

# The eTMF Movement – An Industry-wide Responsibility

*James DeSanti*

The regulatory winds have started to blow again around the topic of Trial Master Files (TMF), but this time they're emanating from Europe and blowing west. Europe is taking the lead in providing regulatory direction and guidance out of sheer necessity. With 27 member states in the European Union (EU), all face the issue of EU-wide approvals as well as approvals from a national level. With the advent of global clinical trials, however, this will also have major implications for North American companies. And as the guidance becomes more stringent in terms of access and availability, pharma organizations are starting to proactively look at their TMF systems and determining whether a more strategic investment should be made in terms of technology.

Technology vendors are scrambling to bring new solutions to market for the conversion of TMF systems to Electronic Trial Master File (eTMF) solutions. With Europe still predominately on paper when it comes to TMF, the conversion could be massive in terms of effort and cost. However, the benefits greatly offset these obstacles for both the regulatory side of the equation (transparency and patient protection) and the sponsor side (reduced cost over the long term, transparency, patient protection, reduction in headcount).

Although Europe and North America have similar issues with TMF, they differ in terms of what systems are used, how they are implemented, the regulatory issues, and future direction. The regulatory landscape in particular for these two regions differs on this topic and requires careful navigation to understand both their current position and future direction.

In May 2007, the FDA released a guidance report for "Computerized Systems Used in Clinical Investigations." <sup>1</sup> Because "FDA's acceptance of data from clinical trials for decision-making purposes depends on FDA's ability to verify the quality and integrity of the data during FDA on-site inspections and audits," <sup>1</sup> the document had to include recommendations for how trial data was collected, managed, analyzed, and submitted. Among others, the oft-referred-to ALCOA guidelines were referenced (Accurate, Legible, Contemporaneous, Original, and Attributable).

However, a June 2010 Reflections paper from the European Medicines Agency (EMA) on "expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials" <sup>2</sup> took this a bit further and provided a breakdown of the general principles to be adhered to in terms of electronic data capture. Per section 6.1, "the

basic concept of source data is that it permits not only reporting and analysis but also verification at various steps in the process for the purposes of confirmation, quality control, audit or inspection." <sup>2</sup> This document expanded upon the ALCOA guidelines to include four more conditions to be considered regarding trial data and its corresponding reports: Complete, Consistent, Enduring and Available when needed (CCEA).

Each of these four conditions should be present in both paper-based and electronic trials; however, when using an eTMF system a sponsor can rest assured that their data and records are:

- Complete – Computers can check data and records for completeness in fractions of a second, 24 hours a day at a fraction of the cost of human review.
- Consistent – Edit checks can be placed within the system to check for consistency and provide electronic notifications to the responsible party or parties if there are issues.
- Enduring – Electronic records can be stored in multiple places indefinitely at a fraction of the cost of paper solutions.
- Available when needed – This is the most significant one,

providing regulators, sponsors, and sites with available data when needed. With global trials, operated by global companies, seeking global submissions, the documents must, in turn, be “globally accessible.” And with the advent of remote monitoring, documents now also need to be accessible remotely.

While the combination of both the ALCOA principles and CCEA conditions currently provides adequate guidance and oversight from the EMA, more modifications will have to be made in the future to properly align all industry parties.

Keeping this in mind, sponsors are now faced with the choice of whether to move forward with an investment in an eTMF system or stick with their paper-based practices. To make an informed decision, they must first consider what data and documents they must collect, analyze, and submit. The term “essential documents” is the bedrock foundation of both TMF and eTMF; however this definition will most likely be redefined during the transition from TMF to eTMF. For example, the FDA definition of “essential documents” is not specific. This is a challenge for a sponsor running a multisite, global trial. Each site could be operating under various definitions of what they perceive constitutes an essential document. However, for sponsors deploying an eTMF system, all documents are immediately classified as essential, and, as such, are captured within the system.

The list for what constitutes as “essential” can go on and on – for instance, correspondence could be classified as essential, requiring all emails to be indexed, reviewed and included. However, as a consequence of the industry’s inexhaustible

appetite for data generation and retention, the size of these files will most likely grow as storage, retrieval, and retention capabilities become ubiquitous within the technology. The upside, of course, is that sponsors will no longer struggle with the different interpretations of essential documents – *all* documents will be retained and therefore available at their fingertips.

Europe is leading the charge for guidance and standardization around eTMF for another reason – the FDA’s “guidance” still follows the path of interpretation versus clearly defined standards. While interpretation suggests flexibility and, in turn, less oversight, the reality is that standardization will ultimately be the most cost-effective universal approach. A clear understanding of what the guidance is at the beginning of any project will help sponsors make more strategic investment decisions at the outset, versus scrambling to make changes after the fact. The latter, as we all know, can be a much more timely and costly path.

In many areas of clinical research, organizations such as CDISC provide invaluable assistance in generating, educating and supporting standards. Since TMF is not currently supported by this assistance, there are other organizations starting to provide insight in both standards and pathways forward. For example, the DIA has a Clinical Data Management Special Interest Area Committee (SIAC) dedicated to creating a global forum to share, evaluate, and disseminate information on processes, standards, and technologies for the management of clinical data. While this committee has begun to put forth templates from which guidance and/or standards will be

launched, it will take a more global and industry-wide commitment to keep pace with the changing landscape of clinical trials.

The clinical “Eco System” (Sponsors, CROs, technology providers) is also going to be disrupted, as the enforcement of these regulations requires different products to be introduced, potentially integrated and deployed. Technology providers will develop the source products that larger service organizations will then implement across their sponsor client base, and this trickle effect across the industry will likely take place over time.

There will be those tempted to introduce an eTMF system on top of their paper-based platform without making the full commitment to replace the original platform altogether. While it may be the instinctive choice, choosing to bridge the gap between TMF and eTMF utilizing integration would be a mistake. History too often repeats itself in our industry and not to the benefit but rather the detriment of the industry’s evolution. The tendency to rely on technology integration rather than replacing systems altogether is a chronic industry pattern. eTMF and TMF have different approaches and, ultimately, results cannot be reconciled with one platform or system. Sponsors should make the decision to either stay with paper and the suppliers that support this platform, or follow a strategic movement toward a commitment to install an eTMF system on a global basis. This is the only option consistent with the path toward global harmonization.

The move toward eTMF is indeed a long-term commitment that is not without challenges. Sponsors must recognize that a dedicated

movement towards eTMF will likely require an adjustment of sponsors' existing processes, people, and infrastructure. However, the long-term advantages far outweigh the short term challenges and with a true vendor/sponsor partnership approach, this process can be significantly eased and even accelerated. For this movement to work effectively there must first be the facilitation of a knowledge transfer whereas both parties (vendors and sponsors) must be decisive up front in their decision to move toward eTMF completely. Standard Operating Procedures (SOPs) should be readily available for editing for the sponsors, who should not have to endure the time or the cost of SOP generation. Work instructions and work practices should be transferred to the sponsors quickly and cost effectively so they can switch from generation mode to edit mode. Following this model will require less manpower and ultimately less cost. Job descriptions, training programs, and most importantly validation

processes need to be transferred to the sponsors, or made readily available, at cost structures that facilitate adoption and not impede it.

This is just a sample of the measures both sponsors and technology vendors must consider for an industry-wide move to eTMF to be successful. If sponsors and their partners make the decision to commit to eTMF, the regulatory bodies around the globe can remain focused on the importance of bringing life-saving drugs to market at a quicker pace. With Europe at the forefront passing guidance and standardization that requires data and records to closely follow the ALCOA + CCEA guidelines, we are one step closer as an industry toward universal adoption. For sponsors to keep pace, an investment in an eTMF system must be considered as a mission-critical, strategic decision.

#### References

1. U.S. Department of Health and Human Services, Food and

Drug Administration (FDA), Office of the Commissioner (OC), *Guidance for Industry Computerized Systems Used in Clinical Investigations*, <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.PDF>

2. International Conference on Harmonisation / Good Clinical Practice, *The Principles of ICH GCP*, <http://ichgcp.org/2-the-principles-of-ich-gcp/> ■



*James DeSanti is founder and CEO of Pharma Vigilant.*