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TMF Trackers: Powering Your TMF for Inspection Readiness

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A Trial Master File (TMF) consists of the "Essential Documents…that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with all applicable regulatory requirements." (ICH E6 Good Clinical Practice, Section 8.1)

A sponsor auditor or regulatory (i.e., government) inspector uses the TMF to understand why the trial was conducted, how the trial was conducted, and the trial's outcome. The ICH E6 Good Clinical Practice guidance provides a list of essential documents. However, these documents do not give the full picture. Specifically, they do not explicitly identify documents that are expected, missing or discrepant, nor do they explicitly explain the history of the TMF's construction. (Notes to file can provide some of this information, but not in a systematic or visible way.) Without this information, it is very difficult for auditors, inspectors or even sponsor personnel to make sense of the TMF. As a result, TMF deficiencies can be left unresolved and thereby delay regulatory approvals.

Furthermore, not only must a TMF be ready for inspection when submitted for regulatory review, it must be ready for inspection at any time during study. In other words, regulatory inspectors, auditors and sponsor personnel must be able, at any time, to understand the state of an incomplete TMF.

TMF Trackers

TMFs can contain thousands of documents, authored and reviewed by numerous people at many locations. As a result, keeping track of the documents that have been submitted — or are missing, duplicate or need work — is a major undertaking, *even* with an electronic TMF (eTMF). Fortunately, there are simple tools to manage this monumental task: TMF trackers.

A TMF tracker is simply a list of documents with their status and other relevant data. With TMF trackers in hand, regulatory inspectors, auditors and sponsor personnel can easily assess the condition of the TMF and pinpoint documents that are missing or known to need work. TMF trackers provide accountability for important aspects of a clinical trial.

At minimum, sponsors should use the following trackers:

- **Document Amendments.** The protocol, informed consent form (ICF), and investigator's brochure can change multiple times during a study. Sponsors must ensure that IRB/EC approvals are obtained expeditiously and that sites use the correct versions of the protocol, consent form, and any other sponsor document.
- **Site Documents.** The TMF must include site documents like Form FDA 1572, investigator CVs, medical licenses, and financial disclosures, regulatory authority interactions, and correspondence (e.g., between the site and the sponsor). (Conditional formatting in your tracker can automatically flag expiring or expired documents, such as investigator CV and IRB approvals.)

Figure 1. TMF Tracker for Site Documents

Study	Country	Site Number	Study Personnel	Role	Document Type	Issue Date	Expiration Date
Gen-231	US	144	Cambell, Frank	PI	Medical License	31-Mar-2016	31-Mar-2018
Gen-231	US	144	Cambell, Frank	PI	CV	5-Jun-2014	5-Jun-2016
Gen-231	US	144	Cambell, Frank	PI	ICH-GCP Training	18-Sep-2015	18-Sep-2017
Gen-231	US	144	Morgan, Mark	Sub-I	Medical License	31-Mar-2016	31-Mar-2018
Gen-231	US	144	Morgan, Mark	Sub-I	CV	14-Aug-2014	14-Aug-2016
Gen-231	US	144	Knox, Jennifer	RN	Medical License	12-Feb-2013	12-Feb-2015
Gen-231	US	144	Knox, Jennifer	RN	CV	4-May-2016	4-May-2018

- **Safety.** Adverse event reports and related documents, as well as IRB/EC and regulatory authority submission dates, are of special interest to regulatory inspectors.
- **Monitoring Visits.** Site monitoring visits generate visit confirmation letters, visit reports, follow-up letters, and other visit-related documents.

Figure 2. TMF Tracker for Monitoring Visits

Study	Country	Site Number	Type of Visit	Visit Date	Visit Report	Visit Confirmation Letter	Visit Follow-Up Letter
Gen-231	US	145	IMV	23-May-2016	Present	Present	Present
Gen-231	US	103	IMV	2-Dec-2015	Present	Present	Present
Gen-231	Canada		PSSV SIV IMV COV	5-Sep-2015	Present	Missing	Missing
Gen-231	US			13-Jul-2016	Missing	Missing	Present
Gen-231	Canada			3-Aug-2015	Present	Present	Present
Gen-231	Canada	213	IMV	19-Nov-2015	Missing	Missing	Missing
Gen-231	US	145	IMV	7-Jul-2016	Missing	Present	Present

In addition, trackers can be used to maintain additional information, such as site selection and initiation dates, enrollment information, site IRB information, and vendor type and service. If such information is in your clinical trial management system (CTMS), you can, for example, determine that a site visit has occurred and a monitoring report should thus soon arrive.

Conclusion

Regulatory authorities expect study sponsors to maintain their TMFs in inspection-ready form at all times. Managing a clinical trial requires no less diligence. TMF trackers are simple and very useful tools to accomplish this objective.

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