eTMF EXCHANGE MECHANISM STANDARD BUSINESS CASE

SAVE MONEY AND STAY INSPECTION-READY WITH TIMELY TMF CONTENT EXCHANGE

An emerging standard reduces the complexity and cost of exchanging TMF content. With interoperability between different eTMF systems, sponsors can consolidate content from multiple sources without mapping or custom interfaces. The eTMF Exchange Mechanism Standard promises to reduce update backlogs and the risk of negative inspection findings.

Keefer Consulting, Inc.

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EXECUTIVE SUMMARY

Clinical trial master file (TMF) managers face an ongoing challenge in keeping TMFs inspection-ready while incorporating content from clinical research organizations (CROs), partners, and others. Failure to be continuously ready for inspections affects the timeliness, completeness, and quality of trial records. It stresses project resources when team members must locate documents missing from the TMF. Minimizing negative TMF inspection findings would free study teams to focus more on managing successful trials.

Metadata terms describe documents. Parties exchanging TMF content frequently record metadata differently. Electronic trial master file (eTMF) software vendors define proprietary metadata for their products. Exchanging parties map metadata from the sending system to the receiving system. Mapping is resource-intensive and can cause delays. Content from multiple sources compounds the problem.

eTMF software limits viewing to one TMF at a time. Including content from other sources centralizes control, but sponsors must map the metadata from every source. This can take weeks or months, as building system interfaces is complex and costly. Some sponsors require content providers like CROs to use the sponsor's eTMF, although CROs are often more productive using their own systems.

The TMF Reference Model names and defines documents commonly used in managing clinical trials. It does not describe how to exchange content. Those working on the various TMF Reference Model committees are volunteers. The group lacks formal authority to govern the model as a standard. Participating companies adopt whatever parts of the model they consider applicable to their operations.

Sponsors need a standard to reduce the complexity and cost of exchanging content. Such a standard would support interoperability between different eTMF systems. Sponsors could consolidate content from multiple sources without mapping. Custom eTMF interfaces would be unnecessary. CROs could use their own systems. The standard would facilitate frequent TMF updates and reduce negative inspection findings.

The electronic Trial Master File Exchange Mechanism Standard (eTMF-EMS) meets these criteria. It extends the TMF Reference Model. eTMF vendors and integrators map proprietary metadata to a single exchange protocol. Repeatable processes replace one-off mapping projects. Sponsors can forgo costly programming of custom interfaces. Greater efficiency can free teams to focus on managing studies. eTMF-EMS promises faster preparation for inspections and lower migration and integration costs.

INSPECTION PREPARATION DELAYS

The EMA Good Clinical Practice Inspectors Working Group emphasizes the timely filing of documents:

> *Contemporariness of trial master file…"at all times"... means that the TMF should have all documentation added in a timely manner during the trial, as this greatly assists the successful management of a trial...This is particularly important for more complex TMF arrangements with multiple parties involved.*[1]

Failures in exchanging content occur often in "complex TMF arrangements with multiple parties":

- A CRO transfers interim TMF content to a central TMF.
- A sponsor migrates TMF records to a new CRO.
- Partners exchange TMF content during drug development.
- A sponsor transfers TMF records to an institutional review board (IRB) for approval.
- A sponsor migrates TMF content after acquiring a new compound.
- A CRO or sponsor migrates TMF records after upgrading its eTMF system.

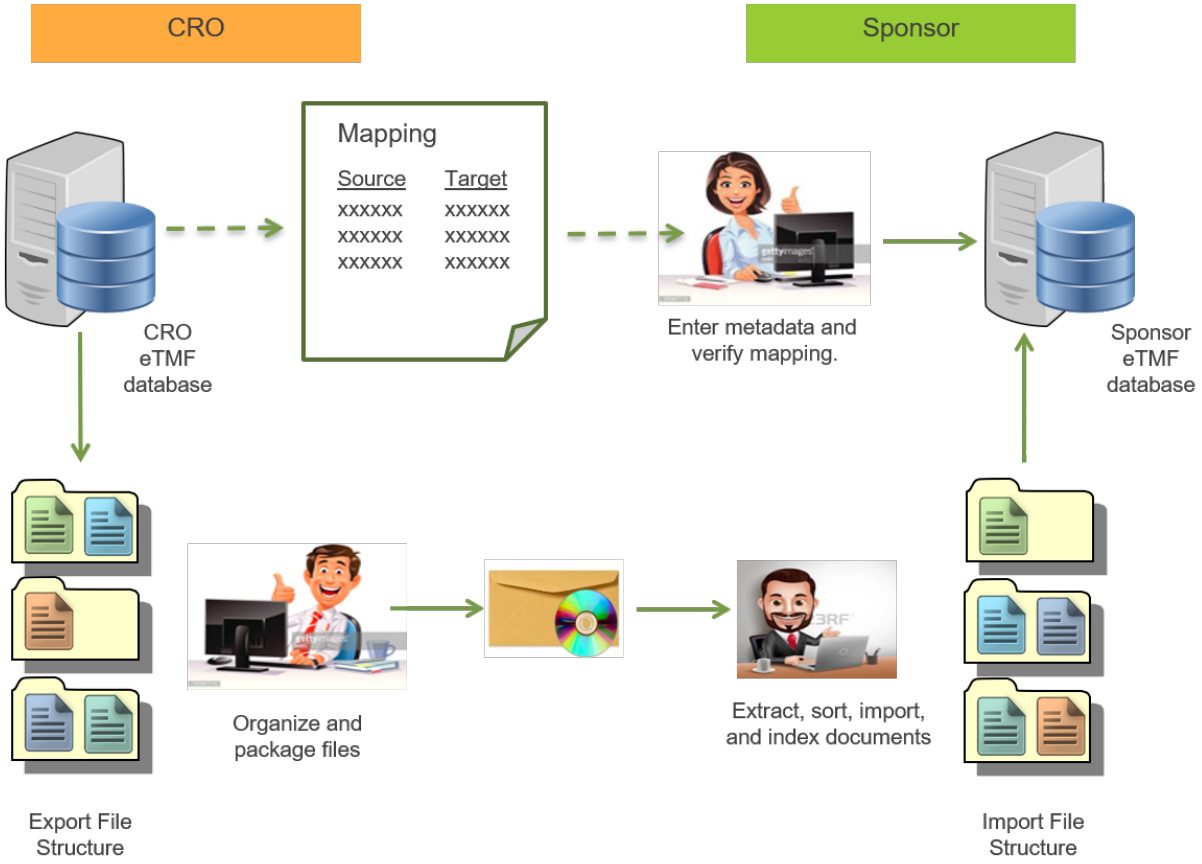
Project teams must respond quickly when inspections occur, yet updating and transferring content between parties can take weeks or months to complete. Regulators see an incomplete view of the trial without the integration of site, CRO, and sponsor content. Negative inspection findings may result and consume the attention of key people responsible for managing trials.

[1] Good Clinical Practice Inspectors Working Group (GCP IWG), (2018, December 06), Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

CONTENT TRANSFER

Metadata are terms that describe a document. The sender and receiver involved in transferring TMF content often record metadata differently. This makes it necessary to map the metadata from one system to the other. The result is a largely manual, resource-intensive process that delays updates to the target system. Transferring content from multiple organizations and systems compounds this problem.

Mappings match metadata terms as defined in a source system to those in a target system. They tell the receiving organization what metadata to enter into its eTMF system when creating documents corresponding to the ones it receives. Entry is frequently manual, as shown in the following diagram:



A one-to-one correspondence does not always exist in the mappings. One party may receive a single attribute that they translate to multiple attributes, or a receiver may combine several values from the sender into a single attribute. A custom-developed computer program may partially automate content transfer based on such a mapping.

The process affects three TMF management priorities: it affects timeliness by delaying documents expected from other parties; it affects completeness when a centralized TMF does not contain delayed documents; and it affects quality by failing to integrate site, CRO, and sponsor content. Resolving such problems can be costly and distract a study team from their focus on managing trials.

eTMF TECHNOLOGY

Electronic trial master file (eTMF) software helps store and track digitized trial records. eTMF systems support collaborative workflows for document approval, QC, and quality review. Other features relevant to inspections include inspector access, query resolution, and audit trails.

eTMFs store metadata to describe document characteristics such as title, author, or creation date. Metadata helps users categorize and search for documents. For example, an inspector may find and view documents associated with a particular country name.

eTMF Vendors have each developed proprietary standards for naming and storing metadata. Mapping is necessary when exchanging content between systems of different vendors and may even be necessary when exchanging content between different versions of the same eTMF product.

eTMF systems allow viewers to see one TMF at a time. Including documents from other sources such as CROs, sites, partners, or IRBs requires indexing and storing copies and entering metadata (often manually) to describe them. A company may invest in custom software to automate the exchange of particular document types between two eTMF systems. However, both manual metadata entry and custom automation involve a slow, costly mapping process.

THE TMF REFERENCE MODEL

The TMF Reference Model is a step toward metadata standardization. It aids communication among TMF stakeholders about naming and organizing documents. Vendors base templates on the model to help customers structure their TMFs. Companies can adapt it to their own SOPs and procedures.

While adaptability has encouraged wide adoption, this flexibility permits widely divergent metadata. In the following example, the Reference Model lists alternate names for the "Trial Master File Plan"[2]:

Artifact Number	Artifact Name	Alternate Names	Sub-artifacts	Unique ID Number
01.01.01	Trial Master File Plan	Records Management Plan Central File Maintenance Plan Filing instructions Filing and archive plan	Core Document List TMF Report TMF Transmittal Form TMF Setup Request	001

An organization may refer to the Trial Master File Plan by any of these names or by a different name. Similarly, an organization may name sub-artifacts as suggested or name them differently. An organization may decide whether or not to assign the unique ID number that the model suggests.

The TMF Reference Model is not an enforceable industry standard. It does not define metadata with the rigor that computers require. It does not standardize document types and attributes. It provides no specification for audit trails or electronic signatures. The TMF Reference Model does not describe a method for exchanging TMF content.

[2] The TMF Reference Model. TMF Reference Model v3.1.0, Released 10-SEP-2018, Excel Spreadsheet. https://tmfrefmodel.com/wp-content/uploads/2018/09/version-3-1-0-tmf-reference-model-v10-sep-2018.xlsx

MULTIPLE INTERFACES

Sponsors sometimes consolidate documents from multiple sources by copying them into one system. While this centralizes control, maintaining interfaces with multiple systems increases complexity. The exchanging parties often use eTMF systems of different versions or from different vendors. The receiving party must map the metadata from each source system to that of the target system. This process may take weeks or months, and delays are common.

Another approach is to require content providers like CROs to use the sponsor's eTMF system. However, many content providers believe they are more productive when using their own systems.

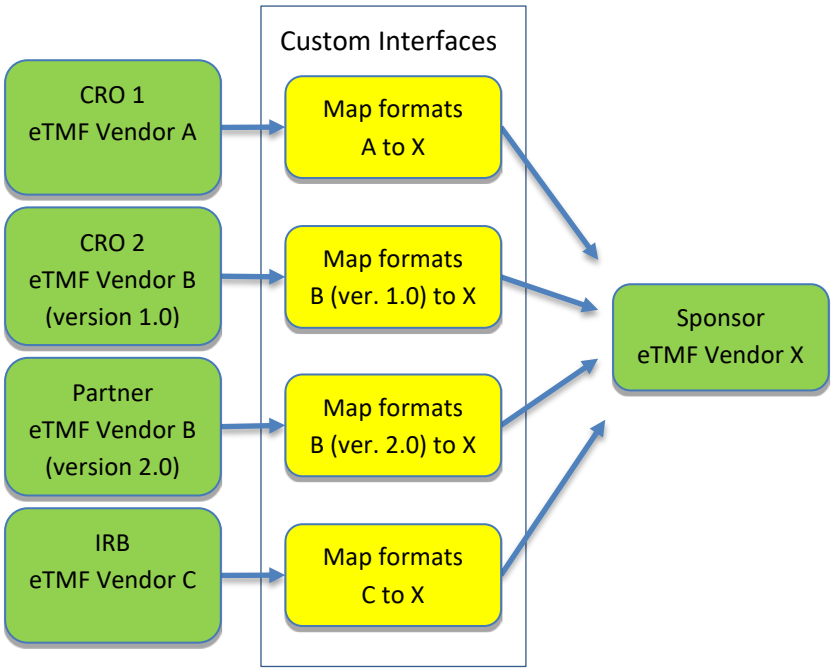
eTMF vendors use proprietary standards to describe TMF records. One eTMF may reject attribute values outside a certain range while another accepts them. Various eTMF versions and customer configurations often store metadata differently. For example, eTMF vendors modified their metadata models to accommodate sub-artifacts when Version 3.0 of the TMF Reference Model introduced them.

An organization may postpone TMF updates to avoid a disruptive mapping process. They may even wait to exchange all content at end-of-study. Such content may contain errors that have accumulated undetected. The TMF may have drifted into a state that no longer describes the trial accurately.

A regulatory inspection may occur anytime. Notice of an inspection can trigger a rush to transfer a backlog of content. It becomes easy to overlook errors that could lead to negative findings.

Multiple interfaces with CROs, partners, IRBs, and others increase complexity. This complexity can reduce resiliency to business events. A sponsor may replace a CRO, upgrade its eTMF system, or acquire a new drug. Events like these make it necessary to remap metadata or update software.

The diagram at right shows a "Custom Interface" for each source system. The sponsor maps the metadata from each source system to its own metadata. Developing each interface requires internal or external IT resources. IT developers work with TMF stakeholders to understand the mappings. Implementing and testing each custom program could involve additional stakeholders. Initial costs include those for development and for opportunities lost as the study team becomes distracted.



A NEED FOR STANDARDIZATION

eTMF systems help improve timeliness, completeness, and quality. The TMF Reference Model helps organize and communicate TMF content. Still, mapping remains a bottleneck in exchanging TMF content, which in turn causes delays in sending trial records from a site to a CRO, a CRO to a sponsor, or one sponsor to another in an M&A. Building a complex system of interfaces consumes time and money.

Ongoing readiness for inspections is critical for responding to regulators. Inspectors must be able to locate the current version of any document quickly. Keeping TMF records current could reduce time to prepare for inspections. Faster preparation and fewer findings would help keep projects on track. Reducing complexity would reduce costs.

Trial sponsors and CROs need a standard to reduce the complexity and cost of exchanging TMF content.

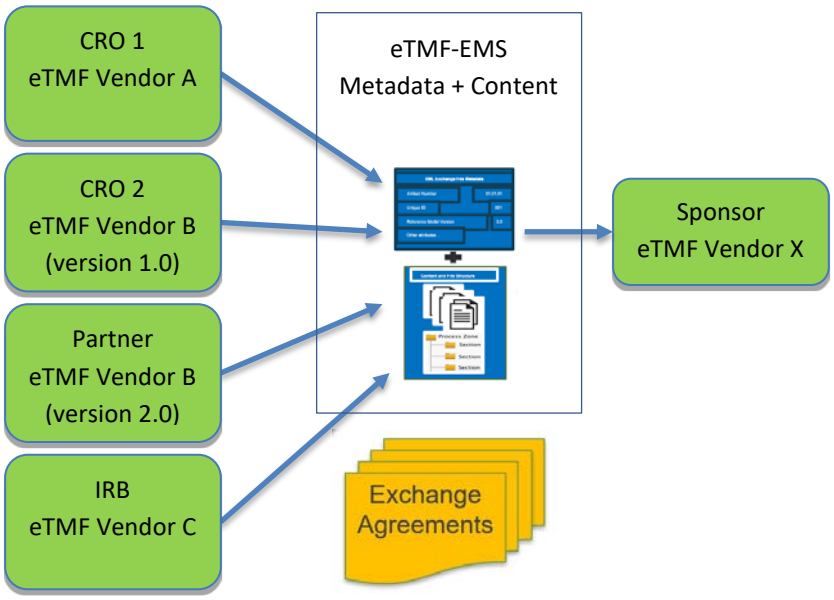
- Such a standard would support interoperability between multiple parties and eTMF systems.
- Sponsors could consolidate content from multiple sources without mapping metadata.
- Investing in custom eTMF interface development would be unnecessary.
- CROs could work in their own systems with any sponsor.
- The standard would reduce TMF update backlogs and reduce the risk of negative findings.

The electronic Trial Master File Exchange Mechanism Standard (eTMF-EMS) meets these criteria.

eTMF-EMS

eTMF-EMS extends the TMF Reference Model. The Reference Model provides a common language for business stakeholders; eTMF-EMS provides a common protocol for computers. eTMF-EMS is open and vendor-agnostic. It is based on the electronic common technical document (eCTD) standard that pharmaceutical companies use to transfer information to regulatory agencies. Any system developer may create an eTMF-EMS interface. eTMF-EMS supports the exchange of content in either direction.

Vendors of eTMF and other clinical or regulatory systems may offer eTMF-EMS interfaces as product extensions. Standard interfaces eliminate the need for mapping metadata and developing custom interfaces. A sponsor can receive TMF content from multiple sources in the eTMF-EMS format. Similarly, a CRO can send TMF content to multiple sponsors in the same standard format. The diagram at right shows how eTMF-EMS extensions replace one-off mapping projects with repeatable processes.



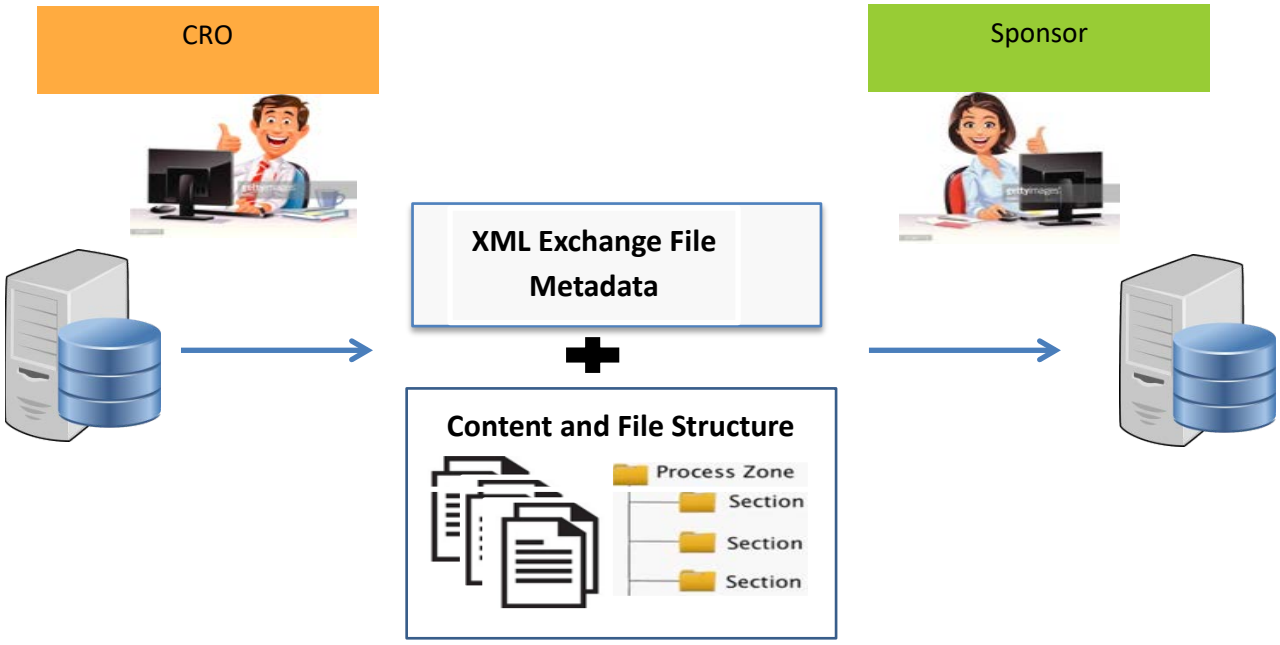
eTMF-EMS is based on the TMF Reference Model which does not standardize metadata. However, eTMF-EMS defines standard metadata terms for use in content exchange and describes how parties may adopt non-standard attributes through an *exchange agreement*. A party receiving TMF content negotiates an agreement with each of its content providers.

Parties using an exchange agreement need not invest in programming by eTMF or systems integration vendors. Changes to metadata over time may require updates to the exchange agreement, but not to computer code. An easier preparation process frees stakeholders to focus on study management and TMF oversight.

FUTURE VERSIONS

eTMF-EMS Version 1.0 supports automatic transfers from one eTMF into the database of another eTMF. Such transfers free the receiving party from manually extracting documents from source files. The receiver also avoids sorting extracted documents and importing them into its eTMF system.

Future versions would automate processes such as document indexing by study, TMF, and version and would replace manual entry or custom updating of metadata not specified in eTMF-EMS Version 1.0[3].



[3] eTMF-EMS Version 1.0 specifies metadata based on TMF Reference Model attributes; future versions will likely specify additional Reference Model metadata. The eTMF-EMS specification also describes Exchange Agreements that allow sending and receiving parties to define attributes not yet specified. The receiving party may either enter such non-standard metadata manually or develop custom programs that would update its eTMF database.

RETURN ON INVESTMENT

Common use cases include the following:

- Transfer interim TMF content to a central TMF
- Migrate TMF records to a new CRO
- Transfer TMF records for IRB/EC approval
- Transfer a final TMF from CRO to sponsor
- Archive TMF content and metadata
- Migrate TMF content after an acquisition
- Transport records after upgrading an eTMF system

Benefits include:

- Minimize negative TMF inspection findings
- Reduce update backlogs
- Prepare more quickly for inspections and submissions
- Eliminate custom programming
- Reduce costs of migration and integration
- Free staff to focus more on TMF timeliness, completeness, and quality

Costs include:

- Proof-of-concept development
- Stakeholder participation
- Training

Many companies may not have assessed the costs of TMF exchange processes. Resolving the problems this whitepaper identifies may yield significant savings for eTMF-EMS adopters.

CONCLUSIONS

Continuous readiness for TMF inspections helps minimize negative inspection findings. Frequent updates of documents and audit trails through eTMF-EMS help maintain a timely trial record. Keeping the TMF current helps ensure that the artifacts expected at each point in a trial are available. This gives regulators what they need to assess TMF quality across time periods, processes, and events.

Mapping content and metadata from multiple sources to a centralized eTMF takes time. Building system interfaces to automate such mappings is complex and costly. eTMF-EMS standardizes selected attributes of the TMF Reference Model. It supports interoperability between different eTMF systems without mapping. This results in faster preparation for inspections and lower migration and integration costs.

QUESTIONS WORTH ASKING

SPONSORS AND CROs

- Are we risking inspection findings that our TMF lacks timeliness, completeness, or quality?
- Would adopting eTMF-EMS to eliminate long, inefficient mapping processes reduce that risk?
- How much do our current processes for mapping TMF content cost in time and money?

eTMF VENDORS

- Would our customers value eTMF-EMS compliance?
- Would a focus on eTMF-EMS compliance differentiate our product and lead to greater sales?

SYSTEM INTEGRATION VENDORS

- Would removing the mapping burden for our customers offer a significant opportunity?
- Could we earn customer good will by lowering the costs we charge for TMF migration services?

ALL STAKEHOLDERS

- Could the drug development industry benefit from standardizing the exchange of TMF content?
- Would embracing eTMF-EMS now contribute to industry-wide acceleration of drug development and reduction of costs?

RESOURCES

eTMF-EMS Specification
https://tmfrefmodel.files.wordpress.com/2018/06/etmf-ems-v1-0.pdf

Technical Framework
https://github.com/TmfRef/exchange-framework

XML Schema
https://github.com/TmfRef/exchange-framework/blob/1.0.01/TmfReferenceModelExchange.xsd

LinkedIn Group
https://www.linkedin.com/groups/12136956/ or Search "TMF Exchange Mechanism Standard (EMS)"

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The goal of this whitepaper is to help clinical and regulatory operations leaders understand what their processes for updating TMFs may be costing in money and lost opportunities.

Keefer Consulting Inc. http://keeferconsulting.com/ helps biopharmaceutical companies improve R&D productivity and compliance through effective management of clinical and regulatory data. Ken Keefer, Principal Consultant, served as project manager in the development of the eTMF Exchange Mechanism Standard, Version 1.0 for the TMF Reference Model.

To assess how your company can reduce TMF update backlogs and the risk of negative inspection findings, contact Ken Keefer at 215-462-1601 or kkeefer@keeferconsulting.com, or schedule a call at https://calendly.com/kenkeefer/15min.

The views and opinions expressed in this whitepaper are those of Keefer Consulting Inc. and should not be attributed to DIA, the TMF Reference Model, or the TMF Reference Model Exchange Mechanism.