CRA/CRC Professional Training Program

Module 4- Clinical Research Site Management-CTMS

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Objective

- Review the day-to-day operations of a Clinical trial study, development of site SOPs.
- Review eClinical tools to empower site management and compliance
- Review the technical challenges of operating a global clinical drug development process
- Review EDC, IWRS, Drug Management, CTMS systems

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Who regulates Clinical Research at the FDA?

- CBER – Center for Biologics Evaluation and Research is the unit within the FDA that ensures the safety and efficacy of vaccines, blodd and blood products, tissues, cells, gene therapies for the prevention, diagnosis and treatment of human diseases. Once the INDA submission is made to the FDA and approved, the Rx is then required to file the Biologics License Application, BLA to introduce a biologic product into interstate commerce under 21 CFR 601.2. This will approve the biologic for marketing.

- CDRH – Center for Devices and Radiological Health is the branch of the US FDA responsible for the premarket approval of all medical devices, as well as overseeing, the manufacturing and performance and safety of devices.

Management of a Clinical Trials

- General Considerations for managing global studies:
  - Diversity of rules and regulations in each region
  - Protocol Design and how to approach identifying critical data points
    - Identify critical data points to quality factors
    - Focus on activities essential to the critical data points
    - Engage stake holders in the design
    - Establish how to review critical data points
  - Drug/ Device Development Planning
    - Quality and Manufacturing
    - Human Pharmacology
    - Exploratory and Confirmatory

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Management of a Clinical Trials

- Design element- Population, control group, Response Variables, Interventions, statistical analysis
- Management of Study Vendors-
  - Laboratory, Drugs, printed materials, study supplies from start-up to close out
- Conduct and Reporting
  - Study Conduct
    - Protocol Adherence
    - Training
    - Data Management
    - Access to Data, interim data, data lock
    - Safety considerations

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Management of Study Vendors-

- Vendor Management in Clinical trials is essential because it ensures
  - Proper Data capture
  - Provide access to real-time data quality
  - Streamline the communication process and provide quality oversight
  - CRO can outsource vendor management in the RFP or FSP model.
  - Best practices exist when the FSP model is managed across all models in a risk- based monitoring approach. This model proactively mitigates risk-based on triggers and red flags, provides quality oversight and supplier governance.

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Management of Study Vendors-contd..

- Screening and Randomization → IRT, Bracket, IVRS, IXRS, IWRS
- Laboratory Services/ Shipping → Can be central or local labs- Lablinks, Covance, LabCorp
- Radiology Services → Sponsor can use a corelab, or local
- Biopsy Services → Usually done locally. However, the biopsy sample is required to be shipped to a corelab for assay.

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Management of a Clinical Trial..

- Study Conduct - the role of ethics committees and Independent Safety Management Board.
  - The safety, rights and well-being of the subjects participating in research must be protected by (1) the use of Informed Consent and (2) Review of the ethics committee.
  - Ethics Committees - can be institutional or central - CRAs must ensure a favorable approval of the ethics committee is obtained prior to scheduling a Site Initiation Visit and it does not elapse at the site.
  - PI oversight is essential to ensure proper review of study staff delegated duties
  - Site must have SOPs to document site processes and ensure site is following those processes.

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Management of Clinical Trial..

- Management of Patients – without patients (subjects) we cannot do the work that we do. Note the difference between a patient Vs subject.
- All trials must be posted on clinicaltrials.gov- this is usually how patients find patients based on the disease or condition.
- The subject must receive, given enough time to review the information on the ICF and sign an informed consent before any protocol assessments can begin.
- The subject must meet all inclusion criteria to be eligible to participate in the study.
- Informed Consent is a continuous process and subject must provide verbal consent for all study activities.

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Data Safety Management Board..

- Independent Data Safety Management Boards, DSMB are appointed by the sponsor to manage safety data collated during the study.
- DSMB are used to assess clinical safety data when there is potential for high risk and mortality end points in industry-sponsored trials.
- There is no FDA regulation required for the use of DSMB (see FDA guidance on the Establishment and Operation of Clinical Trial Data Monitoring Committees OMB Control No. 0910-0581). However, the use of DSMD is required in the emergency use of an IP where ICF is accepted.
- Each study that decides to use a DSMB will include in the protocol when an interim analysis is required and the DSMD will issue a recommendation for the study to continue or not based on the safety data reviewed.

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Clinical Research Site Management

the process of coordinating and managing a clinical study from the perspective of day-to-day operations of a clinical research study, from planning site logistics and constructing timelines for the study-initiation visit to closing out a study.

Sponsors, CROs, and the clinic site must have SOPs and work instructions on how tasks are completed and documented.

CROs contract will determine if the CRO will use the sponsor SOPs or not. The clinic site must have processes in place with SOPs to support that the site is following its processes.

As a CRA, this will be one of the most vital responsibility, you must follow your CRO SOPs as a CRC you are expected to follow your site SOPs in completing tasks.

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CRA Role in Site Management

- The CRA is the independent Clinical Research Associate hired by the CRO to act as the sponsor liaison, who travels to the clinic site to document and oversee every aspect of a study. You are the Protocol Site Manager.
- The CRA is required to maintain continuous communication with the site until the end of assignment for a smooth CRA transition at all sites.
- The CRA is responsible to conduct the list of visits;
  - PSSV/ SQV – Pre-study Site Visit/ Site Qualification Visit
  - SIV – site Initiation Visit-
  - Phased SIV Visit
  - SIV Booster Visit
  - IMV/RMV – Interim Monitoring Visit- Routine Monitoring Visit
  - COV – Close Out Visit

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How does a CRA manage research Sites?

- CRA Personality check – You will not be successful if you are confrontational, or argumentative, remember, the site is not obligated to do the study, the sponsor needs the site more that the site needs the sponsor, so your goal is to ensure a smooth operation of the study at the site and report back to the sponsor who then makes the final decision.
- The site staff does not work for the sponsor, they are paid based on the CSA or CTA, the clinical trial agreement. Every request must be courteous and time appropriate. You cannot send a data query resolution at 9AM and expect a response at 5 PM on the same day. The site has other studies they manage as well. TIME MANAGEMENT IS THE KEY
- Respond to sponsor emails within 24 hours!!!!! You will be fired if you do not respond even when you are traveling. Check you emails on a daily basis! If you are on vacation and you do not have a back-up, CHECK YOUR EMAILS!!!!!

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Managing a Clinical Research Site

- New Hire Rules – Exhaust all your resources before you call your Project Manager. You are not required to know everything about your job but YOU must KNOW where to obtain the information you NEED- SOPs
- Training Period – Is not for you to call your family and friends, read your SOPs, Work instruction and

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How does a CRA manage research Sites?

ALL EMAILS CORRESPONDENCE MUST BE PROFESSIONAL AT ALL TIMES. SITE STAFFS ARE NOT YOUR FRIENDS. YOU ARE THERE TO DO A JOB!! DO NOT ACCEPT ANY FAVORS FROM SITE STAFF.

YOU MUST ARRIVE ON TIME FOR ALL YOUR VISITS.

YOU CANNOT CANCEL A SCHEDULED CLINIC SITE VISIT ON THE DAY OF THE VISIT UNLESS YOU MISS YOUR FLIGHT OR YOU FALL SICK, THERE IS NO EXCEPTION. YOU WILL BE FIRED!!!

YOU MUST OBEY ALL THE SITE RULE AND OBSERVE THEIR SOPS. ENSURE TO READ ALL THE SITE SOPS. REMEMBER THEY CAN ASK THE SPONSOR TO REPLACE YOU.

THERE IS NO FDA REQUIREMENT FOR A CONFIRMATION LETTER TO BE SENT BUT YOU MUST SEND A FOLLOW-UP LETTER WITHIN **10** DAYS OF THE VISIT. FOLLOW THE SPONSOR/CRO SOP!!

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Conducting a PSSV/SQV

- The purpose of this visit is to assess the site for **qualification** and **resources** to conduct the study.
- At this visit, the focus is to obtain as detailed information as possible to support the site qualification questionnaire.
- Before you contact the site, recall that the site has already completed a site questionnaire with the sponsor. Your job will be to verify all the information on the site questionnaire and obtain documentation for site qualification.
- At minimum, the site must provide the following documents during a PSSV
  - PI – CV and ML
  - Names of sub-investigators (if known)

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Conducting a PSSV/SQV

- Ensure an NDA is on file before scheduling your visit.
- Review the study Monitoring plan and work instructions to educate yourself on your job role
- Review the PSSV checklist to know what you need to accomplish on your visit.
- Review the site questionnaire completed by the site staff.
- Call the SC to schedule the visit
- Send a confirmation letter of your visit using the study template, if any, (you can always create a PSSV CL) and include what you will be discussing at the PSSV, add the protocol synopsis version date, Lab collection document, other assessment document as required.
- Obtain Lab accreditation CLIA, CAP, radiology accreditation,

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Conducting a PSSV…contd.

- Obtain the SOP on how AEs are reviewed by the clinical team
- Obtain SOP for the site Informed Consent Process
- Obtain SOP review of SUSARs- Suspected Unexpected Serious Adverse Reactions.
- Obtain site SOP for local IP destruction
- Obtain site SOP for natural disaster plan and business continuity plan
- Obtain PI evidence of education, experience and training
- Discuss protocol synopsis and site plan for patient recruitment,
- Ask it there are competing studies and obtain PI plan for recruitment.

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Conducting a PSSV… contd

- Discuss PI experience in previous similar studies and find out what the recruitment barriers are if any
- Does the study require a blinding plan? Obtain the blinding plan.
- Conduct a walk round of the facility only in the areas where research will take place, the clinic area, IP storage, Lab collection and storage.
- Find out if the site will use a local or central IRB- review the site process for the IRB submission
- Discuss the budget and contract process and who handles it, obtain name and contact.

Conclusion of a PSSV

- Review the protocol synopsis and pertinent operations of the study and find out site challenges in previous similar studies.
- Find out if the PI has the availability to oversee the study- how many studies does PI oversee and are recruiting.
- Discuss if the site will utilize a satellite site for recruitment
- Does the site have human capital to support he clinical study
- Thank the PI and site staff in attendance
- Set realistic expectations on site selection plan from the sponsor.
- Never tell a site they will not be selected no matter how disappointed you are at the set-up. Let the sponsor know you will not select the site in your report and let the sponsor decide.

Conclusion of a PSSV/ SQV

- Provide a quick email to the sponsor on the questions from PI and site staff in order to obtain response and add to your report.
- Submit your SQV/PSSV report in 3 days!! The SOP may say 5 days but always strive for 3 days because anything can happen. It is better to be early than to be late.
- Once you receive your review back, complete the corrections and submit for the 2nd round of review.
- Obtain SQV report finalization and post to the TMF
- Send an SQV/ PSSV follow-up report to the site

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System features