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Investigative Site Files and Trial Master Files Should Talk to Each Other

By Sholeh Ehdaivand and Norman M. Goldfarb

In a previous article, we discussed the MAGI eISF+eTMF Initiative.[1] In summary, the major deliverable of a clinical study is an organized collection of documents called a Trial Master File (TMF). Electronic TMF ("eTMF") systems have been widely adopted to streamline the process of collecting study documents and preparing then for submission to the FDA and other regulatory authorities. More recently, research sites have been adopting electronic regulatory binders ("eISFs"— electronic investigative site files) to collect and manage their documents. Most of these documents end up the sponsor's eTMF, so there should be a way to efficiently transmit these documents, literally at the click of a button.

The following organizations are participating in the initiative: ACRP, ActivMed Practices & Research, AstraZeneca, BAF Consulting, Clinical Site Partners, Complion, Florence Healthcare, Forte Research, Health Sciences North, InnovoCommerce, Kinetiq, LMK Clinical Research Consulting, Master Control, Medpoint Digital, Mulcahy Consulting, Syneos Health, Texas Heart Institute, Vanderbilt Institute for Clinical and Translational Research, and Veeva Systems.

Commercial eTMF systems utilize a standard reference model (table of contents) developed under the auspices of the Drug Information Association.[2] However, a corresponding reference model has not been standardized for sites. The MAGI eISF+eTMF Initiative has been developing such a model. Once it has been finalized, the Initiative will map the ISF reference model to the TMF reference model so all eISF and eTMF systems can speak the same language, making "at the click of a button" a reality.

Appendix 1 presents a draft version of the Initiative's ISF reference model. We invite readers to send their suggestions for additions, deletions, changes and clarifications to Sholeh Ehdaivand at the email address below.

References

1. "Investigative Site Files and Trial Master Files Should Talk to Each Other," Betsy Fallen, Sholeh Ehdaivand, Norman M. Goldfarb, and Amy Lounsbury, Journal of Clinical Research Best Practices, August 2017.
2. "Trial Master File Reference Model," Drug Information Association (DIA) Document and Records Management Community, available at https://tmfrefmodel.com/.

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Appendix 1. Draft ISF Reference Model

Category	Document	Description
3rd Party Contracts / Vendor Communications	3rd Party Contracts / Vendor Communications	TBD
3rd Party Contracts / Vendor Contracts	3rd Party Contracts / Vendor Contracts	To document agreement of study requirements between other parties (aside from the Sponsor, CRO, and Investigator/Institution) involved in the conduct of the study
Agreements	Insurance	TBD
Clinical Research and Study Training	Evidence of Good Clinical Practice Training	Evidence and certificates related to good clinical practice (GCP) training (e.g. CITI Program Training)
Clinical Research and Study Training	Evidence of Human Subject Protection Training	Evidence and certificates related to human subject protection and/or HIPPA training (e.g. required institution specific training, CITI Program Training)
Clinical Research and Study Training	Evidence of study-Related Training	Evidence and certificates related to study-specific training
Clinical Research and Study Training	General Related Training Materials	Training materials that are not study-specific and used to train the site staff. Materials may be related to systems (e.g. IATA, EDC), etc.
Clinical Research and Study Training	Other Training Materials	Other training materials used to train the site staff
Clinical Research and Study Training	study-Related Training Materials	Training materials that are study-specific and used to train the site staff. Materials may be related to systems, protocol specifics (e.g. Protocol, Rater Training), etc.
Clinical Site Monitoring Visits	Clinical Site Monitoring Action Items	To document action items not otherwise documented in a Site Monitoring Visit Report
Clinical Site Monitoring Visits	Clinical Site Monitoring Visit Correspondence	To document monitoring related correspondence not otherwise documented in a Site Monitoring Visit Report (e.g. Monitoring Visit Confirmation Letter)
Data and Safety Monitoring Documents	Data and Safety Monitoring Plan or Communications	Describes processes to be followed for Data and Safety Monitoring. May be included in Protocol.
Data and Safety Monitoring Documents	Data Safety Monitoring Reports	Data and Safety Monitoring reports generated during the study
Draft Documents	Draft Documents	Sponsor provided ICF template(s), unapproved subject materials and advertisements
Financial Disclosure Forms	Financial Disclosure Forms	To document financial disclosures, certification documentation and conflicts of interest for research staff, which include but are not limited to: completed disclosure forms of financial interests and arrangements of clinical investigators (e.g., FDA Form 3455/3454, NIH COI , clinical investigator financial certification (Canada)).
Financial Documentation	Financial Documentation	Includes all invoices, receipts, payment summaries relating to the study

IB | Product Insert	Acceptance of Investigator Brochure	Signature page to document that relevant and current scientific information about the investigational product has been provided to and reviewed by the investigator.
IB | Product Insert	Package Insert(s) - Instructions for use	Materials available in the legal pharmacologic description of a drug or device, subject to detailed regulatory specifications, including approved chemical and proprietary names, description and classification, clinical pharmacology, approved indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence information, over dosage discussion, dosage and administration, formulations and appropriate references.
Informed Consent Documents	Assent	TBD
Informed Consent Documents	HIPAA	May be combined with the ICF
Informed Consent Documents	ICF	The appropriate written information (content and wording) has been given to subjects regarding the study to support their ability to give fully informed consent and to document their consent to study participation in writing. If applicable, must also include the child assent form (blank model / template).
Investigator Qualification Documentation	CV	To document qualifications and eligibility of any investigators who conduct study and/or provide medical supervision of subjects. Include any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows). To include updates, one-page CVs, and biographical sketches.
Investigator Qualification Documentation	Medical License	A valid and current medical license for the state/country/region where the clinical study is being conducted.
Investigator Qualification Documentation	Other Staff Member CV	TBD
Investigator Qualification Documentation	Principal Investigator CV	To document qualifications and eligibility of the Principal Investigator to conduct study and/or provide medical supervision of subjects. To include updates, one-page CVs and biographical sketches.
Investigator Qualification Documentation	Principal Investigator Medical License	A valid and current medical license for the Principal Investigator for the state/country/region where the clinical study is being conducted.
Investigator Qualification Documentation	Research Staff CV	To document qualifications and eligibility of site personnel other than the Principal Investigator or investigators to conduct study and/or provide medical supervision of subjects.
Investigator Qualification Documentation	Site Staff Qualification Supporting Information	TBD
Investigator's Brochure | Product Insert	Investigator's Brochure	To provide relevant and current clinical and non-clinical data on the investigational product(s) that is related to the study of the product(s) in human subjects

IRB/EC Approvals and Correspondence	IRB/EC Approval - Initial Submission	Documentation received from IRB/EC of record in response to submission indicating approval/acknowledgement of the initial (and applicable resubmission) submission of the study and study materials. Records referenced by the approval (such as a Protocol that has been approved) should be filed elsewhere in the TMF, as appropriate, as long as there is identification of the approved record within the IRB/EC letter or acknowledgement.
IRB/EC Approvals and Correspondence	IRB/EC Approval - Study Closure	Document detailing the termination of a study – whether upon completion or premature termination.
IRB/EC Approvals and Correspondence	IRB/EC Approvals - Amendments	Documentation received from IRB/EC of record in response to submission indicating approval/acknowledgement of study and any specifications or modifications. Records referenced by the approval (such as a Protocol that has been approved) should be filed elsewhere in the TMF, as appropriate, as long as there is identification of the approved record within the IRB/EC letter or acknowledgement.
IRB/EC Approvals and Correspondence	IRB/EC Approvals - Annual Reports	Regular reports concerning study conduct, other than safety reports, issued to the IRB/EC by the sponsor/3rd Party and/or investigator. These could include items like continuing reviews
IRB/EC Approvals and Correspondence	IRB/EC Correspondence	Formal correspondence to and from the IRB/EC to the Principal Investigator, e.g., notification of actions needed
IRB/EC Approvals and Correspondence	Reportable Events	Unanticipated problems, noncompliance, adverse events, serious adverse events and other reports to IRB/EC per local policy and regulations
IRB/EC Approved Documents	Advertisements	Including posters, ads, brochures, Dr. to Dr. letters, etc.
IRB/EC Approved Documents	subject Materials	Including questionnaires, survey, subject compensation materials, process charts, etc.
IRB/EC Documentation	IRB/EC Roster | Federal Wide Assurance	Documentation that the IRB/EC consists of a reasonable number of members who collectively have the qualifications and experience to review and evaluate the science, medical aspects and ethics of the proposed study. Documentation that the IRB/EC is performing its function according to written operating procedures and is in compliance with GCP and applicable regulatory requirements.
IRT Documentation	IRT Manual	TBD
Laboratory Documentation	Lab Manual	TBD
Laboratory Documentation	Lab Normal Reference Ranges	To define normal values and/or ranges for laboratory or other technical procedures or tests that allow for medical decisions to be made. May be included in a Lab Manual or other similar document.

Laboratory Documentation	Lab Qualifications	To document recognition and approval by an authorized accrediting body applying known acceptable standards, that the central or local facility is competent to perform required test(s) and support reliability of results; if applicable.
Laboratory Documentation	Retained Samples	Records the location and storage conditions of all body fluid or tissue samples (biosamples) being held at the study site.
Protocol	Protocol	Describes the objective(s), design, methodology, statistical considerations and organization of a study. Inclusive of all protocol amendments.
Protocol	Protocol Deviations	Records instances of non-compliance/ deviations to the protocol.
Protocol	Protocol Signature Page	Evidence of investigator and sponsor agreement to the protocol. Inclusive of all protocol amendment signature pages.
Reports	Clinical Study Report	TBD
Reports	Interim Clinical Study Report	TBD
Serious Adverse Events (SAE)/Unanticipated Problem Documents	External Safety Reports	To document serious adverse events at outside institutions. Submitted to regulatory authorities according to local IRB/EC policy.
Serious Adverse Events (SAE)/Unanticipated Problem Documents	Serious Adverse Events	To document serious adverse events (as defined in the protocol) at local institution and reported to local IRB/EC according to local policy.
Serious Adverse Events (SAE)/Unanticipated Problem Documents	Unanticipated Events	Unanticipated problems or protocol deviations or noncompliance forms. May include, deviation, exceptions.
Site Monitoring Visits	Site Close Out Confirmation Letter	To prepare for monitoring visit
Site Monitoring Visits	Site Close Out Follow Up Letter	Follow-up letter summarizing the visit and discussing any critical findings or action items.
Site Monitoring Visits	Site Close Out Monitoring Visit Report	To document study activities are completed for site closure prior to study completion. may include confirmation letters/emails.
Site Monitoring Visits	Site Initiation Confirmation Letter	To prepare for monitoring visit
Site Monitoring Visits	Site Initiation Follow Up Letter	Follow-up letter summarizing the visit and discussing any critical findings or action items.
Site Monitoring Visits	Site Initiation Visit Report	To document that study procedures were reviewed with the investigator and the study personnel and confirm the site meets requirements to begin study participation. study initiation can be conducted via an Investigator Meeting, visit at the site and/or other contact.
Site Monitoring Visits	Site Monitoring Confirmation Letter	To prepare for monitoring visit
Site Monitoring Visits	Site Monitoring Follow Up Letter	Follow-up letter summarizing the visit and discussing any critical findings or action items.
Site Monitoring Visits	Site Monitoring Visit Log	To document monitoring visit dates and attendees
Site Monitoring Visits	Site Monitoring Visit Report	To document site visits monitoring study conduct and compliance of the site.
Site Monitoring Visits	Site Qualification Confirmation Letter	To prepare for monitoring visit

Site Monitoring Visits	Site Qualification Follow Up Letter	Follow-up letter summarizing the visit and discussing any critical findings or action items.
Site Monitoring Visits	Site Qualification Report	To document onsite visit to determine qualification of site to participate in the study. For example may include the following documentation: EDC qualification, Confirmation Letters / Emails, site profile form.
Sponsor Correspondence	Relevant Communication	Zone-specific agreements, significant discussions or relevant information, but not specifically listed in this Reference Model. Types of correspondence may include, but not limited to: letters, memo, electronic communications and faxes. Should not include monitoring visit follow-up letter.
Study Communication	Investigator Newsletter	TBD
Study Communication	Note to File	Important decisions regarding study conduct, such as notes to the Study File
TBD	Ancillary Committee Approval	Documentation received from an ancillary committee in response to submission indicating a decision regarding the submission and any specifications or modifications.
TBD	Ancillary Committee Correspondence	TBD
TBD	Ancillary Committee Submission	Evidence that study information has been submitted to an ancillary committee for review. Submission Cover Letter, Acknowledgement of Receipt, Deviation, Exception, etc. (i.e.: RAC, MRI review board, etc.)
TBD	Biosketch	NIH, NCI, and AHRQ typically require use of the biosketch in applications for grants and cooperative agreements. A biosketch is used to highlight each individual's qualifications for a specific role in the proposed project. Education, Training, Employment, Certification, and License.
TBD	Clinical study Agreement	To document agreement of study requirements between sponsor or 3rd Party and site/ Principal Investigator. Includes indemnity unless separate document created.
TBD	Clinical study Budget	TBD
TBD	Clinical study Grants	TBD
TBD	Completed Case Report Form	TBD
TBD	Confidentiality Agreement	A document between the sponsor and an outside party (Investigator or Institution) that defines the terms and basic criteria to assure that the party (or parties) receiving confidential information will maintain confidentiality and will not use that information for any purpose other than that described in the Agreement. May also be present in the Clinical study Agreement
TBD	Data Sharing Agreement	To document agreement between sponsor and Site Staff (e.g., national or regional data privacy requirements); often contained in Clinical study Agreement
TBD	Documentation of Corrections to Entered Data	TBD

TBD	Enrolment Log	To list the chronological enrolment of subjects in the study. May be combined with the screening log.
TBD	Feasibility questionnaire	Evaluation of a site feasibility for a potential study. Completed by site at request of Sponsor or CRO. Feasibility Survey, Site Feasibility Form, etc.
TBD	Form FDA 1572	Form FDA 1572
TBD	Head of Facility CV	To verify that the Head of Facility is suitably qualified to lead and oversee the management and reporting of results; may be included with Certification / Accreditation; may be found in the User Manual.
TBD	Investigators Agreement	A document between the sponsor and an outside party (Investigator or Institution) that defines the terms and basic criteria to assure that the party (or parties) receiving confidential information will maintain confidentiality and will not use that information for any purpose other than that described in the Agreement. May also be present in the Clinical study Agreement
TBD	IP Accountability	Records investigational product allocation to subjects and reconciliation prior to IP return.
TBD	IP destruction documentation	TBD
TBD	IP Excursion	Records instances of excursions of investigational product from the acceptable pre-defined condition ranges during transit or storage at a site.
TBD	IP Recall Documentation	TBD
TBD	IP Sample Label	A sample of each IP label type (for every pack and every language) to be used in the study; approval status must be clear. All stages of label text development are included within this artifact.
TBD	IP Storage	Records how investigational product has been stored at a site.
TBD	Lab Sample Export Documentation	TBD
TBD	Lab Sample Shipment Documentation	TBD
TBD	Lab Sample Storage Condition Log	TBD
TBD	Material Transfer Agreement	TBD
TBD	Non-IP Documentation	TBD
TBD	Principal Investigator Conflict of Interest Conflict of Interest Other Conflict of Interest	To document financial and/or non-financial conflicts of interest for research staff, which include arrangements of clinical investigators.
TBD	Regulatory Approval Notification; other communications	Regulatory approval or authorization as well as other communications
TBD	Sample Case Report Form	Demonstrates how the data prescribed by the protocol will be collected on paper or electronic forms.
TBD	Screening Log	To list all subjects who were screened for the study including screen failures. May be combined with the enrolment log.
TBD	Shipment Records	Records shipment of investigational product to/from a site.

TBD	Site Signature and Delegation of Responsibilities Log	To document delegation by the Principal Investigator of study specific tasks to site personnel conducting the study (for reference when reviewing wet-ink-signed or initialed study documentation).
TBD	Source Data	TBD
TBD	Subject Eligibility Verification Forms and Worksheets	TBD
TBD	Subject ID Code List	Confidential list of the names of all subjects linked to their study numbers. May be combined with enrolment and screening log(s) but has specific confidentiality considerations.
TBD	Team Correspondence (internal)	TBD
TBD	Unblinding Documentation	TBD
TBD	Unblinding Procedures	To describe the plan and procedures to be taken should the action of breaking the blind for an individual subject be urgently needed, or when interim or final unblinding occurs.