Site monitoring visit

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Standard Operating Procedure

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This SOP is applicable to all TAPAS Group members and designees.

1 Aim

To describe procedures before, during and after a monitoring visit.

2 Background

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that the investigator and study staff continue to fulfil their obligations regarding conduct and reporting according to protocol procedures, Standard Operating Procedures (SOPs), ICH topic E6: Guideline for Good Clinical Practice (GCP), ISO 14155 for medical devices and the applicable regulatory requirement(s) and that the facilities continue to be adequate.

The determination of the extent and nature of monitoring should be documented in a monitoring plan and will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring before, during and after the trial.

The monitor is the main line of communication between the sponsor and the investigator and he/she should submit a written report to the sponsor after each trial-site visit or relevant trial related communication.

3 Procedure

3.1 Prior to site monitoring

Responsibility:	**Action:**
Monitor/Consultant	1. Schedule monitoring visit. 2. Check monitoring plan (M03/F7) for study specific site monitoring activities. 3. In case of First Dosing visit, ensure SOP M04 is followed as well. 4. If applicable, ensure that the procedures in SOP M05, Laboratory visit, and SOP M06, Pharmacy visit, are performed. 5. If applicable, collect study materials to provide to the site. 6. Prepare visit, making use of previous (visit and/ or contact) reports, letters, documents, and essential documents checklist. 7. Generate or, if applicable, ask data management to generate an outstanding query report and review the report. 8. If applicable, check if new SAEs were reported since study start or last monitoring visit 9. In case eCRF is used, check eCRF completion

10. In case an Electronic Patient Dossier (EPD) is used, assure that monitoring access is arranged prior to the monitoring visit.
11. Confirm monitoring visit in writing and include open action item list and list of materials (such as ISF, signed ICFs) to be available during the monitoring visit.

3.2 During site monitoring

Responsibility:	**Action:**
Monitor/Consultant	1. Ensure informed consent procedure is correctly performed by trained site staff and documented in medical records. Written informed consent forms (ICF) should be obtained prior to the performance of any study-related procedure, including any study related washout of previous medication. Complete or update ICF log (M03/F5) during ICF review. 2. Check completion of subject screening and enrolment log (M03/F2) and subject identification log (M03/F3). 3. Check the subject's medical records based on the monitoring agreements with the sponsor as laid down in e.g. the monitoring plan (M03/F7). Check for example: date of inclusion into the trial, identification of the trial and the study medication, responsible investigator, in- and exclusion criteria, the medical history, concomitant medication, efficacy and safety data. 4. Review the (e-)CRFs and check them on completeness and legibility. 5. Compare the (electronic) source documents with the (e-)CRF data for the parameters indicated in the monitoring plan. Check if all (Serious) Adverse Events have been reported, if applicable. 6. Check if all procedures (e.g. sequence of assessments) have been performed according to the protocol. 7. Resolve discrepancies with authorised investigator site staff. 8. Resolve query reports with authorised investigator site staff, conduct Source Data Verification (SDV) if necessary and ensure that all query reports are adequately completed and signed and dated if applicable. 9. Obtain completed and unused CRF pages and complete CRF page tracking form (M03/F6). If applicable.

10. Check if all outstanding actions to be taken by the site were followed-up appropriately including the availability of the necessary documentation to demonstrate that the action was taken.
11. Check the contents of the Investigator Site File for any updates, including the presence of correct versions of essential documents (e.g. Investigator's Brochure). Update essential documents checklist (M02/F2).
12. Check if the Site signature and delegation of Duties log (M02/F3) is still up to date and if all applicable documents related to site staff (e.g. CV, GCP certificate, training documentation (M02/F4) and/or financial disclosure form) are available.
13. Collect any (copies of) essential documents.
14. Where applicable perform the following activities related to the investigational product(s) (see also SOP M06, Pharmacy visit):
    - check the investigational product storage (access restrictions, environmental controls/monitoring, temperature log)
    - check expiry dates
    - check if additional investigational product is needed
    - verify that the receipt, use, and return of investigational product are controlled and documented adequately
    - compare these records with the left-over investigational product and the data in the CRFs
    - collect returned investigational product, if applicable
    - If applicable complete the investigational product transfer form (M11/F1) and/or specification form (M11/F2) and send returned investigational product to the sponsor
15. Where applicable perform a Laboratory visit to perform activities such as: check storage of laboratory samples, temperature log, shipment documentation (See also SOP M05, Laboratory Visit) .
16. Check facilities and equipment, if applicable.
17. Make an inventory of any supplies needed at the investigator site.
18. Complete site monitor log (M03/F4). Have site staff sign the log as evidence of site monitoring.
19. Communicate/discuss with investigator or other authorised investigator site staff the following
    - deviations from protocol, study specific agreements, ICH GCP, ISO 14155 and

applicable regulatory requirements: findings and recommendations. In case of deviations, complete Protocol Deviation Log (M03/F8). In case the site continuous to deviate from the approved protocol, study specific agreements and/or regulatory requirements, escalation to sponsor is required.
- enrolment rate
- change in study personnel (M02/F3)
- if facilities are considered no longer adequate to safely and properly conduct the trial; ensure these issues are solved
- financial issues, if applicable

20. Make appointment for the next monitoring visit.

3.3 Following site monitoring

Responsibility:	**Action:**
Monitor/Consultant	1. In case the site continuous to deviate from the approved protocol, study specific agreements and/or regulatory requirements, escalate to sponsor. That should be done immediately if the deviations have impact on the rights, safety and well-being of trial subjects and/or on the reliability of trial data. In consultation with the sponsor, inform the site of corrective and preventive actions to be taken
	2. Complete the site monitoring visit report (M03/F1) within the timelines as specified in the monitoring plan.
	3. In case the sponsor does not sign the report and monitoring is delegated to another TAPAS Group partner or to an external consultant (no TAPAS Group partner), the consultant is required to sign the report as evidence of review.
	4. Provide the signed monitoring visit report to the appropriate sponsor personnel for information, review and sign-off, if applicable. In case the sponsor signs the visit report, request sponsor personnel to return a copy of the duly signed report.
	5. If applicable, send collected CRF pages and completed query reports to data management and file copies in a fireproof cabinet.
	6. Forward any essential documents retrieved from the site, to the sponsor.
	7. Store essential documents, to be kept by the consultant, in the appropriate study files.

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8. Complete or update the essential documents checklist (M02/F2), ICF log (M03/F5) and the protocol deviation log (M03/F8).
9. Within the timelines as specified in the monitoring plan, send a follow-up letter (or email) to the investigator, indicating major action points. Provide a copy to the sponsor for filing in the Study Master File.
10. For any contact moment that doesn't require a complete monitoring visit report, the Contact Report Form (M03/F9) should be completed.

4 References

- Guideline for Good Clinical Practice E6 (R2) (EMA/CHMP/ICH/135/1995)
- EU Directive on GCP for the Conduct of Clinical Trials (2001/20/EC)
- Per 31 January 2022: EU Regulation on clinical trials on medicinal products for human use (536/2014)
- EU Directive on GCP regarding IMP (2005/28/EC)
- GMP Annex 13 of the Guide to Good Manufacturing Practice: Manufacture of investigational medicinal products
- 21 CFR, Part 11 Electronic Records and signatures
- ISO 14155, third edition 2020-07
- EU Medical Devices Regulation (EU 2017/745)

5 Applied forms

Form number M02/F2: Essential documents checklist
Form number M02/F3: Site signature and delegation of duties
Form number M02/F4: Site training log
Form number M03/F1: Site monitoring visit report
Form number M03/F2: Subject screening and enrolment log
Form number M03/F3: Subject identification log
Form number M03/F4: Site monitor log
Form number M03/F5: ICF log
Form number M03/F6: CRF page tracking form
Form number M03/F7: Monitoring plan
Form number M03/F8: Protocol deviation log
Form number M03/F9: Contact Report Form
Form number M11/F1: Investigational product transfer form
Form number M11/F2: Investigational product specification form

6 SOP history

Previous Version:	Effective Date:	Description of Implemented Changes:
1.0	13-JAN-2012	• Adapted forms
1.1	13-JUN-2013	• Added on front page 'This SOP is applicable to all TAPAS Group members and designees' • Added section 4 References • Added in several sections references to SOP M04, M05 and M06 • Added several additional steps and checks to perform
2.0	21-JAN-2014	• New template frontpage • 3.1 added "Check monitoring plan for study specific site closure activities. • 5 added "Form number M03/F7 and Form number M03/F8".
3.0	30-NOV-2016	• Added Form number M03/F9, Contact Report Form • Some minor corrective changes
4.0	07-SEP-2017	• Corrected reference after GCP update R2 • Added several additional steps and checks to perform: 3.1.8, 3.1.9, 3.1.10, 3.1.11, 3.2.6 and 3.2.11 • Added Form number M02/F4, Site training log • Some minor corrective changes
5.0	07-SEP-2020	• Added reference CTR (536/2014), ISO 14155 and EU Medical Devices Regulation (EU 2017/745) • Moved 3.3 action 7 to 3.2 action 14 • Updated 3.2.10 and 3.2.19; added 3.3.1 based on audit observations. • Some minor corrective changes