

Unit 4: Investigational Product, Filing, Monitoring and Close Out

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4.1 The investigational product: procurement and supply

The investigational product is the pharmaceutical form of the active substance, or the placebo, being tested or used as a reference in the trial, and mishandled product silently invalidates science: a degraded, mislabelled or wrongly dispensed product means the trial no longer knows what its participants received. The product is manufactured under good manufacturing practice for clinical use, packaged and labelled for the trial, with labelling that identifies it as an investigational product for trial use, the trial, the sponsor, the storage conditions, the expiry or retest date and the participant or kit identification the blinding system requires, and shipped to sites under the conditions its stability demands, with temperature control and monitoring where the product needs it. Receipt at the site is a documented act: identity, quantity, condition and temperature record are checked against the shipment advice before the stock is accepted. In most institutions the trial pharmacy is the receiving, storing and dispensing point, because the disciplines of this unit, custody, conditions, records, reconciliation, are the pharmacist's ordinary professional disciplines applied to an unlicensed product.

4.2 Storage, dispensing, accountability and reconciliation

Storage at the site applies pharmacy standards of custody with trial additions. The product is held in a secure area with access limited to authorised, delegated staff, under the labelled conditions, with temperature monitored and recorded and excursions reported to the sponsor and assessed before the affected stock is used. Stock is segregated by trial and, where the design requires it, by treatment code, with blinded stock handled so routine handling cannot reveal assignments. Dispensing follows the protocol and the randomisation system exactly: the right kit, for the right participant, at the right visit, recorded at the moment of dispensing with participant code, date, quantity and the dispenser's identity. Accountability is the continuous ledger binding these acts: quantities received, dispensed, returned and held, reconciled against each other so every unit is accounted for at every moment, discrepancies investigated and explained in writing at once and not at close out.

4.3 Essential documents and filing procedures

Essential documents are the documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced, in the definition of ICH GCP, and the filing procedures of this unit keep them complete, current and retrievable. The set spans the trial's life: before it, the brochure, signed protocol, approved consent forms, approvals, agreements, investigator qualifications, laboratory references and product and shipping records; during it, revised versions with their approvals, correspondence, signed consent forms and source documents, accountability records, monitoring reports and safety reports; after it, destruction records, final reports and the clinical study report.

4.4 The Trial Master File: preparation and maintenance

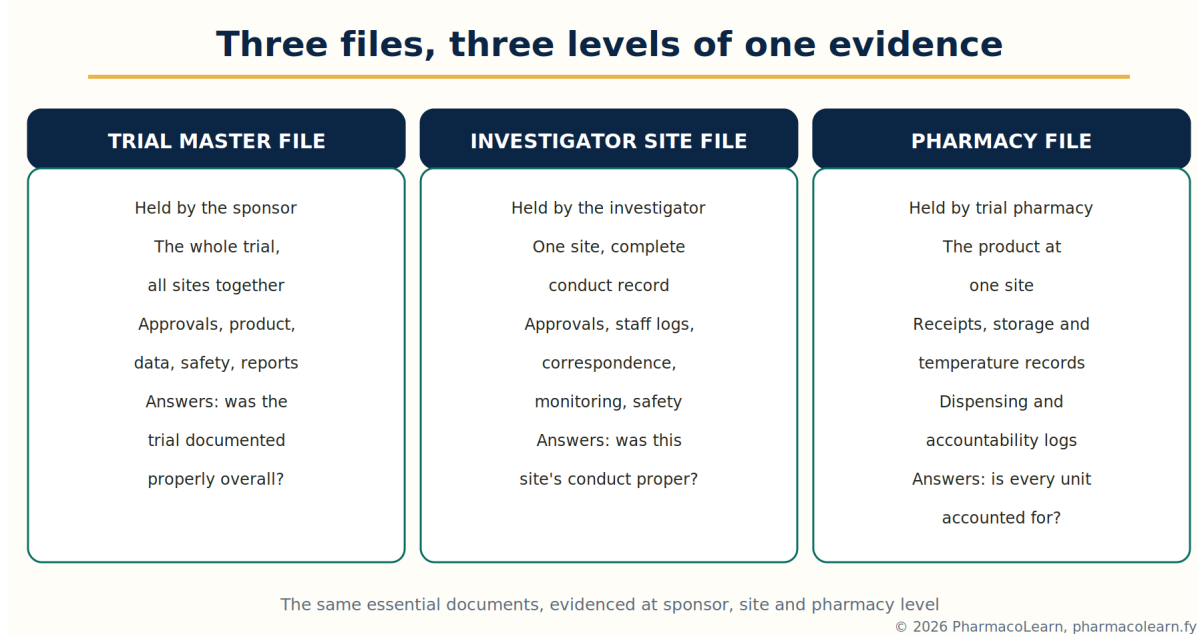
The Trial Master File, or TMF, is the sponsor side collection of the essential documents for the whole trial, the master record from which the trial's conduct across all its sites can be evaluated. Its preparation begins at start up, before the first document exists to file: a file structure is established, in modern practice following a recognised reference model, with sections for trial management, regulatory, ethics, site, product, data,

safety and statistical documentation. Maintenance is the continuing duty: documents filed as they arise, completeness checked against the structure at intervals, increasingly by electronic TMF systems that flag what is missing. The TMF is the sponsor's whole trial file; the files of the next section are its site level counterparts, and the same document commonly exists in both, the approval letter in the site file where it authorises the work and in the TMF where the sponsor proves it held it.

4.5 The Investigator Site File and the Pharmacy File

The Investigator Site File, or ISF, is the site level counterpart of the TMF: the essential documents held at the site, by the investigator, from which that site's conduct can be evaluated: the current brochure and protocol with their approvals, approved consent forms in every language in use, agreements, staff qualifications, delegation and training logs, laboratory references, product information, site correspondence, monitoring reports, safety reports, and the screening, enrolment, visit and deviation logs of daily conduct. The Pharmacy File is the specialised file of the trial pharmacy: product receipt and shipment records, storage temperature records, dispensing and accountability logs, randomisation and unblinding procedures and records where the pharmacy holds them, preparation records where the pharmacy prepares doses, return and destruction documentation, and pharmacy delegation and training records. The comparison is the examination content of this section.

File	Held by	Scope	Question it answers
Trial Master File	Sponsor	The whole trial, all sites	Was this trial conducted and documented properly overall?
Investigator Site File	Investigator at the site	One site, complete conduct	Was this site's conduct proper, approved and evidenced?
Pharmacy File	Trial pharmacy at the site	The product at one site	Can every unit of product at this site be accounted for?



lived. Its preconditions are the open gates of Section 3.7. The visit report lists attendees, topics, documents verified and conditions outstanding, and only after it, and the sponsor's written activation, may the site screen and enrol. Conduct, in the syllabus's filing sequence, is the trial as lived between initiation and close out, under one rule: the records must allow a stranger to reconstruct, for every participant, what was planned, what was done, what differed and why. Reporting flows outward during conduct, progress to the sponsor, safety reports on their faster track, deviations as required, and the continuing ethics submissions of Section 1.9; follow up covers the participant after treatment ends, safety follow up until events resolve or stabilise, and the site's open items, queries answered and findings corrected.

4.7 Clinical trial monitoring: purpose and the monitoring visit

Clinical trial monitoring is the act of overseeing the progress of a trial to ensure that it is conducted, recorded and reported in accordance with the protocol, standard operating procedures, GCP and the applicable regulatory requirements, in the guideline's definition, and it is the sponsor's principal instrument of quality during conduct. Its purposes divide into protection, of participants, consent verified, eligibility checked, safety reporting watched, and verification, that reported data are accurate and verifiable from source, product accountability holds, and the approved protocol is the protocol conducted. The preparation and conduct of the monitoring visit follows a working pattern. Preparation: the monitor reviews the site's status, data entered, queries outstanding, safety reports and previous findings, and agrees the visit's focus and access with the site. Conduct on site: review of consent forms, source document verification against the CRF, product and pharmacy review, facilities and file review, and staff discussion and retraining where gaps appear, in the detail of Section 4.8. Findings are discussed with the investigator before the visit ends, because a problem the site understands and owns is a problem already half corrected.

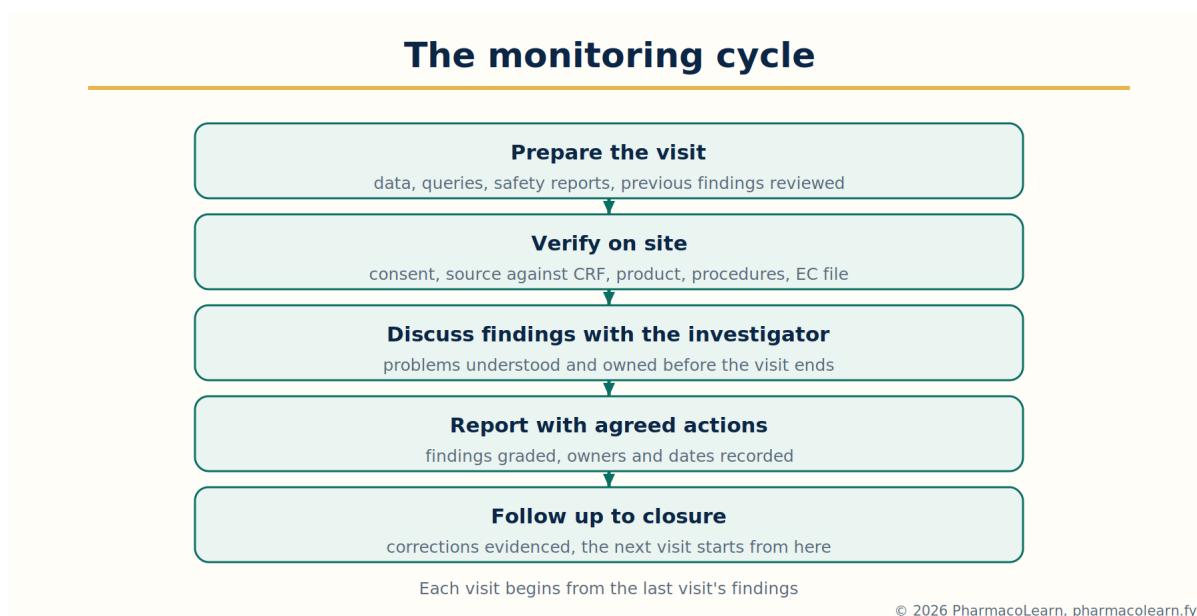


Figure: Monitoring as a cycle, not an event. Each visit begins from the last visit's findings and ends by creating the next visit's agenda.

4.8 What the monitor reviews: source, CRF, consent, product, procedures, communications and safety

The syllabus enumerates the monitoring review, and each item is a distinct verification with its own evidence. Source documents, the original records, hospital charts, laboratory reports, the diary cards of Section 3.6, are compared against the CRF and the data system, the discipline called source data verification: reported data must exist in source, agree with source, and source must contain nothing reportable that was not reported. The consent review checks every enrolled participant for the approved

version, signature and date before the first procedure, and re consent where amendments required it. Product review checks storage, temperature records, accountability arithmetic, dispensing against randomisation and blinding. Procedure review checks eligibility evidence, visit timing, delegated staff and documented deviations. EC communications are checked for current approvals and acknowledged reports, and safety reporting is checked against the site's own source records, hunting the event recorded in the chart that never became a report. Together the six reviews answer the monitoring question in full: is this site protecting its participants and producing data that can be believed.

4.9 Monitoring visit reporting and follow up

The monitoring visit is completed by its report, a controlled document with its own discipline. It is written promptly after the visit, in the sponsor's format, and records the visit's facts: date, attendees, documents and data reviewed and the extent of source verification, product and facility checks, and then its findings, stated specifically enough to be acted on, the participant codes, documents and discrepancies involved, classified by seriousness, with the discussion held with the investigator and the actions agreed, their owners and their dates. The report file sits in the TMF and the ISF among the essential documents.

4.10 The close out visit, archival, reconciliation and destruction

The close out visit is the sponsor's final monitoring visit to a site, held when the site's trial work is complete, the last participant's involvement ended, and the data entered and queried to resolution, and its purpose is to convert a working site into a closed, archived and fully evidenced one. Its conduct works the syllabus's list. Study related documents are collected or confirmed: the sponsor retrieves the documents and copies it requires, verifies that the site file is complete for archive, and leaves the site its complete record.

Investigational product is reconciled completely, every unit received, dispensed, returned, held or destroyed accounted for in the final arithmetic of Section 4.2. Archival follows the standard: essential documents retained by sponsor and investigator for the periods the applicable rules and agreements prescribe, in storage protecting them from loss, damage and unauthorised access, retrievable for the whole period; premature destruction of trial records is a serious breach. Residual product is returned to the sponsor or destroyed as the sponsor's instruction and the applicable rules direct, and destruction at site is authorised, witnessed where required, and documented with product, quantities, method and date, never performed as housekeeping on a site's own initiative. The close out visit report gathers all of it: documents collected and archived, product reconciled and its disposition, open items and their disposition, and the monitor's confirmation that the site is closed.

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