BEST PRACTICES FOR ACHIEVING TMF QUALITY

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BEST PRACTICES FOR ACHIEVING TMF QUALITY

- Utilizing the TMF Reference Model
- Harnessing the power of an eTMF to drive quality and ensure inspection readiness
- Strategies for successfully implementing an eTMF

TRIAL MASTER FILE

The collection of documentation that allows the **conduct** of the clinical trial, the **integrity** of the trial data and the **compliance** of the trial with GCP to be evaluated.....

...the TMF being a **stand-alone** set of documentation that does not require additional explanation from the associated sponsor or site staff.

Article 16 of Directive 2005/28/EC

TMF REFERENCE MODEL

- Originated in 2009 as a single unified interpretation of regulations and practices across the industry
- Provides a standardized structure for organizing the TMF
- Comprised of 11 different zones that are made up of subsections and artifacts with content at the trial, country, and site level

11 ZONES

- ✓ Trial Management
- ✓ Central Trial Documents
- ✓ Regulatory
- ✓ IRB/IEC and other Approvals
- ✓ Site Management
- ✓ IP and Trial Supplies
- ✓ Safety Reporting
- ✓ Centralized Testing
- ✓ Third Parties
- ✓ Data Management
- ✓ Statistics

TMF Reference Model

TMF Zone		Section		Artifa	
1	Trial Management	1.1	Trial Oversight	1.1.1	Trial Mast
1	Trial Management	1.1	Trial Oversight	1.1.2	Trial Man
1	Trial Management	1.1	Trial Oversight	1.1.3	Quality Pl
1	Trial Management	1.1	Trial Oversight	1.1.4	List of SO
1	Trial Management	1.1	Trial Oversight	1.1.5	Operation
1	Trial Management	1.1	Trial Oversight	1.1.6	Recruitme
1	Management	1.1	Trial Oversight	1.1.7	Communi
1	Trial Management	1.1	Trial Oversight	1.1.8	Monitorin
1	Trial Management	1.1	Trial Oversight	1.1.9	Medical M

TMF Reference Model

Version 2.0 | 25-Jun-12

Sponsor Files - X: applicable; NO - Not applicable
Investigator Site Files - XS: artifact specific for one site; XG: general artifact for all sites; NO: not for ISF; NO-CS: generally not for ISF apart from for limited countries

	TMF Zone		Section		Artifact name	Alternate name	Definition / Purpose	Core or Recommended for inclusio	ICH Code	Artifact name in v1.0 EDM Reference Mod	Unique ID Numb	TMF Artifacts (Non-device)		TMF Artifacts (Device)		Investigator Initiated Study Artifacts M: mandatory, D: dependent upon the type of study, R: recommende	Process Based Metadata		Used to define paper TMF format ar electronic metadata		
												Sponsor Docum	Investigator Documen	Sponsor Docum	Investigator Documen		Process Numbe	Process Name	Trial Level Documer	Country/ Region Level Documen	Site Le Docum
13	01	Trial Management	01.01	Trial Oversight	01.01.01	Trial Master File Plan	Records Management Plan File plan Filing instructions Filing and archive plan	To document how records for the trial will be managed and stored during and after the trial, including procedure and documentation for archiving and destruction. To include TMF filing structure to be used.	Recommended	5.5.7		001	X	NO	X	NO	R	12	Develop Trial Management Strategy	X		
14	01	Trial Management	01.01	Trial Oversight	01.01.02	Trial Management Plan	Project Management Plan	To identify overall strategy for timelines, management and conduct of the trial and typically makes reference to other artifacts.	Recommended	2.2		002	X	NO	X	NO	R	12	Develop Trial Management Strategy	X	X	
15	01	Trial Management	01.01	Trial Oversight	01.01.03	Quality Plan		To outline the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled. Relevant parts may include but not be limited to a plan written for internal oversight of study quality management, an audit plan, data verification steps; also includes escalation in the event of a quality issue being identified and all corrective and preventative actions determined.	Recommended	5.1		003	X	NO	X	NO	R	12	Develop Trial Management Strategy	X	X	
16	01	Trial Management	01.01	Trial Oversight	01.01.04	List of SOPs Current During Trial		To document which standard operating procedures (SOPs) and which versions were in effect for the duration of the trial, and trial-specific procedures created for the trial. To include Sponsor and third party SOPs. This artifact does not include the SOPs themselves	Core	5.1.1		004	X	NO	X	NO	M	12	Develop Trial Management Strategy	X	X	
17	01	Trial Management	01.01	Trial Oversight	01.01.05	Operational Procedure Manual	Study Reference Manual Work Instruction	To describe trial-related processes not covered by formal standard operating procedures. Includes manuals given to sites for ISFs and vendor study-specific manuals	Recommended	5.1.1		005	X	XG	X	XG	R	12	Develop Trial Management Strategy	X	X	
18	01	Trial Management	01.01	Trial Oversight	01.01.06	Recruitment Plan		To document the planned subject enrolment/recruitment goals during the trial, including contingency plans.	Recommended	5.6		006	X	NO	X	NO	R	12	Develop Trial Management Strategy	X	X	X
19	01	Trial Management	01.01	Trial Oversight	01.01.07	Communication Plan		To document communication strategy and plans between trial stakeholders, including communication escalation procedure/steps.	Recommended			007	X	NO	X	NO	R	12	Develop Trial Management Strategy	X	X	
20	01	Trial Management	01.01	Trial Oversight	01.01.08	Monitoring Plan		To describe how monitoring will be implemented during the trial, including strategy for source data verification.	Core	5.18.3		008	X	NO	X	NO	M	12	Develop Trial Management Strategy	X	X	
21	01	Trial Management	01.01	Trial Oversight	01.01.09	Medical Monitoring Plan		To describe how medical surveillance of trial subjects will be assured during the trial.	Core	5.16		009	X	NO	X	NO	M	12	Develop Trial Management Strategy	X		
22	01	Trial Management	01.01	Trial Oversight	01.01.10	Publication Policy		To describe the policy for publishing the trial results if publication policy is not captured within the protocol.	Recommended	6.15		010	X	NO	X	NO	R	12	Develop Trial Management Strategy	X		
23	01	Trial Management	01.01	Trial Oversight	01.01.11	Debarment Statement		To certify whether the applicant, or any of its principals, is currently debarred, suspended, proposed for debarment, or declared ineligible to receive federal awards; whether within the past three years the applicant, or any of its principals, has been convicted of or had a civil judgment rendered against it for, or been indicted for, commission of fraud or certain criminal offenses; and whether the applicant has had any federal award terminated for cause or default in the past three years. Often part of the site qualification process.	Recommended		Debarment Certification	011	X	NO	X	NO	R	16	Set up site(s)	X		X
24	01	Trial Management	01.01	Trial Oversight	01.01.12	Trial Status Report		Routine trial status progress report generated by the sponsor or 3rd Party and distributed to trial stakeholders.	Recommended	5.18.4 (g)		012	X	NO	X	NO	R	21	Manage Project / Report on Progress	X	X	
25	01	Trial Management	01.01	Trial Oversight	01.01.13	Investigator Newsletter		To inform investigative staff of common implementation issues and of the progress of the trial.	Recommended			013	X	XG	X	XG	R	21	Manage Project / Report on Progress	X	X	
26	01	Trial Management	01.01	Trial Oversight	01.01.14	Audit Certificate		To document that an audit was performed. (Does not contain the audit report.)	Core	8.4.4		014	X	NO	X	NO	D	27	Conduct Audit(s)	X	X	X
27	01	Trial Management	01.01	Trial Oversight	01.01.15	Filenote Master List	Note to File Master List	To provide a consolidated list/index of file notes generated during the trial.	Recommended			015	X	NO	X	NO	R	21	Manage Project / Report on Progress	X	X	X
								A document identifying the potential hazards associated with the trial,														

Version 2.0 | Version 2.0-mark-up from V1 | Overview | Instructions and Glossary | Computer System Validation | Feedback Form

VERSION 3

- Released after DIA meeting in June
- Some revisions to Version 2 structure with minor content revisions
- Addition of sub-artifacts
- Application of interoperability

UTILIZING THE TMF RM WITHIN YOUR ORGANIZATION

- Using the RM to establish organizational core content – often referred to as “Content List”

- Review each artifact to determine the following
  - Terminology is consistent
  - Artifact is relevant
  - Identify metadata

- Establish a study specific map
  - Assign content owner
  - Identify location – during study and at archive

eTMF AS A BUINESS TOOL

- eTMF moves content from the filing cabinet to the electronic environment
- TMF content held in an electronic environment must be 21 CFR, Part 11 compliant
- An eTMF can be a very powerful business tool

eTMF AS A BUINESS TOOL

- TMF Quality
  - Completeness
  - Timeliness
  - Record Quality
- Time stamped records
- Remote review of the record in real-time
- Metrics

USING THE eTMF TO ASSESS TRIAL QUALITY

- Metrics Reporting
  - Completeness Reports
  - Quality through metadata
  - Timeliness

- Specific artifact review
  - Monitoring Reports
  - Investigator File Review

eTMF AS A BUSINESS TOOL

- CRO – oversight of alignment of study with study plans
- Sponsor – oversight that CRO activities are in alignment with the study plans
- Poor quality TMF raises concerns of the overall study quality

INSPECTION READINESS

- eTMF alone is not enough
- Quality Control of eTMF is critical to ensuring inspection readiness
  - Using the TMF map as a tool in evaluating TMF completeness

CONSIDERATIONS WHEN IMPLEMENTING AN eTMF

- TMF Structure – Standard Indexing
- Metadata to be tracked
  - System dependent
  - Searchability
  - Consider information that will enhance business operations
- Establish conventions

CONSIDERATIONS WHEN IMPLEMENTING AN eTMF

- Organization wide implications
  - Functional area needs
  - Impact on processes beyond TMF content

- Business partner implications

Challenges

CHALLENGES TO IMPLEMENTING eTMF

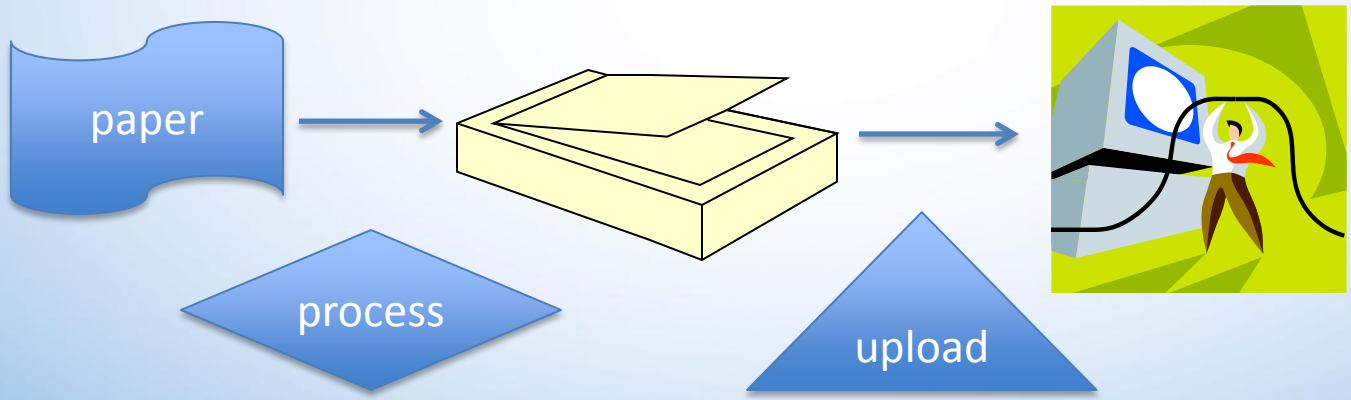
- Convincing internal business units that they contribute TMF content
- Business partners that have not adopted the TMF RM
- Content held in different locations – secure vs non-secure solutions

MANAGING EXISTING TMF CONTENT

- Document plan for converting from paper to electronic environment – include QC process

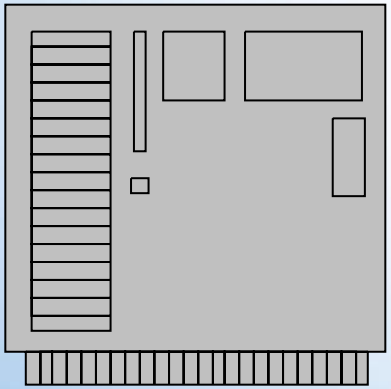
MANAGING EXISTING TMF CONTENT

- Integrating paper content into the eTMF environment

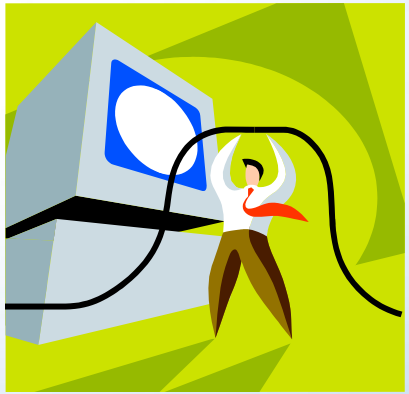


MANAGING EXISTING TMF CONTENT

- Integrating electronic content into the eTMF environment



upload



Files on shared drive

MANAGING EXISTING TMF CONTENT

- Document what was done, by whom, and results of QC check

Establishing the Authoritative Source

ESTABLISHING PROCESS

eTMF must be compliant with 21 CFR, Part 11

STANDARD PROCESS

- Maintaining Standard Indexing
- Study Set-up
- Quality Control Activities
- TMF Plan
- Maintaining System Control of the TMF
- TMF Archiving

STANDARD PROCESS

- Procedural documents
- Supporting forms
- May go through a few iterations until it works for your organization.

eTMF implementation is an opportunity for process improvement

Balance this with an implementation plan

ENSURING eTMF QUALITY

- TMF Plan
  - Includes plan for ensuring quality
- Regular quality review
  - Start-up
  - Risk based
  - Quarterly on-going review
- Document review

AT RISK CONTENT

- Amendments (country specific versions, translations)
- ICFs (country, local, translations, QC checklist)
- Ethics and regulatory submissions (translations)
- Monitoring reports (confirmation letters, reports, follow-up letters, sponsor review)

KEYS TO TMF QUALITY

- Standard indexing
- Standard process
- Using the TMF to drive study quality
- TMF Oversight
  - Ongoing QC for completeness, timeliness, document quality
  - Sponsor review

Questions??

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ABOUT: DWD & ASSOCIATES

- Quality Management Systems
- TMF Management
- Site Management with focus in Phase I/Early Development
- Sponsor Services

ABOUT: TRANSPERFECT

- 20+ Years in Global Clinical R&D:
  - Translation & Language Service in 175+ languages
  - eTMF Technology & TMF Services
  - Part 11 Compliant eClinical Suite
  - Global Call Center Services

TRANSPERFECT TECHNOLOGY

- Portal
- eTMF
- eISF
- Study Start-Up
- eFeasibility
- SAE Notifications
- Endpoint Adjudication
- Safety Database
- Document Collaboration
- LMS & Training
- Non-Clinical Doc Mgmt
- Licensing & Alliances