CLINICAL INFORMATICS NEWS

How Effective Are Study Startup Regulations?

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By Craig Morgan

The clinical trials sector is highly regulated, and justifiably so. Biopharmaceuticals that patients need and depend on must be safe and effective, which is why international regulations for Good Clinical Practice and an array of regulatory guidances focus on how clinical trials should be conducted. But study startup (SSU), one of the most complicated and challenging parts of the clinical trials process, has surprisingly few guidelines. With limited regulations focused on this early part of clinical trial execution, what does it mean to be compliant? It is a fair question at a time when SSU execution is singled out as needing improvement, particularly with the growing number of costly protocol amendments. Fortunately, cloud-based technology built to aggregate data from multiple sources can provide transparency into SSU status in real time, making compliance more achievable.

Compliance is a major subject for stakeholders charged with managing documents that should be audit-ready, but in looking across a multitude of international regulations, it is difficult to find a definition. To address this regulatory gap, many have turned to the trial master file (TMF), or eTMF, a sponsor's permanent collection of essential documents meant to enable reconstruction and conduct of a clinical trial. As part of that effort, a sub-group of the Document and Records Management Community of the Drug Information Association (DIA) oversees the TMF Reference Model, which provides an infrastructure for filing these documents using standardized taxonomy, nomenclature, and metadata. Now in its third version, the Reference Model is divided into zones, sections, and artifacts that break down the clinical process to a granular level to track numerous critical functions. It records how clinical trial obligations were fulfilled, reflects the quality of data produced, and demonstrates compliance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements. Yet, despite its broad scope, Section 8.1 of the ICH-GCP guidelines denotes that only a minimum set of documents are essential, so it remains unclear how even a well-executed TMF that is ready for regulatory review ensures compliance. Research by Hecht et al. supports this notion, stating that currently, no quality characteristics have been defined for TMFs to a level of completeness needed to ensure acceptable quality.

This uncertainty about compliance is evident when it comes to protocol amendment-related issues that often confound the SSU process, such as:

- Completeness of all documentation pertaining to each amendment
- Lineage of each document

These challenges continue because achieving SSU compliance requires a route other than the TMF. As a tool for reconstructing study conduct and for archival purposes, the TMF is designed to maintain completed essential documents for 30 years. It is not intended to track clinical trial operations on a daily basis, i.e. SSU document completion, as a trial unfolds. That role is better served by solutions purpose-built for providing insight into operations in real time. Significantly, those technologies can determine the status of each SSU function much sooner than is possible with completed documents that do not flow into the eTMF until just prior to study activation. This is a major benefit, especially for tracking progress of amendments and the degree of documentation needed to ensure they are properly implemented.

Amendments Are Difficult

According to research from the Tufts University Center for the Study of Drug Development, protocols have become more complicated in recent years. In a typical Phase III study, for instance, the total number of endpoints grew to 13 over 2011–2015 versus just seven a decade earlier. At the same time, the number of procedures jumped to 163, up from 97 in the 2001–2005 timeframe, a 68% increase. With this rising complexity, amendments have become more commonplace—sometimes occurring within 30 days of protocol completion—and they are costly. Tufts research suggests that sponsors are implementing at least one substantial global amendment for nearly 60% of all clinical trial protocols, which tends to reduce the number of patients enrolled while lengthening clinical trial timeframes and costs, averaging $141,000 for a Phase II study and $535,000 for Phase III.

Because of this growing complexity, proper tracking of amendment-related documents is gaining in importance as part of an overall shift toward process improvement. This is driving stakeholders to move beyond the TMF Reference Model as a tool for compliance, as it focuses only on the minimal amount of completed essential documents needed for archival purposes. For example, artifacts in the Reference Model are labelled as “Core” or “Recommended”, which may encourage stakeholders to overly emphasize core functions for purposes of regulatory inspection. But, to streamline SSU operations, such as protocol amendment documentation, “recommended” functions add value and should also be considered (Chart 1). Complementing this effort, cloud-based technology can play a key role with its ability to identify a document’s source—its lineage—through data from consolidated clinical trial solutions, showing its many versions, its translation into multiple languages, and review by monitors. This level of transparency would not be available through the eTMF alone.

Sponsors Define Their Own Path

When it comes to improving SSU compliance, clinical trial regulations are frustratingly vague. With the exception of the so-called Gray Guide, released in 2012 by the UK's Medicines and Healthcare Products Regulatory Agency, which suggests moving beyond the minimal number of essential documents to include all documents needed to reconstruct the trial conduct, there is little else when it comes to regulatory direction. For example, the updated ICH-GCP E6 (R2) guideline, released in November 2016, has an expanded section on Essential Documents (Section 8.1), but it focuses mostly on ensuring the investigator maintains control of the case report form data reported to the sponsor. The Food and Drug Administration (FDA) has not offered any guidances on the subject of the TMF beyond ICH-GCP E6 (R2), and the recent clinical trial regulations put forth by the European Medicines Agency mention the TMF, but mostly in the context of archiving essential documents.

With such minimal guidelines to plot a course toward compliance, sponsors are defining their own strategies. Pfizer, for example, has identified three key steps to determine eTMF quality:

- Completeness
- Document quality, i.e. are they accurate, properly indexed, and retrievable
- Timeliness, whereby the documents are flowing into the TMF during the study so they are available in a timely manner

These topics are built into the Reference Model, but additional guidance is needed to address how to achieve compliance. Without specific regulatory guidance, companies are stepping up to devise their own compliance-based standard operating procedures. They are raising the bar, possibly by including the recommended steps mentioned in the Reference Model as a way to trace document lineage and provide transparency for stakeholders trying to understand how a trial is unfolding and why an amendment is needed.

Issues that generate amendments stem from the protocol and impact an array of documents, such as the informed consent form, the investigator's brochure, the Investigational New Drug file in the US and the Investigational Medicinal Product Dossier in Europe. With clinical trials playing out on the international stage, multiple regulatory bodies and languages are involved, and the volume of documents generated by amendments is overwhelming. This scenario requires stakeholders to examine how to streamline process improvements and provide the level of transparency needed to enhance the quality of clinical trials while operating in a compliant manner.

Craig Morgan *is a technology and life sciences management professional with more than 15 years experience in the application of informatics and bioinformatics to drug discovery. He currently heads up the marketing and brand development functions at goBalto, working with sponsors, CROs and sites to reduce cycle times and improve collaboration and oversight in clinical trials.*

Craig Morgan
Head of Marketing | goBalto