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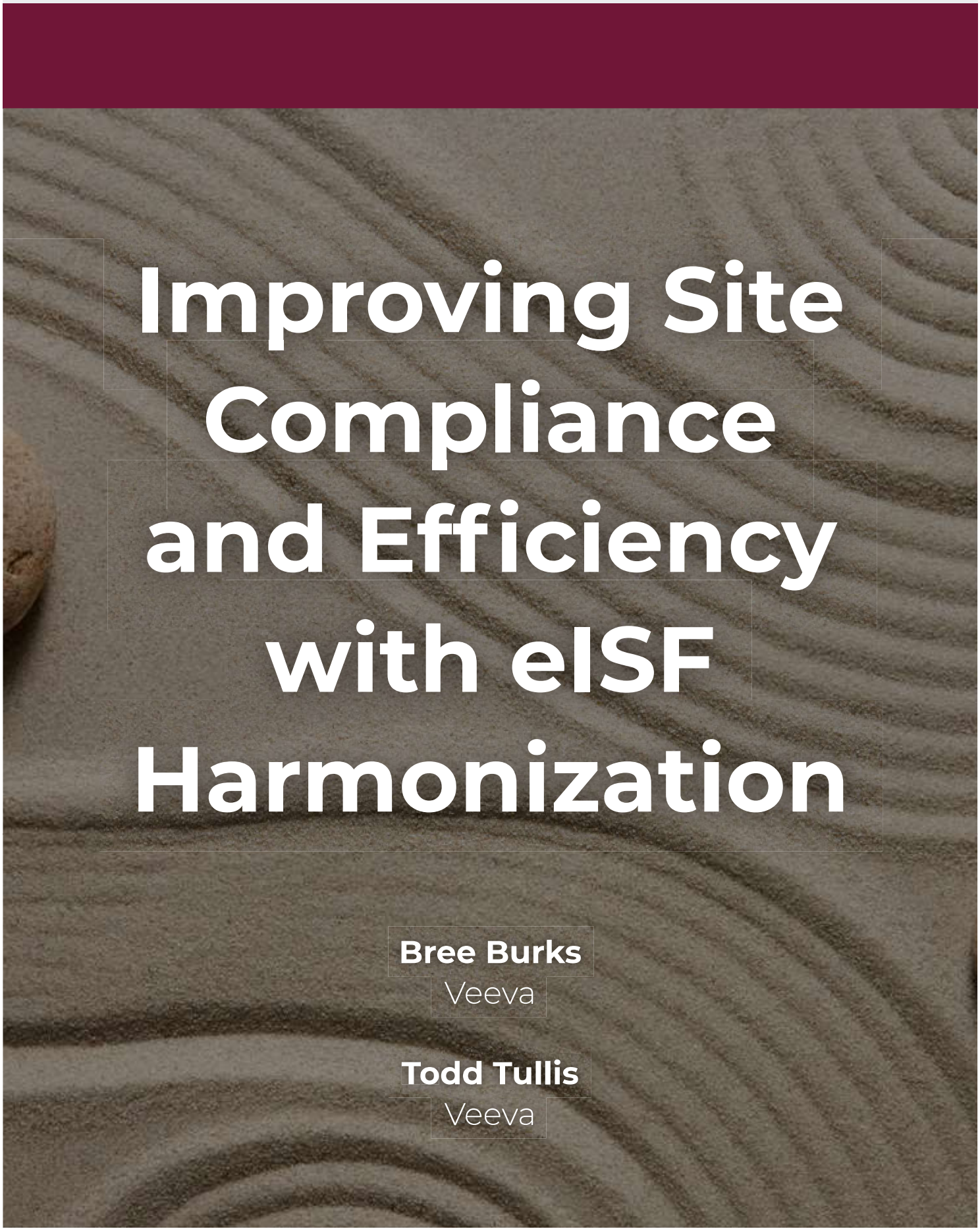

# Improving Site Compliance and Efficiency with eISF Harmonization

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Clinical research sites face a growing number of regulatory, technical, and administrative hurdles associated with maintaining compliance. From this growth in complexity, the ability to produce documentation detailed enough to support compliance and quality data has overwhelmed regulators, sponsors, and, most of all, research sites. Standardization represents a significant opportunity to improve record keeping and simplify compliance at sites.

## Sponsors Standardize on the TMF Reference Model

In 2009, sponsors and industry professionals from the **DIA Documents and Records Management Community** discovered that the list of essential documents listed in International Council for Harmonisation-Good Clinical Practice (ICH GCP) guidelines did not provide a complete scope of the actual records managed in their trial master file (TMF), the sponsor's official record of the clinical trial. Document nomenclature and filing conventions varied wildly across teams and organizations, and **inconsistencies in structure** from one TMF to another made it difficult to speak the same language, review quality and completeness, and evaluate potential mergers and acquisitions.

documents to a comprehensive taxonomy complete with standard nomenclature to enable consistent filing. As sponsors and CROs digitized their records, the TMF Reference model structure was integrated into document management and electronic trial master file (eTMF) systems to streamline adoption and simplify information exchange. While adoption of the reference model is not mandatory for regulatory compliance, its use is recommended to improve processes and harmonization.

## Bringing Standardization to Sites

While sponsors have enjoyed the benefits of the TMF reference model and eTMF systems, sites continue to execute each protocol without a standard model – and mostly on paper. The problem is exacerbated when sponsors enforce varying binder structures on sites. As a result, the investigator site file (ISF) has no standard taxonomy, is unique to each study site, and is often managed on paper. Without a standard, sites face increasing difficulty maintaining consistency and compliance across all their studies.

Some suggest that sites should use the TMF reference model. However, it is difficult for sites to adopt the reference model because it was developed primarily from a sponsor perspective, is much larger in scope than is necessary, and its terminology is not intuitive for sites.

“The growing complexity across small research sites and large academic medical centers necessitates greater standardization in regulatory maintenance,” said Jessica B. Collins, associate director, program for investigator-initiated trials, at Vanderbilt Coordinating Center. “We struggled to fit the TMF Reference Model into our practice as the nomenclature and structure didn’t meet our needs. Defining a standard model for investigative sites benefits both sites and sponsors through greater compliance, time savings, and competency.”

Several industry groups, sponsors, and sites agree that **a reference model for sites is needed**. An ISF reference model will standardize filing structures and provide the following benefits:

- **Maintain compliance:** ICH GCP E6(R2) contains a list of minimum essential documents only. An eISF reference model would standardize filing expectations for documents collected, including

the completeness of the eISF easily and without manipulating any paper documents.

- **Improve competency:** Clinical research professionals can be trained easily and effectively with a model that presents regulatory standards and associated materials in an organized and structured way. Site staff can begin study start-up immediately without the need to create a custom file structure. Site coordinators can more easily transition between studies without relearning a file structure.
- **Drive consistency:** Standard nomenclature reduces confusion about a document's contents and reduces the time spent locating a document. Workflows, such as routing documents for review and signature, can be automated within electronic systems to improve efficiency and ensure adherence to SOPs.
- **Simplify collaboration:** Monitors can more easily transition between study sites and get up to speed on new sites. A standard data model will also lay the foundation for document exchange between eISF and eTMF systems. The standardized file structure and metadata of a comprehensive reference model facilitates implementation of an eISF and simplifies integration with other eClinical tools, including CTMS, IRB, and other systems.

The result would be improved compliance, efficiency, and better study outcomes — a clear win-win for all study stakeholders.

## Prior Attempts to Standardize the ISF

Because of the benefits of an ISF reference model, several draft models have been proposed in the last decade. Of the models that have gained greater attention, no one model has gained widespread use. The two most common weaknesses are due to approaching the development with a checklist or folder structure mindset.

Checklists of paper documents that should be filed in a site's paper regulatory binder have existed for decades. Expected document checklists, although a useful tool, distract stakeholders from thinking critically about the study-specific circumstances and associated documents of their study. Both ICH GCP and the TMF Reference Model User Guide caution against

Other ISF reference models are biased towards old-fashioned paper folder structure practices and simply map a site's documents to digital file folders. People are used to storing and managing electronic documents in digital folder structures because they closely resemble paper folders. However, this doesn't provide sites the guidance necessary to modernize their own processes. Without a comprehensive ISF model built with electronic purpose-built systems in mind, sites can't align on broader standards, old habits risk returning, and the proverbial can is kicked further down the road.

## Real World Solution for Sites

A true reference model requires a mindset shift away from traditional paper and folder structures and must be comprehensive enough to support a site's transition into digital and purpose-built systems. Technology-based ISF solutions must fully address the present and future needs of sites in order to add value.

"Our overall goal is to extend new therapies for humanity," said Collins. "The efficiency gains of standard naming conventions, keyword searching, automated workflows, and real-time reporting would help us achieve that goal."

At minimum, a comprehensive eISF reference model would provide a standard attributes, or metadata, to each study document, such as record type, document date, status, study ID, and filing location. These metadata attributes uphold naming conventions, simplifies searching, drives reporting, determines user access, and streamlines the transfer of documents into the sponsor's eTMF.

Beyond these fundamental attributes, standardizing other elements such as signature requirements and originality status help save site stakeholders time by reducing confusion and unnecessary cycles.

Ultimately, the goal of a comprehensive model is to achieve the long-term benefits of standardization, including increased quality, reduced regulatory risk, better visibility through reporting, and process automation, which will ultimately lead to happier sites and better study results.

better meet their regulatory obligations by freeing up precious resources and returning a site's focus to what is most important: the thoughtful care of patients and the production of knowledge that heals.

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