

CRA TRAINING

BASIC IV

SITE MONITORING

INTERIM MONITORING VISIT (IMV)

DAN SFERA

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HOW THE ICH-GCP DEFINES IMVS

- What does the ICH-GCP say?
 - As per section 5.18.1 of the ICH-GCP guidelines, "The purpose of trial monitoring is to verify that: The rights and wellbeing of human subjects are protected. The reported trial data are accurate, complete, and verifiable from source documents. The conduct of the trials is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s)."

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DEFINING IMV

- Also known as Routine Monitoring Visits, or just Monitoring Visits, an interim monitoring visit is a visit that occurs after the sites is initiated and up until the site is closed out.
- It can also be seen as a periodic visit conducted to assess the progress of a clinical trial, verify adherence to the protocol and check the data quality, subject safety and compliance with ethical and regulatory requirements.
- As CRAs we are to ensure that the sites are compliant with all regulations, subject safety is assured, and that the data is being captured in a timely and reliable manner.

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FREQUENCY OF INTERIM MONITORING VISITS

- The frequency (number of monitoring visits) depends on the number of subjects that the site has enrolled. For example, if Site A and Site B are initiated on Day 1 and by Day 15 Site A has enrolled 20 subjects and Site B has enrolled just 2. Site A will be getting more routine visits from the CRA than Site B.
- However, according to the Institute of Clinical Research, "most company Standard Operating Procedures (SOPs) and the study monitoring plans require IMVs approximately 4-6 weeks intervals, depending on the complexity of the study and the number of subjects recruited."
- It should be noted that monitoring frequency can also be specified in the protocol of the study and/or any other trial related documents line the monitoring guidelines/plans.
- In an ideal monitoring situation, the first monitoring visit should occur within a week or so of the first subject being recruited. This really helps in fishing out the initial problems the site may be having relating to their preparedness for the trial. As always, it depends on the protocol and/or other trial related guidelines or documents.

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WHAT DO YOU DO TO PREPARE FOR AN IMV?

- Preparation and Planning: Preparing and planning for an IMV may differ from study to study and also as per the protocol and other trial guidelines (including the SOPs of the company you work for). However, the following are universal prep activities for most CRAs.
 - Schedule your visit; make an appointment with a site at the end of your monitoring visit for the next one or how you would make the first IMV after your Site Initiation Visit
 - Make sure your appointment takes into consideration the availability of the PI
 - Try to avoid the busiest times/days of the clinic or site. Identify the site's research days since those are the best days to visit.
 - Always confirm your appointment two weeks or so before your visit, if it has been a while since you last paid them an IMV.
 - Contact the site a few days before your visit to confirm the time and to remind the site coordinator/clinical research coordinator of the documents you will need to review.
 - Schedule time with the PI, if necessary.

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WHAT DO YOU DO TO PREPARE FOR AN IMV? CONT'D...

- Check to confirm that you will have access to the Investigational Product (IP) during your visit.
- If you are visiting a hospital make sure you organize an appointment with the pharmacist or other relevant departments involved in the trial.
- Review the study protocol and the amendments. Make sure what you are reviewing is the latest IRB approved copy of the protocol.
- Review previous monitoring reports. This helps you to refresh your memory on how the site is doing and what you will be looking at during your visit.

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WHAT DO YOU DO TO PREPARE FOR AN IMV? CONT'D...

- Make you carry what is generally referred to as a “Monitoring Pack.” They usually contain trial documents such as, SDV forms, spare SAE forms, latest correspondence, etc. Also, do not forget your post-it notes, monitoring notes, paper clips, pre-paid envelopes if something at the site need to be shipped when you are there, tape, etc., and most importantly do not forget to take copy of the protocol and the ICH-GCP guidelines. With available technologies today some people may carry with them an iPad or have everything saved in electronic files in their laptops.
- Do not forget a visit planner so that you can check if subjects have been visiting within the timelines allowed by the protocol.
- And any other study related material that your employer may need you to take to the sites as per your company's SOPs.

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WHAT SHOULD YOU DO DURING AN IMV?

- When you arrive on site you need to re-confirm with the study coordinator the intent/objectives of your visit and also how long it will take. Typically, an IMV is a day or two.
- Your monitoring team should provide you with a monitoring visit checklist; if not you should make one for yourself and have your Line Manager/Project Manager/Lead CRA review it for you before you start using it. The following are typically what you will be reviewing on site:
 - **Informed Consent Form (ICF):** Ensure every subject has signed an IRB approved consent form (the latest IRB approved version) and no study procedures were performed prior to the ICF being signed. For example: check lab draw times and ECG reading times.
 - **Serious Adverse Events:** Check for SAEs, if the SAE has not been reported inform the study coordinator and Sponsor immediately.
 - **Protocol Compliance:** In the source documents and patient medical charts, you can verify time the procedures were conducted and if they were conducted per the protocol. If a site is not compliant, note all deviations found, inform the PI and follow deviation reporting guidelines.
 - **SDV:** Check to ensure data in the charts/source matches the data in the case report forms

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WHAT SHOULD YOU DO DURING AN IMV? CONT'D...

- IP (Investigational Product): The protocol you are assigned to will explain how the IP should be stored, dispensed and returned. You need to account for how much IP was shipped/received (all shipments), dispense and returned. Count them and compare to shipping records (your IATA training should come in handy).
- Regulatory Binder: Determine if any logs or forms need to be updated or collected. Regulatory binder review may be periodic, depends on study team and protocol.
- Site Status: Determine if site has new staff or if staff has left. And confirm needs new study supplies. Is the site in good shape overall??
- Ongoing issues from previous visits: Be sure to try close out action items at the end of every visit
- Review findings with the PI: At the end of the visit, review all findings with the PI and SC; if necessary, escalate concerns to project managers or clinical team lead.
- Next Visit: Schedule your next visit.

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TAKE NOTE OF THESE!

- Concomitant Medications: Concomitant Medications (ConMed) is a drug or biological product, other than a study drug, take by a subject during a clinical trial.
 - The protocol normally state at what time the medication should be documented on the ConMed list/log or if the drugs is prohibited and must be discontinued
 - Concomitant Medications Log: Medication, dose, unit, regimen, route, start date, stop date, ongoing? And indication
- Adverse Events (AEs): An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
 - Types of AEs: Serious or non-serious, expected or unexpected, study related, possibly study related and not study related
 - Grades of Adverse Events: Grade 1 (Mild AE), Grade 2 (Moderate AE), Grade 3 (Severe AE), Grade 4 (Life-threatening or disabling AE), Grade 5 (Death related to AE)

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TAKE NOTE OF THESE! CONT'D...

- Serious Adverse Events (SAEs): A serious adverse event is defined as an untoward occurrence that results in:
 - Death
 - Is life-threatening
 - Requires hospitalization or prolonged existing hospitalization
 - Persistent or significant disability or incapacity
 - Consists of a congenital anomaly or birth defect
 - Is otherwise considered medically significant by the investigator

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TAKE NOTE OF THESE! CONT'D...

- In the back of the FDA Form 1572 you will find information on what the PI is agreeing to when they accept to be part of a clinical trial. It is by this document that the PI is held to be accountable for protecting the rights of the study participants and also promising to place their safety and wellbeing above all other variables in the study.
- PI Contact (Communicating with the Principal Investigator)
 - When communicating with the PI, your responsibilities are to communicate your findings and concerns at the conclusion of your visit. Whatever discrepancies and inadequate information must be discussed.
 - Sample issues: Lack of SC attention to details, numerous mistakes, discrepancies between source documents and EDC, protocol deviations and violations, omissions and corrections, study visits out of window, unreported AEs or SAEs, training or licenses expired, site delegation log not updated with new study team members (at site level), lack of PI involvement, or no progress note at all (progress notes usually have very little but important details), not acknowledging CS (clinically significant) or NCS (not clinically significant) on lab reports for values that are out of range, signing off on labs (noting that they have been reviewed) is 2 to 3 weeks after results have been returned on site, difficult to reach or communicate, doesn't return phone calls or emails, etc.

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TAKE NOTE OF THESE! CONT'D...

- Assessing PI Oversight
 - In research, investigators sometimes hear messages from the FDA (warning letter to investigators) such as, “You failed to personally conduct or supervise the clinical investigation...your lack of supervision resulted in significant findings as detailed below, and raises significant concerns with respect to data integrity and how you protected rights, safety, and welfare of study subjects...”
 - Significant problems happen when oversight is lacking, not well defined or documented, which can impact the rights and safety of all participants and the integrity of the research data.
 - It is important to ensure your assigned PI is present and actually documented data and participating in the trial as study visits are occurring. To ensure this you need to cross reference progress note signature and date with lab acquisition dates, AE entry or update, ConMed entry or update or source document dates)

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TAKE NOTE OF THESE! CONT'D...

- The clinical trial is a team effort; however, the PI is still ultimately responsible for the clinical trial.
- The PI is responsible for providing adequate supervision of those on the team to whom task have been delegated (appropriately)
- What is appropriate delegation? PI must delegate tasks to those who are qualified by education, training, experience, and licensing (as appropriate) to perform those tasks.
- Most inappropriate designated study task: screening evaluation, physical exams and obtaining informed consent.
- PIs must ensure data is documented correctly And legible. Oversight must be documented at each study visit via progress notes, signature on scales, lab requisitions, AE or ConMed updates or changes

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WHAT DO YOU DO AFTER THE MONITORING VISIT?

- The following actions are necessary after you have conducted a routine monitoring visit:
 - Complete your monitoring visit report immediately after your visit so that you do not forget to record anything. It is recommended that you write your report either during your visit (if you have your laptop available) or as soon as you get back into the office following a visit (some CRAs write their report in the airport and some are using voice recorders these days)
 - Always send a follow-up letter to the PI, copying in the study coordinator (SC), to make them aware of the tasks you completed during your time at site and to highlight any actions and issues they need to follow up on before your next visit. Remember to thank them for their time.
 - Similarly, make sure you act on any issues you recorded in your report as soon as possible after the visit so that you do not find them unresolved when you start preparing for your next visit.

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CRA Training:

- ☐ Basic I: GCP for Site Monitors
- ☐ Basic II: Site Selection
- ☐ Basic III: Site Initiation
- ☐ Basic IV: Site Monitoring
- ☐ Basic V: Site Close-out
- ☐ Advanced: I: Source Documents
- ☐ Advanced II: Site Regulatory
- ☐ Advanced III: Protocol Deviations, IP Accountability, Miscellaneous

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