the adequacy of informed consent administration procedures (proper documentation, version used, location, pt given copy, etc)*	Yes	No	Not done	Not applicable
	x			

A cumulative log is attached.

Comments:

PC wrote Notes-To-File for subjects 0002/TJW, 0005/GJT, and 0011/RPH regarding the Informed Consent deviations that were noted during my last visit.

- ***0002/TJW**: The revised ICF was inadvertently not presented to the subject at the Week 24 on 21-Sep-04, and there is no documentation that the subject signed the form at a later date.*
- ***005/GJT**: Dr. Chang saw the subject for the consent form review on 04-Oct-04, but he inadvertently did not sign the form. AG signed the form on 11-Oct-04 although he did not participate in the consenting process.*
- ***0011/RPH**: AG did not see the subject at the Study Day 1 visit on 17-Sep-04, although he determined that the subject met all eligibility criteria prior to the visit. He signed the form on 20-Sep-06, although he did not participate in the consenting process.*

AG was informed of these findings in my follow-up letter of 23-Oct-06.

Monitoring Visit Report Review

Informed Consent:

Pt. Number	Pt. Initials	IC Version (1) App'd: 14 Jun 2004	HIPPA form: 14 JUN 2004	IC Version (Amendment5) App'd: 27 AUG 2004	IC Version (for natalizumab) Approved: 18-Feb-2005	IC Version (annual renewal) Approved 28-Apr-2005	IC Version (6) App'd:	Comments
		Date Signed bySubject						
0001	GAC	14-Jul-04	14-Jul-04	11-Oct-04	will sign same version with new expiration date	6/7/05		
0002	BAR	21-Jul-04	21-Jul-04	01-Nov-04	will sign same version with new expiration date	7/15/05		
0003	JJP	NA	16-Nov-04	16-Nov-04	04-Mar-05	5/24/05		
0004	MAL	NA	23-Nov-04	23-Nov-04	07-Mar-2005	6/1/05		

Monitoring Visit Report Review

Phoenix Clinical Research

CRF Review

Monitoring Visit Report Review

CRF Review

Monitoring Visit Report Review

CRF Review

1. **Were CRFs and source documentation reviewed?** [Help] *Please provide details regarding adequacy of source documentation, status of monitoring notes left at the site, etc.*	Yes	No	Not done	Not applicable
	X			

Comments: Eighteen Subjects were enrolled in this study. An additional subject transferred from Dr. Fox's site in Round Rock Texas. All subjects have either completed or withdrawn from the study. All CRFs have been reviewed with the exception of 28-Day Follow up visits that remain for subjects 015, 016,amd 018.

Subject 014 JMR: Week 96, Cumulative sections, Termination, 28 day follow-up

Subject 015 KMK: Week 96, Cumulative sections, Termination, (Pharmacogenomic blood draw complete.

Subject 016 JMR: Week 96, Cumulative sections, Termination, (Pharmacogenomic blood draw completed), subject was experiencing an MS attack during the week 96 visit. The exacerbation page was not completed as the e site was awaiting the exacerbation to resolve.

Subject 018 DAH: Cumulative sections, Termination, (Pharmacogenomic blood draw completed).

Monitoring Visit Report Review

Protocol Deviation

1. **Were any protocol deviations noted?** [Help] *Please provide details not contained in attached log. Forward the complete list of deviations to the CTL.*	Yes	No	Not done	Not applicable
	X			

Microsoft Excel Worksheet

Comments:

- Patient 069-0002 had her scheduled SD1 visit on 17/May/06 and Week 13 visit on 03/Aug/06, instead of 09/Aug/06, thus Week 13 visit was out of the acceptable 84 ± 3 days visit window after SD1 visit. The patient performed all visit specific tasks on 03/Aug/06 but started the last study drug cycle on the scheduled date 09/Aug/06.

Monitoring Visit Report Review

SAEs

Pt. Number	Pt. Initials	DER #	Date Reported to IRB / IEC	Brief Description of Event and Follow-Up
0003	*GRA*	*230000S04USA*	*9/27/04*	*Subject terminated secondary to severe depression.*

Monitoring Visit Report Review

Phoenix Clinical Research

ISF

Monitoring Visit Report Review

ISF

1. **Was the Investigator File reviewed?** [Help] *Please provide details regarding changes to staff, outstanding items from the IF, etc.*	Yes	No	Not done	Not applicable
	X			
Comments: IF was reviewed and everything is complete.				

Monitoring Visit Report Review

ISF®

1. **Was the Investigator File reviewed?** [Help] *Please provide details regarding changes to staff, outstanding items from the IF, etc.*	Yes	No	Not done	Not applicable
	X			

Comments:

The Monitoring Log was signed. There have been no changes to study staff. Amendment # 6 was submitted to the IRB and will be reviewed this week. Per the IRB a revised ICF was not required since none of the subjects will participate in the Pharmacogenomics.

The SECC was signed on 12 June 2006 and sent to Serono.prior to this visit.

The Amendment 6 signature page was signed 26 June 2006 and sent to Serono prior to this visit.

Both forms are present in the IF.

All IND Safety Reports have been submitted to the IRB with the exception of the last 2 (230001EO6ARG and 230002EO6FRA). Since the IRB does not require submission of these reports unless a change to the ICF is needed, they will be submitted with the final report.

Monitoring Visit Report Review

Phoenix Clinical Research

ISF

Please ask your CML to provide you with the Investigator File Tracking Log

Monitoring Visit Report Review

Phoenix Clinical Research

LABs

1. **Were laboratory and specimen handling procedures reviewed?** [Help] *Please provide details regarding changes to lab facility, personnel or normal values, storage/shipment of specimens, certification expiration, etc.*	Yes	No	Not done	Not applicable
	X			

Comments:

A central laboratory (Esoterix) is used. All reports were reviewed by CB in an appropriate time frame and were signed and dated and placed in the specific patient chart. They were available for my review. All blood samples have been shipped per Protocol.

1. **Were laboratory and specimen handling procedures reviewed?** [Help] *Please provide details regarding changes to lab facility, personnel or normal values, storage/shipment of specimens, certification expiration, etc.*	Yes	No	Not done	Not applicable
	x			

Comments:

Ambient lab samples are being collected, processed, and shipped according to Quintiles specifications.

The site is not participating in the PK portion of the trial.

Monitoring Visit Report Review

Phoenix Clinical Research

LABs

1. **Were laboratory and specimen handling procedures reviewed?** *Please provide details regarding changes to lab facility, personnel or normal values, storage/shipment of specimens, certification expiration, etc.*	Yes	No	Not done	Not applicable
	X			

Comments:

Noelia Becerril (study nurse) has a good control of the frozen samples that have already been sent to Esoterix and the ones that are stored at site. The samples currently stored at site are: week 72 primary samples and back up samples for week 48 and week 72 visits.

She is going on maternity leave in October but she thinks she will be able to organize the 2 shipments of frozen samples before (the last W96 visit is on the 5th of October)

What it has not been done correctly is the record of storage temperatures. At the beginning of the study was done more or less correctly but since June 05 the temperatures have been recorded very sporadically (there are a few records for December 05, February and March 06. Then there is a measurement in 4/April/06 and no more since then). That means that for those intervals of time we only have the maximum and minimum storage temperatures for the whole period (always below –20ºC)

It seems that at the beginning of the study the lab staff accepted this task but when the person that started to record the temperature in the logs left the lab they stopped doing it. The study nurse said that she had asked them in several occasions and they had told her they were doing it but when we went to check and collect the temperature logs during this visit we found out that they had done it very occasionally.

We commented this problem with Dr. Izquierdo who immediately called the lab and asked them to assign a person for this task (Rocío Suárez), so I hope that at least from now on they will record the temperatures (at least during the week). The file note that had been left for PI's signature was changed to document everything in one note. It was signed by the study nurse and Dr. Izquierdo.

I checked again the characteristics of the freezers and they told me that the freezer has a back-up system in case there is a shortcut and there is an alarm that rings when the temperature reaches a pre-determined value (-15ºC), so if there had been any problem we would know it.

Monitoring Visit Report Review

IMP

1. **Were Investigational Product & other study supplies reviewed?** [Help] *Please provide details regarding drug accountability, storage conditions, destruction/return of IP, etc.*	Yes	No	Not done	Not applicable
	√			

Comments: IMP is stored in a limited access locked, temperature monitored IMP storage locker/room. The temperature log is current for the IMP storage area. The pharmacy signature log is complete. The site has received IMP shipments with TempTale4 recordings exceeding IMP temperature tolerance. This information was forwarded into Liz Gedney at Serono for submission to the Qualified Person.

Monitoring Visit Report Review

IMP

1. **Were Investigational Product & other study supplies reviewed?** [Help] *Please provide details regarding drug accountability, storage conditions, destruction/return of IP, etc.*	Yes	No	Not done	Not applicable
	X			

Comments: Thirty-six wrappers of lot 67B0604E, which were dispensed to subject 001 on 26 Oct. 2005, (that were not available for inventory during 14 April monitoring visit) were inventoried and destroyed. An additional 36 wrappers of lot Y00B9200, dispensed to subject 001, were inventoried and destroyed.

As subject 001 discontinued the study, all remaining non-dispensed drug was collected from the site and sent to MDI. Nine kits, (108 syringes) were returned. All drug has been accounted for with ample documentation, No drug remains on site or in the subject's possession.

Appropriate destruction/return forms will be submitted with this report.

Monitoring Visit Report Review

Phoenix Clinical Research

IMP

	Yes	No	Not done	Not applicable
1. Were Investigational Product & other study supplies reviewed? [Help] *Please provide details regarding drug accountability, storage conditions, destruction/return of IP, etc.*	X			

Comments:

BTM completed the authorization section of the drug accountability logs and verified the destruction of used returned syringes. Unused returned drug was sent to MDI.

There is currently no Rebif or Copaxone in stock. No subjects have used or unused drug in their possession.

The following drug was destroyed on site:

Rebif-lot # 67B1710E-82 used syringes

Rebif-lot # RB448A-71 used and 1 defective unused syringes

Copaxone-lot # 538242-167 used syringes

Copaxone-lot # unknown-175 used syringes

The following unused drug was returned to MDI:

Copaxone lot # 538242-90 syringes

Rebif lot # RB448A-14 syringes

Following is a summary of drug dispensing/returns:

Subject # 0011-dispensed 180 syringes of lot # 538242-returned 37 unused and 175 used syringes on 8/10/06

Subject # 0012-dispensed 72 syringes of lot # RB448A-returned 72 used syringes on 9/21/06

Subject # 0013-dispensed 60 syringes of lot # RB448A-returned 14 unused syringes on 9/6/06

*Subject # 0013-dispensed 12 syringes of lot # 67B1710E-returned 82 used syringes on 9/27/06 **there were returns from other visits included here but unable to ascertain which visits and which lot #'s-there are 28 syringes that cannot be accounted for-per subject there are NO used or unused syringes at home.*

*Subject # 0014-dispensed 180 syringes of lot # 538242-returned 53 unused and 167 used syringes on 8/18/06. **per source note-170 dosing days between visits (3 missed doses)-164 empty dose packs returned and 53 unused returned-3 dose packs thrown away in error.*

Monitoring Visit Report Review

IMP

- In order to simplify the report and keep an accurate log, please use the IMP Accounting Log and attach it to your report.
- If attached, then the only comment required would be to "see attached log for drug accounting".
- The only exception would be for issues found surrounding IMP (i.e. temperature deviations, improper kit dispensed, issues with blinding, IVRS, etc)


take a
COFFEE
BREAK
you deserve it

Clinical Trial Feasibility

Evaluation visit

Study Initiation

Study Monitoring

Study Close-out

Clinical Trial Conduct

Study Close-out

Reasons

- **Study complete and finished**
  - Enrolment has stopped
  - All subjects completed their study-related activities
  - Data complete and correct

- **Studies may be terminated early for both positive and negative reasons**

Study Close-out

Positive reasons for early study termination

- **IMP so beneficial that it won't be ethical to conduct a trial during which Pts might not be receiving active treatment**
- **Overall enrollment met in the trial; so all sites are being closed even if they did not complete the site enrollment goal**
- **Statistical stopping criteria were met and endpoint reached**

Study Close-out

Phoenix Clinical Research

Negative reasons for early study termination

- IMP unsafe
- IMP not effective
- Not possible to find and enroll sufficient study subjects
- Potential product not viable for marketing
- Problems in manufacturing or product stability
- Company run out of funds
- Change of strategy
- Protocol too difficult to execute
- PI loses interest in the trial
- Compliance or other problems at the site

Study Close-out

Closeout procedures

- **eCRF:**
  - ✓ All data verified and frozen
  - ✓ All queries answered and closed
  - ✓ Database lock
- **Drug accountability**
  - ✓ Final inventory done
  - ✓ All study drug packaged and returned to Sponsor or for destruction
  - ✓ Drug Inventory Forms filed in ISF

Study Close-out

Closeout procedures

- **ISF**
  - ✓ **Full review of ISF**
  - ✓ **Use a checklist to ensure that nothing is overlooked :**
    - All approvals & re-approvals
    - All ICF versions filed….
    - Amendments
    - Latest IBs & all AOR
  - ✓ **Double-check all signed ICFs**
  - ✓ **If applicable, file Pharmacy File & Lab File in the ISF**
  - ✓ **Put outer label for every file: Do not destroy before ….**
  - ✓ **Finally, make sure the ISF is archived**

Study Close-out

Closeout procedures

- **Final Report to IRB/IEC**
  - ✓ **Enrollment summary (n enrolled Pts, drop-outs…)**
  - ✓ **Adverse Events summary**
  - ✓ **Any other requested information from IRB**
  - ✓ **Provide copy of Report to Sponsor and file the Report in ISF**
- **Administrative issues**
  - ✓ **All outstanding payments resolved**
  - ✓ **Unused study material returned or destroyed (lab kits…)**
  - ✓ **Other provided material retrieved unless stated otherwise (laptop, weight scale….)**
  - ✓ **Keep study records as long as possible**

Study Close-out

Closeout procedures

- **Close-out Letter**
  - ✓ **Thank the site for their participation; include everyone in the email you send to the site staff**
  - ✓ **Mention about potential audits & inspections**
  - ✓ **Publication policy**
  - ✓ **ISF storage and duration of storage**
  - ✓ **Medical records not to be destroyed**

- **Final Visit Report**


FRAUD
SCIENTIFIC
MISCONDUCT

Fraud and Misconduct

Definition

- Intentional recording and /or reporting of false or misleading information or data pertaining to a study or a business activity
- To knowingly , willingly and repeatedly fabricate statements , data or information in order to deceive.
- Fabrication of data is deliberately falsifying data or creating fictions data to deceive.
- Including withholding of data

Fraud and Misconduct

Phoenix Clinical Research

Who commits fraud?

- Investigators
- Study coordinators
- Data management personnel
- Lab personnel
- IRB staff
- CRAs and sponsor personnel
- FDA

Fraud and Misconduct

Prevalence of fraud

- Difficult to determine but still considered rare
- Reported to significantly impact 1-5% of pharmaceutical clinical trials – F. Wells, *Reuters Health, January 2002*
- Only ~3% of FDA inspections uncover serious GCP violations resulting in Warning Letters

Fraud and Misconduct

Phoenix Clinical Research

Consequences of Fraud

- *Sponsor* – Data validity compromised, submission jeopardized, additional costs
- *Investigator* – Penalties, legal expenses, disqualification/prohibition, license revocation, incarceration, ruined career
- *Institution* – Lawsuits
- *Subject* – Safety at risk, loss of trust in clinical trial process
- Fraudulent investigators are often used by multiple sponsors on multiple trials
- A small number of investigators can have a broad impact on many NDA submissions
- One fraudulent investigator, Dr. Fiddes, was involved in 91 submissions with 47 different sponsors

Fraud and Misconduct

Scientific Misconduct

Any significant non compliance of ICH GCP

- Failure to comply with regulatory regulations contractual requirements protocol requirements, company policies and SOPs
- Does not include honest errors or differences in opinion or judgment of data or isolated inadvertent mistakes
- Many sponsors now are black–listing investigators with serious non compliance issues

Fraud and Misconduct

Possible Warning signs of fraud at site

- Information that is omitted on purpose that could have influence on the outcome of the study
- SAEs not being reported or downgraded
- Making patient records unavailable at visits
- Removing subjects from study for no reason
- Changing lab results
- Copying patient CRFs for another subject
- Creating fictional patients

Fraud and Misconduct

Possible Warning signs of fraud at site

- Lost or not performing lab results taking place more than usual
- Results that are very similar to protocol expectations
- Not as many findings and SAEs as other sites
- Changes in diary cards , very close hand-writing on several consents forms
- All source records & CRFs completed with the same pen
- Signatures that don't match with other documents for the same patient
- Questionable subject visit dates (Weekends, holidays, staff vacations)
- Repeated data for several patients

Fraud and Misconduct

Possible Warning signs of fraud at site

- High staff turnover
- Staff are disgruntled, fearful, anxious, depressed, defensive
- High pressure work environment
- Obsession with study payments
- Absent investigators
- Lack of GCP training
- Unusually fast recruitment

Fraud and Misconduct

Responsibilities of the CRA

Altough none of the above proves that there is fraud or misconduct at a site , the monitor should always be very aware of all the signs and follow them closely during each visit

Fraud and Misconduct

Responsibilities of the CRA

- Try to determine the standard method of keeping records at the site for the study protocol
- Verify the existence and accuracy of the source date against what is recorded in the CRF
- Any other records that exist regarding data collected must be monitored
- Try to determine if any records or data are missing and if so, request this from the PI or site staff
- Monitor should be as observant as possible for any visible signs

Fraud and Misconduct

Responsibilities of the CRA

- Always question why there is missing information at the site
- Do not accept **NO** as an answer to access source notes
- Make sure everything is documented at each visit and in the MV report

Fraud and Misconduct

Suspected Fraud

- Do not accuse site of anything
- Document factual findings in the MV report
- Inform CPM and Lead CRA of suspicions

Fraud and Misconduct

Strategies to Reduce Fraud

😐 Effective clinical investigator education followed by specific training programs leading to certification thus establishing a standard

☹ Require sponsors/CROs to adequately educate and train CRAs to a very high standard before allowing them to monitor a clinical investigation

Fraud and Misconduct

Strategies to Reduce Fraud

- To attract the highly qualified Investigators, make the investigator selection process more competitive before awarding the clinical trial
  - Thereby enhancing the low prestige associated with new drug trials.

- As part of the selection process, the investigator should complete an application detailing strengths, experiences, education, etc.

Fraud and Misconduct

Strategies to Reduce Fraud

- Limit the individual clinical investigator's participation in clinical research that is consistent with
  - ✓ The size of his/her practice
  - ✓ Training and experience

- To ensure the sponsor is doing all it can to effectively monitor a trial and encourage quality standards in each study, FDA to penalize the sponsor for the misconduct of its investigators

Fraud and Misconduct

Fraud in Clinical Research Notable Cases of Misconduct & Fraud in the United States

Summerlin 1974	Darsee 1981	Breuning 1987	Bak 1990	Singhal 1991	
Straus 1978	Aronow 1983	Berger 1988	Van Thiel 1990	Santo 1991	Borison 1997
Soman 1979	Slutsky 1985	Garfinkel 1989	Terry 1990	Demedluk 1991	Diamond 1997
Cort 1980	Glueck 1986	Stahl 1989	Francis 1990	Rosner 1992	Fiddes 1999
Long 1980	Milanese 1986	Mitchell 1989	Naito 1991	Fogari 1993	
Spector 1981	Imanishi-Kari, 1986	Rincover 1990	Eagan 1991	Pauson 1993	

Fraud and Misconduct

Fraud in Clinical Research Notable Cases of Misconduct & Fraud in the United States

Robert Fiddes, MD – "Of Mice and Men", 60 Minutes, April 1, 2001

Fraud and Misconduct

Fraud in Clinical Research Notable Cases of Misconduct & Fraud in the United States

Richard Borison, MD
"Drug Money,"
48 hours,
July 31, 2000

Fraud and Misconduct

Fraud in Clinical Research Notable Cases of Misconduct & Fraud in the United States

Richard Borison, MD
"Drug Money,"
48 hours,
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Fraud and Misconduct

Fraud in Clinical Research Notable Cases of Misconduct & Fraud in the United States

Bruce Diamond, PhD – "Drug Money," 48 hours, July 31, 2000

Fraud and Misconduct

Fraud in Clinical Research Notable Cases of Misconduct & Fraud in the United States

Paul Kornak – "Abuses Endangered Veterans in Cancer Drug Experiments," New York Times, February 6, 2005

Fraud and Misconduct

Phoenix Clinical Research

How to Prevent Fraud in Clinical Research?

Assurances:

- Qualified personnel
- Adequate and dependable resources
- Adequate records and documentation
- Adequate study subject accrual rate
- Compliance to protocol
- Compliance to regulations and ethics

Fraud and Misconduct

How to Prevent Fraud in Clinical Research?

Assurances:

- Efficient and timely communication
- Understand that clinical research is a collaboration
- Efficient and expert monitoring of the clinical site
- Adequate education of the site and constant
- Reinforcement of commitments

CRA Communication Skills

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CRA Communication Skills

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Being a CRA

- Main link of communication between the Study Site and the Sponsor.
- The CRA is an important entity to the project team and the clinical trial essentially revolves around the CRA.

CRA Communication Skills

CRA Training

The moment a CRA is recruited by a Pharma company/CRO, they should be thoroughly trained on:

- ICH-GCP
- SOP of Pharma Company / CRO
- On - site training

CRA Communication Skills

CRA Training

However, is this enough ?

CRA Communication Skills

CRA Training

The CRA should also know how to handle:

- The Principal Investigator
- The study team
- The site staff
- The most important : conduct of the clinical trial at that site

CRA Communication Skills

The CRA should understand that there are certain other qualities, which in a sense may be considered secondary most of the times, but are actually essential

- Building relationships with the key study staff.
- Good rapport with people

CRA Communication Skills

Site Related Issues

- Site related issues could be perceived as minor at the beginning of the study but can magnify in importance during the course of the study.
- CRAs should know how to analyze any study-related risks and challenges:
  - ✓Interpersonal issues with the Investigator/site team
  - ✓Study finances
  - ✓Lack of expertise in logistic handling
  - ✓Deficiencies in training
  - ✓GCP non-compliance

CRA - Investigator relationship may last for many years: Protect it!

CRA Communication Skills

Phoenix Clinical Research

Qualities required for being a good CRA

- Self-confident, flexible and adaptable to change.
- Able to operate through relationships that are built on trust, respect and loyalty.
- Avoid becoming over-friendly such that the behavior compromises the standards of the trial. In such case, the CRA could be held responsible if problems occur.
- The CRA should therefore be able to maintain an air of friendly professionalism in all aspects of their work.

CRA Communication Skills

Qualities required for being a good CRA

Good Communicator

- Good interpersonal skills
- Able to build a rapport with the study team members at the site.
- Ability to convince the Investigator: "I am right as per the regulations"
- Investigators will not trust CRAs who appear to be more interested in themselves rather than in trying to be of service to either the investigator or the study staff.

CRA Communication Skills

Qualities required for being a good CRA

Good Communicator

- **Avoid :**

- ✓ The tendency to give answers too quickly
- ✓ Not paying heed to what Investigator wants to say
- ✓ Not offering solutions to problems
- ✓ Appearance of being clever and witty
- ✓ Do not weight on being a good speaker, but also weight the ability of being a good listener
- ✓ Being emotional

Earning trust is an activity that can be managed and improved

CRA Communication Skills

Qualities required for being a good CRA

Good Communicator

- ✓ Simply writing exhaustive FU letters and reports is not an effective way of communicating
- ✓ FU letters & Reports should be focused and capture all the points discussed with the site team, your findings, and a corrective action plan for the site (relevant SOP to be followed)
- ✓ The Investigator is a **Clinician First** and he must give preference to his patients. In a sense, the conduct of the clinical study is secondary
- ✓ The monitor should understand how, in the limited time span, maximum output from the study team could be obtained
- ✓ Respect the Investigator's time and commitments. In return the CRAs will be better appreciated by the Investigator for their clinical study

CRA Communication Skills

Qualities required for being a good CRA

Good Observer

- The job of a CRA involves not only monitoring source files, making notes from the patients files, reviewing CRF & identifying typographical, documentation errors, but, observing any mistakes and identifying any patterns in a logical manner.
- Logical SDV helps identify adverse events, missing concomitant medications, errors in IMP accountability.
- By being proactive very serious problems can be avoided.

CRA Communication Skills

Qualities required for being a good CRA

Pro-Activity

- Update about the overall progress of the study in relation to equivalent work proceeding at the other study sites.
- Update the study team after returning from any site visit.
- Discuss about site related issues
- Feel free to ask the Investigator any questions related to the study.
- The CRAs should understand that the Investigator's interest is the only driving force for the study team to perform their jobs at the site.

CRA Communication Skills

Qualities required for being a good CRA

Management

- Manage “People” & “Time”
- CRAs should ensure that all projects should be rated equally important in terms of commitment and that quality time for all the projects should be given
- Working in harmony with the site requires excellent managerial skills and decision-making capabilities from a CRA

Decision Making

- ✓ The CRA is the decision maker at the site.
- ✓ The site team is totally dependent upon the CRA for making the decisions when it relates to study related issues
- ✓ CRAs must know how to resolve problems at site

Phoenix
Clinical Research

Thank You