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Clinical Trials

Introduction to Junior CRA's

Training module A

Summary

Glossary

Abbreviation	Description
AE	Adverse Event
co-inv	co-investigator / sub-investigator
CRA	Clinical Research Associate
CTMS	Clinical Trial Management System
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Data Base Lock
eCRF	electronic Case Report Form
eMR	electronic Medical Records
eTMF	electronic Trial Master File
FU	Follow-up
FUL	Follow-up letter
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification number
IMP	Investigational Medicinal Product
IRB / IEC	Institutional Review Board / Independant Ethics Committee
IRT	Interactive Response Technology
MG	Monitoring Guidelines
PD	Protocol Deviation
RBM	Risk Based Monitoring
SAE	Serious Adverse Event
SDV	Source Data Verification

Trial phases

Phases

Preclinical	Lab testing / cell trials / animal models No humans Efficacy / safety tests FDA request for a new drug – Investigation New Drug (IND) “Many called but few chosen” Duration: 6 years or more
Phase I	Healthy volunteers Safety first No placebo used Dose and preliminary toxicity – low sample size, up to 10 Duration: 1 to 5 years
Phase II	Intermediate efficacy Additional toxicity information Placebo arm is allowed Double-blind option Higher sample size – up to 100 Duration: 1 to 5 years
Phase III	Efficacy / safety validation Risk/benefit profile Additional toxicity information Comparison with standard of care or placebo if not available Possible marketing approval by FDA Higher sample size – up to 1000 Duration: 10 to 20 to collect long term safety and efficacy data FDA can have additional questions: possible additional 5 years
Phase IV	Additional safety data post FDA approval Post-marketing Up to 10.000

Generalities

- Voluntary
- Specific follow-up is needed: required trial visits to the site will be required
- Risks/benefits
- Safety/efficacy
- Advantages
    - Often provides the strongest evidence in support of cause-effect relationships
    - Basis for clinical and public health policy
    - Minimize/eliminate bias and confounding
- Difference between clinical research and medical treatment
    - Medical treatment = approved and based on current guidelines
    - Clinical Research =
        - Side effects? Known and unknow
        - Treatment success
        - IMP (Investigational Medicinal Product): better or equal or worse

- Does the new IMP shows results where none are available yet?

Clinical trials in Belgium: https://clinicaltrials.gov/

Core elements of a Clinical Trial
Research Question
Hypotheses
Trial population – study participants
Recruitment – depending on local regulations
    General mailings
    Targeted mailings
    Mass media
    Screenings
    Physician referral
    Medical record review
    Internet
Allocation
Blinding
    Single / double / triple
Treatment groups
Data
Analytical issues
Interpretation of data and trial results

Trial types / designs

Observational trials – non-experimental
- Observe both exposures and outcomes

Screening trials

Experimental trials: devices / investigational medicinal product / assign exposures / observe outcomes

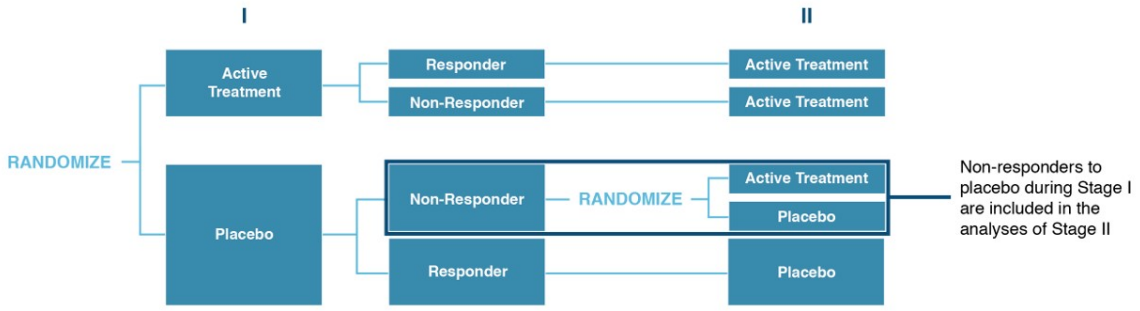
Diagnostic trials

Quality of Life trials

Combination of treatment and QoL

Randomized trials
- Allocation: random (stratified, blocked) / non-random (haphazard, systematic)
- Why randomization?
  - To eliminate bias
  - To reduce/avoid confounding from known and, more importantly, unknown confounders

Target population / study population / randomization / standard treatment vs new treatment



Trial validation and IRB / RA

Trial validation – Regulatory authorities and Institutional Review Board (RA and IRB)

Protection of wellbeing of the participants
Federal law compliance
Informed Consent Form (ICF) and Clinical Trial Protocol (CTP) review with risks/benefits
Ethically / medically and legally acceptable?
Costs / compensations / reimbursements
General Data Protection Regulation (GDPR)

Clinical Trial Protocol (CTP) outline
Experimental trial

Rationale – the research question
    Assessing efficacy / assessing the effectiveness
Types of hypotheses
    Comparative trial
    Equivalence
Schematic of trial design
    Parallel
    Cross-Over
    Mixed
Schedule of trial procedures
Trial objectives and endpoints
Risks and benefits
Trial design
    Inclusion criteria / characteristics of accessible population
    Exclusion criteria / considerations related to adherence to:
        therapy – FU – safety - ethics
Trial population
Treatments if any
Discontinuation and withdrawal
Trial assessments and procedures
Adverse Events
Statistical methods
References
Appendix – if any
Panels – if any

Informed Consent Form (ICF)
Participation to a clinical trial

- Detailed description of the whole trial outline, subject native and comprehensive language
- Introduction performed by site staff
- Site staff contact details
- Time / totally voluntary / raised questions / change of mind: withdrawal at any time
- Duration of every site visit
- Discussion with own general practitioner
- Compliance
- Costs: travel / meals / parking
- Insurance
- Signature of the ICF by all involved parties
- Copy of ICF

<u>Participation to a clinical trial</u>

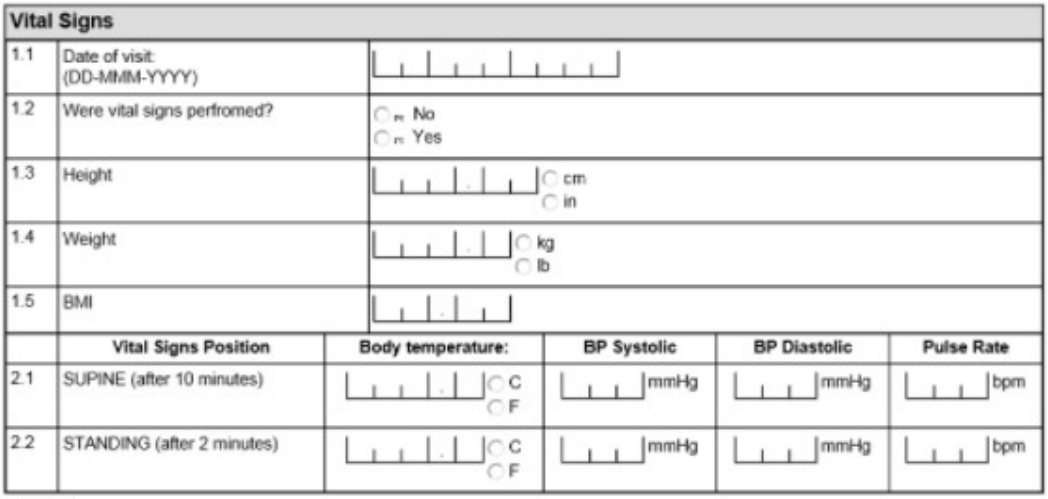
- Access to IMP not yet on the market
- Close follow-up of disease / support / advice / care
- IMP could be more efficient than standard of care
- Contribution to research
- Understanding disease
- Trial participants
    - Target population
    - Accessible population
        - Ideal:
            - High risk for disease
            - Candidates for treatment
            - Rep. of target population
            - Feasibility considerations

- Recruitment
- Follow-up (FU)
- High quality data

- Trial samples

Recruitment begins with design
Response rate is always lower than foreseen
Recruitment period is often longer than expected
Several strategies are required to be implemented to identify best source
Back-up strategies are to be prepared
Recruitment to be monitored
Required resources are often more than expected
Dedicated and trained personal on site is necessary

eCase Report Form (eCRF)



Vital Signs					
1.1	Date of visit: (DD-MMM-YYYY)				
1.2	Were vital signs perfromed?	○ No ○ Yes			
1.3	Height	○ cm ○ in			
1.4	Weight	○ kg ○ lb			
1.5	BMI				
	Vital Signs Position	**Body temperature:**	**BP Systolic**	**BP Diastolic**	**Pulse Rate**
2.1	SUPINE (after 10 minutes)	○ C ○ F	mmHg	mmHg	bpm
2.2	STANDING (after 2 minutes)	○ C ○ F	mmHg	mmHg	bpm

Is an electronic questionnaire specifically used in clinical trials.
Tool used by the sponsor to collect data from each participating subject. All data on each subject are held and/or documented in the eCase Report Form or eCRF.

The sponsor develops the eCRF to collect the specific data they need in order to test their hypotheses or answer their research questions. The size of a eCRF can range from a handwritten one-time 'snapshot' of a subject's physical condition to hundreds of pages of electronically captured data obtained over a period of weeks or months. It can also include required check-up visits months after the subject's treatment has stopped.

The sponsor is responsible for designing a eCRF that accurately represents the protocol of the clinical trial, as well as managing its production, monitoring the data collection and auditing the content of the filled-in eCRFs.

Case report forms contain data obtained during the subject's participation in the clinical trial. Before being sent to the sponsor, this data is usually de-identified (not traceable to the subject) by removing the subject's name, medical record number, etc., and giving the

subject a unique study number. The supervising Institutional Review Board (IRB) oversees the release of any personally identifiable data to the sponsor.

From the sponsor's point of view, the main logistic goal of a clinical trial is to obtain accurate eCRFs. However, because of human and machine error, the data entered in eCRFs is rarely completely accurate or entirely readable. To combat these errors monitors are usually hired by the sponsor to audit the eCRF to make sure the eCRF contains the correct data.

When the study administrators or automated mechanisms process the eCRFs that were sent to the sponsor by local researchers, they make a note of queries. Queries are non-sensible or questionable data that must be explained. Each query has to be resolved by the individual attention of a member of each local research team, as well as an individual in the study administration. To ensure quality control, these queries are usually addressed and resolved before the eCRF data is included by the sponsor in the final clinical study report. Depending on variables relating to the nature of the study, (e.g., the health of the study population), the effectiveness of the study administrators in resolving these queries can significantly impact the cost of studies.

Outcomes / Endpoints

Principal / secondary

Clinical outcomes are measurable changes in health, function or quality of life that result from our care. Clinical outcomes can be measured by activity data such as hospital re-admission rates, or by agreed scales and other forms of measurement.
Outcomes are variables that are monitored during a study to document the impact that a given intervention or exposure has on the health of a given population. Typical examples of outcomes are cure, clinical worsening, and mortality. The primary outcome is the variable that is the most relevant to answer the research question. Ideally, it should be patient-centered (i.e., an outcome that matters to patients, such as quality of life and survival).
Secondary outcomes are additional outcomes monitored to help interpret the results of the primary outcome. They can also provide preliminary data for a larger study. For example. Although investigators may be tempted to monitor several outcomes, the effort and cost to monitor various outcomes may be prohibitive. Therefore, it is essential to decide which outcome(s) to monitor.

CRA Expectations

Feasibility

Site Feasibility process: country and site level

Country	Site
country feasibility planning - timelines identification of key elements confirmation country selection operational plan set of all trial functions/timelines vendors	access feasibility resources Lead CRAs and CPM (timelines) site list creation trial specific feasibility site suggestions evaluation of the proposed site list confidentiality agreement Pre-trial visit training final site selection list confirmation selected sites are in CTMS Lead CRA inform sites about (non)-selection recruitment plans in CTMS

Pre-study visit

A pre-study visit is required before the study initiation visit.
A telephone contact is sometimes allowed in certain circumstances.
CTMS to be updated.

A few documents might be collected – always check data privacy consent conditions and section 8 of ICH E6
Quality of collected data
Compliance of the Investigator, Sponsor and monitor with the standards of GCP and regulatory requirements

Site Initiation visit

CTMS to be updated asap once date is known
To be confirmed:

- site contact details,
- IMP delivery contact details,
- primary contact,
- site access to IRT,
- site staff eCRF training

If training during SIV: eCRF training form is completed for each site staff member.

Site binder:
Administrative colleagues folder structure on common drive
CRAs check essential site documents
Site binder to be final two weeks before SIV
CRA responsible for filing of documents collected at SIV in CTMS

SIV Agenda:
Other departments to visit, which ones?
Site staff present: PI, Co-inv.'s, pharmacist, Lab ..
CRA needs to check if extra Training is required

Check of SIV slides
SIV report to write and provide for review soon after the SIV
Follow-up letter to be written within x after visit (depends on sponsor, to be checked)
Use letter headed paper
To be sent by e-Mail to site staff
Lead CRA to be copied in
To be filed in CTMS by CRA
Plan any outstanding site staff training if applicable

<u>IMP already on site or not at SIV?</u>
If not: to FU and confirm safe delivery by phone + contact report in CTMS

<u>Site staff responsibilities form</u>
Very challenging form 😊

Purpose:

- ✓ The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
- ✓ A staff Signature Sheet should be maintained to document signatures and initials of all persons authorized to make entries and/or corrections on case report forms.
- ✓ 21 CFR Commitment by the investigator that he or she "will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations".
- ✓ CV must demonstrate education, training, and experience that qualifies the investigator/staff as experts in the clinical investigation
- ✓ Must be completed prior to members of the team performing any trial related activity.
- ✓ Must be updated to reflect any changes in the team.
- ✓ Describe requirements with regards to site staff responsibilities
- ✓ Review areas of focus
- ✓ Review common findings
- ✓ Review general guidance

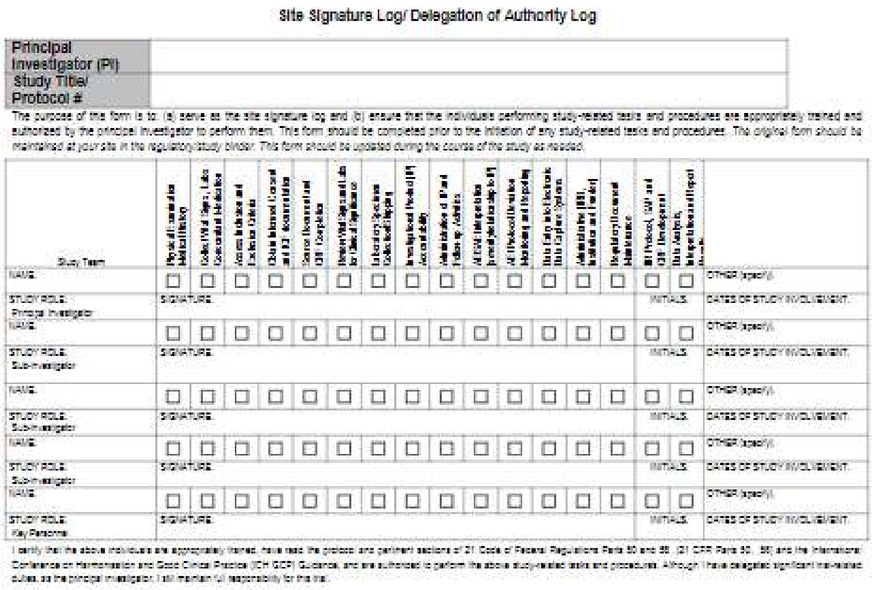
Common errors:

- ✓ Wrong letter codes used for a role
- ✓ Completed by the trial nurse for all site staff
- ✓ Stop dates not confirmed by PI
- ✓ Start date later than confirmation date PI
- ✓ Site staff not trained or inadequate training records for delegated tasks
- ✓ Non-qualified individuals conducting delegating duties
- ✓ Supporting Essential Documentation missing for personnel
- ✓ Incomplete form
- ✓ Form had corrections made to delegated duties (removal or responsibilities) after the authorization date of the qualified investigator
- ✓ Etc.

If task is not listed, use the empty options

Discuss with site and offer guidance with completion

Always check that the person is qualified to perform the delegated task


Site Signature Log/ Delegation of Authority Log

Principal Investigator (PI)	
Study Title/ Protocol #	

The purpose of this form is to: (a) serve as the site signature log and (b) ensure that the individuals performing study-related tasks and procedures are appropriately trained and authorized by the principal investigator to perform them. This form should be completed prior to the initiation of any study-related tasks and procedures. The original form should be maintained at your site in the regulatory/study binder. This form should be updated during the course of the study as needed.

Study Team

NAME: / STUDY ROLE: Principal Investigator / SIGNATURE / INITIALS / OTHER (specify) / DATES OF STUDY INVOLVEMENT

NAME: / STUDY ROLE: Sub-investigator / SIGNATURE / INITIALS / OTHER (specify) / DATES OF STUDY INVOLVEMENT

NAME: / STUDY ROLE: Sub-investigator / SIGNATURE / INITIALS / OTHER (specify) / DATES OF STUDY INVOLVEMENT

NAME: / STUDY ROLE: Sub-investigator / SIGNATURE / INITIALS / OTHER (specify) / DATES OF STUDY INVOLVEMENT

NAME: / STUDY ROLE: Key Personnel / SIGNATURE / INITIALS / OTHER (specify) / DATES OF STUDY INVOLVEMENT

I certify that the above individuals are appropriately trained, have read the protocol and pertinent sections of 21 Code of Federal Regulations Parts 50 and 56 (21 CFR Parts 50, 56) and the International Conference on Harmonisation and Good Clinical Practice (ICH GCP) Guidance, and are authorized to perform the above study-related tasks and procedures. Although I have delegated significant trial-related duties, as the principal investigator, I still maintain full responsibility for this trial.

Identification of source data form
What / when / how
Template to be ready at SIV
To be made site specific
Living document through the trial duration
Location of the source: to check during SIV – this document will be used by any auditor or inspector, for sure
Important: to be updated during the trial if changes

Investigational Medicinal Product (IMP)

Always check CTP, monitoring and IMP guidelines first.

Where to start?
➔ Planning for delivery of trial medication starts at the **Pre-Study Visit** (PSV)

to be confirmed:

- site shipment details (name, address, contact person, phone, email address)
- IMP process on site should be discussed:
  - adequate storage facilities: secure, limited access/temperature controlled
  - Where will returned product be stored?
  - adequate temperature control in storage area (calibrated temperature monitoring device)?
  - who will be responsible for drug accountability? Dispensing? Return? Storage?
  - any other trial specific requirements? Such as an unblinded administrator?

Monitor's task

- Check all IMP related docs first such as CTP, trial medication handling guidelines, IRT set-up and functionalities, etc.
- Check at SIV all involved pharmacists have access to the IRT platform

- Check if IMP has an automatic re-supply via IRT or if this should be done manually
- IRT use: check stock and planned randomization numbers
- Check limited access to IMP by authorized personnel + adequate secure storage is maintained / room temperature / fridge / other
- Temperature monitoring: daily or at least every working day
- Check for temperature excursions/deviations: during IMP delivery or/and on site – Protocol deviations (PD) to be recorded
- Check the expiry date
- Check that returned and quarantined trial medication is stored on another location than the other IMP available for dispensing to subjects
- Perform drug accountability / site inventory at subject level
- Check completion of the IMP Inventory Log / sometimes incorporated in IRT
- Subject level and subject specific drug accountability to check / completion and compliance
- Check temperature recording device – if any
- Check associated calibration certificate and expiry date

Drug accountability

- To be done for all delivered IMP / active or not / comparator included
- Check history of every single box/IMP kit: from arrival to pharmacy, to subject through pharmacy and site and return and back to pharmacy (if applicable) again
- Subjects need to return all used/un-used IMP
- IMP Inventory Log to be up-to-date at any time
- Drug accountability to be done at the subject level, using the subject specific IMP log
- In case of discrepancies: to be documented on IMP inventory log, IRT, eCRF, subject specific drug accountability log and source

Training

- the responsible person(s) at the trial site should be trained in receipt, storage, handling, dispensing, accounting and return of trial medication
- he/she should be familiar with the following documents/processes:
  - ✓ Confirm of IMP receipt in IRT
  - ✓ Handling of t° deviations

- ✓ Update the Inventory Log
- ✓ Completion and Filing of the Temperature Logs
- ✓ Return the in-transit temperature monitoring device (when required)

- Focus on delegation log as well – tasks to be well defined and training documentation available before receipt of 1st IMP delivery

Serious Adverse Event (SAE-AE)

Definition: see exact wording in CTP

SAE can be reported by site staff or discovered during MV
Site uses platform outlined in CTP, fax, email – 24hours of 1st knowledge

Tips
In case of CRA discovering of an SAE during a MV:

- SAEs in source / SAE Form completed, dated, with all information already available
- Severity/seriousness and causality assessed by PI / co-investigator
- In case of supplementary information provided later on (lab results / other investigations / discharge reports) : FU SAE form
- No subject confidential data to be visible => to redact, such as name, address, mobile phone number, hospital ID number. Only subject ID and site number are allowed

SAE reporting requirements must be reviewed with the (co)Investigator and relevant trial site staff during the site initiation visit, at the latest.
CRA should make sure SAE Forms and related contact details are available in the trial binder
Blank SAE Forms should be present in trial file at SIV.
CRA to check SAE details are all documented in source and matches the AE form in eCRF and SAE form.
Every single SAE must be followed up until a final outcome.
Follow up on requests for additional information/clarifications may occur.
All follow-up information is made on a new SAE Form – tick-box “Follow-up #”.

SAE Reconciliation

Reconciliation of SAE data between the clinical databases (eCRF) and the safety database (SAE database) must be performed and completed before to DBL. All data points should be the same.
CRA should check and SDV data between source / eCRF and SAE/FU forms.
All original SAE/FU forms should be dated and signed by PI or co-investigator.

Non-compliance / PD / Serious breach

Protocol deviations

- To be reported in MV report and CTMS
- Major or Minor
- Description of the actual deviation
- Action section to be completed to avoid re-occurrence
- PD to be followed-up and resolved and/or closed

Serious or persistent non-compliance

Occurrence of non-compliance which occur at a frequency or with a unacceptable severity may result in trial site participation termination.
Premature closing of a trial site for this reason should be notified to the relevant authorities according to national legislation.

Serious breach

"A breach to either the CTP or to the GCP which is, to a significant degree, likely to affect the safety e.g. physical/ mental well-being of the trial subjects or integrity of data such as scientific value of the trial"

➔ Immediate action required
➔ Check time window for reporting to regulatory authorities
➔ To be discussed with team

Electronic Medical Records (eMR)

ICH/GCP E6, 5.1.2 "The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities".

If a site is using an electronic source, certified copies should be used as a last resort in obtaining direct access to electronic source data. The first choice will be to work with the site to obtain read-only access to the source records that are in the electronic medical records (eMR).

If the site can't provide access, for example because of an institutional policy that does not allow such access, or the system is not CRF 21 part 11 compliant, then the site will be required to provide certified copies of the electronic medical record.

Hard paper copies printed from electronic systems: the individual printing the data from an eMR must sign the copies and record the date they were printed, and note that they have verified that the data on the hard copy matches the data in the electronic system.

Who can certify the records?

The copies can be certified by personnel that have access and training on the system where the original data is held, such as personnel in a hospital medical records department. This individual must be able to determine that what is being printed

represents a true and complete copy of the medical record. There must be documentation of this person's training on the system available upon request.

The name and position of this person should be identified along with their signature/date

How should the certified copies be presented?

The sites can group pages together and certify the top page of copies by signing and dating directly on it attesting to the fact that the pages are true copies of the original and noting the number of pages attached. The pages in the group must be numbered. In addition, there should be a brief statement written by the person signing/dating the copies that the copies are exact copies of the original data.

The sites can also attach a cover sheet to the copies. The cover sheet should be dated and signed, list the total number of attached pages, and contain a brief statement to attest that they are exact copies of the original data. The attached pages must be numbered.

The site can create a log document that indicates the person who printed the record, the dates of the records and the dates of when the records where printed. This log should also have a statement indicating that the person signing each line attests to the completeness of the records being presented.

The Monitoring Guidelines (MG) should include details regarding the expected process for monitoring source.

The MG should detail, and the CRA should request, to conduct interval EMR source to shadow reviews to ensure on-going compliance with the accuracy and completeness of the certified copies

The CRA should enter comments into the Visit Report and FUL regarding how the study data is provided and monitored at sites. Comments should include what types of source

data is provided and by what means (original paper, eMR, dictation, etc) and detail how the monitoring is performed when certified copies are provided.

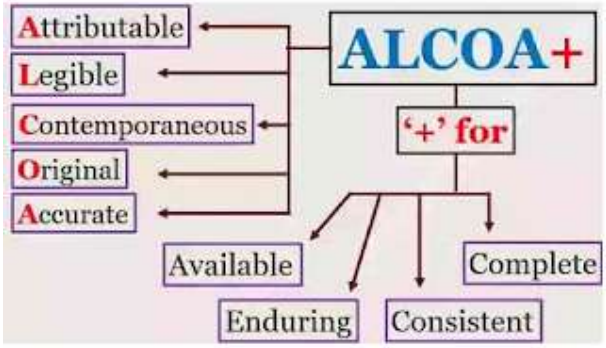
Monitoring visit / on-site – remote call

Main focus areas: Preparation – Objectives – SDV/RBM – Reporting - FUL

Preparation
Check Monitoring Guidelines first
Confirmation via CL on CTMS of the on-site appointment – 1 week upfront
After SIV: CRA will review CTMS and all other systems (such as IRT and eCRF) before every MV + open FU items / any PD / open queries / data entry / recruitment status / outstanding tasks and documents etc.

Objectives of the MV / remote call
CRA will confirm the study conduct in accordance with the CTP, amendments, SOP's, ICH GCP and other local requirements
Early discovery issues/deviations -> Find solutions -> Take actions -> Immediate escalation safety issues/
Identify staff / facilities changes (action required?)
Verify accuracy of trial data
Check safety aspects
Review Investigational Product
Discuss Study Progress/recruitment

SDV / RBM - ALCOAC



See separate training manual

Report

- ✓ Team will provide report completion guidelines
- ✓ Facts – avoid long sentences
- ✓ Bullet
- ✓ SOP terms, where possible
- ✓ Structured, consistent, transparent, complete and understandable
- ✓ Track Issues – for timely closure

FU tasks and FUL

- Plan date of next visit
- Complete Visit Report and send for review within 10 days
- Ensure finalisation / completion within 20 working days
- Follow-up letter/e-mail : send within 12 working days
- Forward any documents collected for filing
- FU of the open tasks
- FU letter:

  - ✓ Content: thank site staff for time during SMV

  - ✓ Send as an attachment to an email (cc CRA lead)
  - ✓ Formal letter template + letter headed paper
  - ✓ Print and take original to file at next SMV
  - ✓ Import copy of letter into eTMF
  - ✓ Submit to Investigator and relevant site staff (main contact)
  - ✓ Summary of activities / main findings
  - ✓ Actions required for unresolved issues at site
  - ✓ Confirm date of next visit
  - ✓ English preferred

Topics to mention:

ICF, source and CRFs
Protocol Deviations
Staff
IMP
Trial file
Other action items with priority and responsibilities
Next visit

Closing visit

Timing of the end of trial visits - soon after DBL - and as per the Monitoring Guideline.
Any open tasks and audits should be closed prior to the end of trial visit.
CRA will plan the visit with the site and any other department such as laboratory and pharmacy + confirm via confirmation letter/email.

Tasks:

- Check any outstanding issues / FU open item / or protocol deviation
- Review any ongoing SAEs and plan for required follow-up
- Review the eTMF for completeness
- Confirm eCRF data has been provided to site on USB stick / web transfer
- All site payment(s) have been raised – except the one for the close-out and archival
- All visit reports, contact reports and associated FU letters must be filed in the eTMF
- Check for materials needed: archival boxes, archive labels, etc…
- All unused IP and other clinical supplies and documents are returned to sponsor or destroyed locally, if approved by sponsor. Any local destruction should be accompanied by documentation of such (certificate of destruction issued & filed in eTMF/ trial file

- archiving facilities to be verified - easily available for e.g. an audit/inspection
- duration of archiving to be checked with site staff
- the investigator is requested to inform sponsor in writing should the archive location change. If archiving of the subject documentation cannot be guaranteed, certified copies of relevant parts of the records should be archived in the trial file
- all subjects screened are recorded in the Subject Screening Log and the log is dated and signed by the investigator
- the Subject Identification List is dated and signed by the investigator
- access to IRT/other systems should be revoked
- access to eCRF should be changed to read only until the site receives an electronic media with the relevant CRFs
- PI (and co-Inv) to confirm if any changes to their financial disclosure since trial start (updated Financial Disclosure may be needed, including changes up to one year post close-out visit).
- Original documents should stay at the trial site if electronic copies have been submitted to the eTMF and are available in the eTMF
- By the conclusion of the end of trial visit all copies of all documents must be uploaded to the eTMF
- Document the visit on the Site Visit Log and ensure a copy has been uploaded to the eTMF
- All Initiated trial sites should have an end of trial visit.
- End of trial Follow-up letter:
    - **Tips:**

- To be sent within 12 working days following the end of trial visit
- Should include the following:

1. state that the clinical phase of the clinical trial has been completed at this trial site remind the investigator eCRF data will be provided via electronic archival media and remote data capture access will be removed following receipt of investigator acknowledgement,
2. advise the investigator not to archive trial file off-site until receipt of electronic media eCRF data and the CTR Synopsis

3. confirm archiving arrangements of clinical trial documents
4. remind investigator that IRB / IEC should be notified, if required, of clinical trial completion and that a copy of all correspondence between IRB / IEC and investigator should be sent to CRA, or that this notification is/will be done by the sponsor, as per national requirements
5. remind investigator about his/her obligation to report financial disclosure changes up to one year after last subject last visit at site
6. reiterate possibility of regulatory authority inspection of trial file post submission.
7. remind investigator to contact the sponsor in case of regulatory authority contact announcing an inspection
8. emphasize investigator responsibility to follow up trial subjects where appropriate, i.e. as described in the Clinical Trial Protocol
9. state that eCRF data discrepancies may be raised and should be resolved before DBL (only if DBL has not taken place prior to the visit)
10. state if IMP inventory has been performed / reconciled and all remaining investigational product collected
11. remind the investigator to file end of trial letter in the trial file
12. if appropriate, send a letter to the service department(s) (e.g. pharmacy, laboratory) confirming the completion of the clinical trial at the trial site

- If a site has been initiated, but no subject has been enrolled, the following also applies:
    - the documents required to be archived are the same as those required to be achieved for a recruiting site
    - all subjects screened should be recorded in the Subject Screening Log, and the log should be dated and signed by the investigator.
    - If no subjects were screened, it should be documented by a statement that no subjects were screened and dated and signed by the investigator
    - The Subject Identification List should be dated and signed by the investigator with a statement that no subject was enrolled
    - access to eCRF / IRT/other systems should be revoked

Notes