# Clinical trial Operations

## Site and Investigator Selection, monitoring


Module 5

# Steps in conducting a clinical trial

- Site identification
- Site startup
- Investigator’s meeting
- Initiation meeting
- Monitoring visits
- IP handling
- AE reporting
- Documentation
- Archieval

# PI Identification

- The single most important activity
- Experience
- Inclination, interest, initiative
- Team - motivated, ability to motivate
- Drive
- Commitment
- Respect timelines
- Brand Names must be included
  - Name
  - Driving force
  - Opinion Leaders
  - Prestige
  - Years of experience

# PI Identification

- Qualification
  - MBBS
  - MD/MS
  - DM/Mch
  - BDS/MDS
- Experience
  - Clinical
  - Clinical Trial
  - Specific Indication Area
- Training
  - ICH GCP
  - Specific
- Who Does it?
  - CRA/CRC/PM
  - Database
  - Sales Dept.
  - Marketing Dept.
  - Cross Reference

# Sites

- More than 60% of sites report increasing difficulty in beginning clinical trials:
  - Poor recruitment
  - Contract & budget negotiation & finalization
  - Protocol complexities
  - CTA Agreement

# Site - Expectations

- Interesting trial
- Good Sponsor
- Ethical & Scientific research
- Ensure protection of rights, well being and safety of all study subjects
- Conducive to partner with multiple players/ organizations

# Sponsors - Expectations

- Adequate infrastructure
- Trained, motivated & experienced research staff
- Professionalism, integrity & Trustworthiness
- Progressive & compatible management
- Organized

# Site requirements

- Which can qualify as the Site?
- Hospitals – Govt. or Pvt.
- Nursing Homes
- Registered Institutional Ethics Committee is a must
- Should have facilities to undertake emergency(ies) as required

# Site - Criteria To Look For

- Location
- Specialty
- PI and Team
- IRB
- Lab support
- Other Equipments
- Commercials
- Space

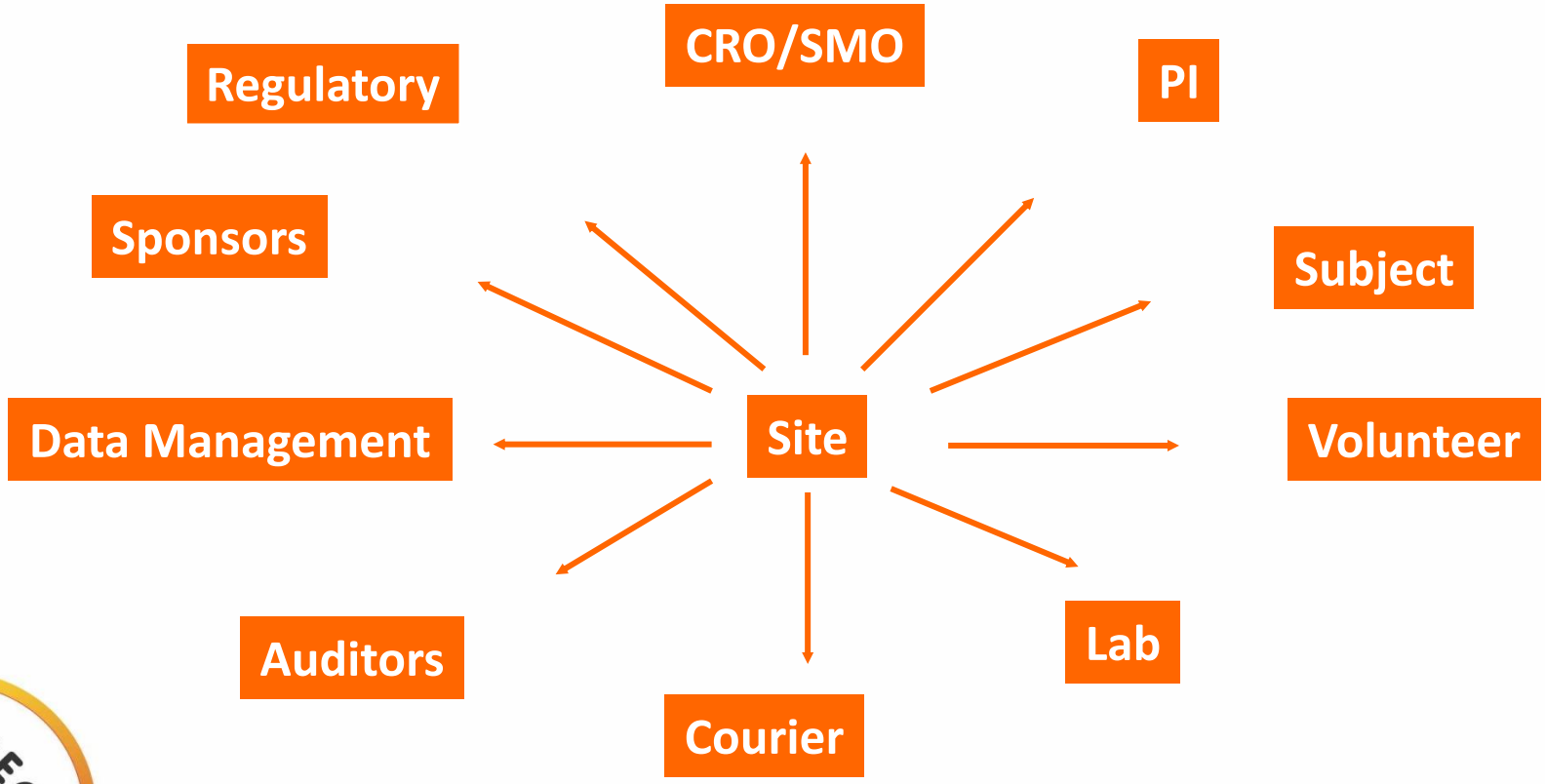
# Site - Criteria To Look For

- Time of staff
- Enrollment timelines
- Target enrollment
- Quick off the block
  - Timeline for:
    - IRB Submission to Approval
    - Contract agreement
    - SIV to FPFV
    - Enrollment per week/month

# Site - Sponsors Criterion

- % age of protocol violations
- Constancy of manpower
- JD of manpower
- SOP
- Turn Around Time for Data clarification
- Monitoring & Audit Reports
- Quality of data

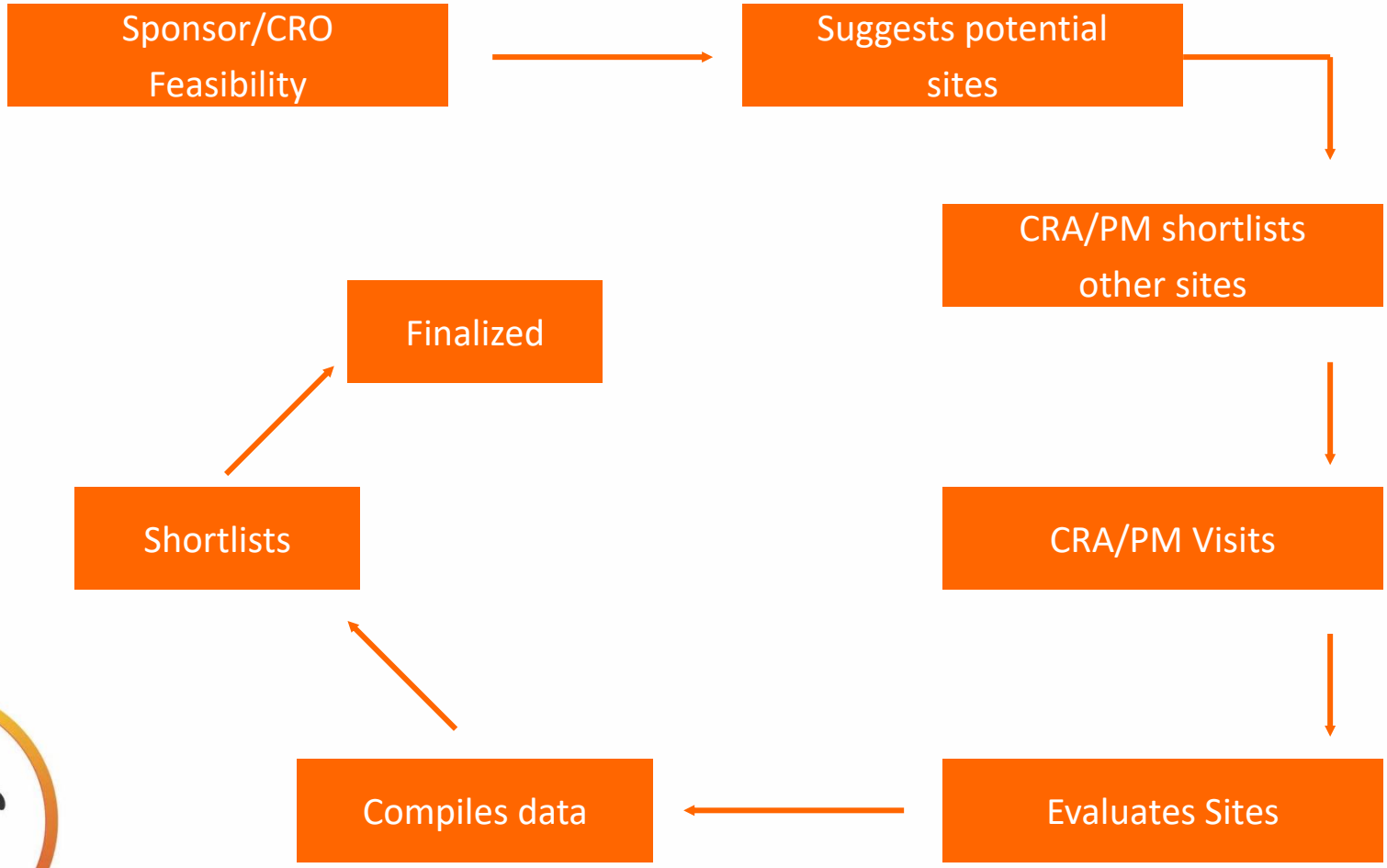
# Multiple Players at site



# Pre-Study Site Visit (PSSV)

- One visit MUST be on-site prior to study initiation
- Outcome decides site's participation
- Conducted by CRA/PM
- Lasts minimum of 2-4 hours

# A Typical Selection Process




# Investigator's Meeting

# Investigator's Meeting

- It has become accepted practice to bring all investigators & support staff together for a joint meeting prior to study initiation

- Investigators meetings provide an ideal platform for training the investigator in specific study procedures (e.g. completion of rating scales) or for demonstrating study specific techniques systems (e.g. electronic data capture)

# Investigator's Meeting

- These meetings are an opportunity to explain GCP, the practicalities of the investigators responsibilities, procedures for serious adverse events (SAE) reporting, CRF correction & query resolution, SDV & auditing

# Investigator's Meeting

- Discussions amongst the assembled group of investigators can often identify problems with the protocol or other issues that have previously gone unnoticed.
- The meeting should address practical issues within the study, reinforce timelines & be a good team building exercise.
- If they are well conducted such meetings can be a key motivator for the investigators & a valuable public relations opportunity for the sponsor.


# Initiation Visit

# Site Initiation Visit

- Starts after a successful PSSV and Sponsor & site are committed to proceed with study

- Purpose is to ensure site is:
  - Familiar with protocol and CRFs
  - Roles of site personnel are clearly defined
  - Common understanding of required procedures
  - All necessary supplies & equipment are ready

# Site Initiation (Training)

- Site training can be conducted three ways
  - Investigator Meetings
  - On-site-initiation visits (SIV)
  - Combination of both

- Investigator Meetings
  - Large, multicenter studies
  - Selected study personnel trained at common location

# Site Initiation (Training) (contd)

- Advantages
  - All investigators hear same information
  - Open forums
- Disadvantages
  - Does not allow one-on-one attention
  - Not all site personnel may attend
  - CRA can not check site supplies/drug

# Before SIV - Check List

- Arrange visit so each team member attends the portion of visit pertinent to their study role
  - Ensure each team member has read study related documents
  - Be prepared to discuss roles & responsibilities of each team member
  - Prepare list of questions/issues as they may relate to:
    - Scheduling of procedures
    - Reporting of AEs/SAEs
    - Sponsor contact numbers
    - Regulations/Guidelines

# SIV Check List – (cont)

- Process & store CTMaterials
- Sponsors may ask site to unpack & do CTM Accountability with CRA
- Assemble/calibrate equipment
- Reserve space to conduct SIV
- Keep investigator informed about visit
- Ensure that PSSV issues addressed
- Organize TMF with documents collected to date

# Pre-requisites

- All agreements in place?
- All documents in hand?
- Material received at site?
- All personnel trained? More Training?
- Site ready for the first patient?

**No enrolment of any study participant before the Initiation visit**

# Monitoring Of Trials

# Act of Overseeing

- Progress of a clinical trial and
- Ensuring that it is conducted, recorded and reported in accordance with
  - Protocol
  - SOPs
  - GCPs and
  - Applicable regulatory requirements

# Types of Monitoring

| Centralized Monitoring | On-Site Monitoring | Off-Site Monitoring |
|---|---|---|
| • Monitoring data quality, critical data reporting, AE/SAE trending, unusual distribution of data, etc.<br>• Proactive and early identification of quality/safety/operational risk/issue (s) based on continuous monitoring of data and key risk indicators<br>• Tracking site performance metrics<br>• Planning/triggering site contacts/visits based on the risk/issue(s) identified | • Critical risk/issue(s) management<br>• Shifting from 100 percent SDV to a risk-based approach for SDV with more focus on critical data related to eligibility criteria, primary / secondary efficacy and safety end points, and key protocol procedures<br>• Percentage of SDV & SDR<br>• In-person engagement, co-ordination with site staff, drug accountability, verification of facility/equipment and overall quality conduct | • Coordinating with the sites for managing risk/issue(s) identified during centralized monitoring<br>• Following-up with the sites as a part of site management activities and to support inquiry management. |

# The people equation

- The monitor is the main communication link between the Sponsor and the Investigator

# Common goal for site and sponsor:

- Protection of human subjects' rights and well-being
- Accuracy, completeness and verification of reported trial data
- Trial conduct in compliance with protocol/ amendments, Good Clinical Practice (GCP), and regulatory requirement(s)

# Who does monitoring?

Monitors/CRAs

- Appointed by sponsor
- Appropriately qualified and trained
- Should have scientific and/or clinical knowledge
- Familiar with investigational drug, protocol, ICF, SOPs, GCP, and applicable regulatory requirements

# Stages of a Monitoring Visit

- Before the visit
- During the visit
- After the visit

# Before the Visit

**The monitor will:**

- Contact site to schedule the visit
- Issue confirmation letter or e-mail

# During the Visit

**The monitor will assess /discuss:**

- Site, staffing, research lab facilities
- Regulatory files and study records
- Any problems and issues identified
- Clinical procedures if possible/ appropriate
- Conduct debriefing meeting at end of visit

# After the Visit

- **The <u>monitor</u> will:**
  - Complete site visit report
  - Submit the report to sponsor
- **The <u>sponsor</u> will:**
  - Distribute site visit report and/or cover letter to the site

# Assessment of Investigator's Files

- All protocol versions, amendments and consents
- All Institutional Review Board/ International Ethics Committee (IRB/IEC) approvals
- Investigator Brochure, if applicable
- Versions / dates of procedure manuals
- Continuing IRB/IEC review
- List of all SAE reports and safety reports
- Specific lab normals (safety labs)

# Assessment of Regulatory Files (ICH E-6 8.2, 8.3 Essential Documents)

- Specific lab certifications and expiration dates
- List of study staff CVs
- Study personnel signature/initial sheet
- Study personnel responsibility list and delegation of responsibilities list (should include anyone who enters data on source documentation and/or CRFs)
- Previous monitoring reports and monitoring log

# Study Product Accountability

- Review of study product accountability documents, e.g.
  - Shipping receipts
- Verification of accountability
  - Comparison of accountability record with actual, physical count
- Assessment of study product storage and handling, e.g.
  - Verification of cold chain maintenance
  - Temperature control of pharmacy

# Protocol-Specific Record Review

- Informed Consent
- Enrollment (inclusion/exclusion criteria)
- Adequacy of Source Documentation
- Timing of AE/SAE Reporting
- Missed Visits
- Protocol Violations and Deviations

# Informed Consent Checks

The approved informed consent form(s) were

- Appropriately obtained, signed and dated by each subject/representative, prior to the start of any study specific procedure
- Signed and dated by the person who conducted the informed consent discussion
- Retained for each subject with the site study records

# Research Laboratory Assessment

- Protocol related tests conducted by this lab
- Details of sample collection
- Sample flow from collection to lab
- Data flow from lab report to CRF
- Location of sample processing/analysis
  - (On/Off site?)

# Laboratory Samples

- Regularly check for changes in local lab. reference ranges, submit revisions to data management either electronically or using the standard form for reference ranges, file a copy in site file

- If a central laboratory is used, ensure investigator has any revised ref. ranges

# CRF Review

- eDM- check data has been submitted appropriately
- Review agreed data entry/query resolution timelines
- Resolve outstanding DQs and submit response
- Original diary cards and other subject-completed forms should remain with site study records whenever possible.  When this is not possible a certified (signed/dated by investigator or designate) copy or transcription will remain at site

# Typical errors in the CRF

- Some boxes left blank
- DOB year = 2050
- Ticked female but not completed contraception
- Ticked on oral contraception but OC not entered on con med page
- AEs and con meds in notes but not entered into the CRF
- Ticked for concurrent disorders (eg asthma) but no con meds completed

# Other Monitoring Activities

- Sign and date the Site Visit Record with a member of the site staff
- Address any other issues and corrective actions required

# Observation of Clinical Operations

Observation of clinical operations when appropriate AND with participant's consent

- Informed consent process
- Screening and enrolling process
- Administration of study product
- Obtaining laboratory samples

# Follow-up on Previously Identified Issues

The monitor  will attempt to resolve previously identified issues during this visit to the extent possible, e.g.

- Informed consent issues
- Outstanding corrections on forms
- Missing documents in the regulatory files

# Debriefing Meeting

- The pre-visit letter will request time for a debriefing meeting
- At least Investigator and Study Coordinator should be present
- Monitor findings will be presented and discussed
- The monitor may recommend re-training to research staff for some identified issues

# Protocol waiver vs violation

**Protocol waiver:**

Prospective,

requested by investigator and approved by medical monitor or clinician

Mainly based on I/E criteria

**Protocol deviation or violation:**

Retrospective

Found during monitoring etc

Based on I/E criteria, compliance, drug accountability etc

Violation is a severe deviation
(often safety concerns)

# Close Out Site Visit

**The monitor ensures the following:**

- IRB notified in writing of study completion/ withdrawal
- Appropriate accounting and disposition of study product and other study supplies completed
- Planned future use of remaining stored laboratory samples determined and appropriate
- Final report submitted to IRB/IEC and sponsor