# TMFs become key differentiator for CROs as stakeholders demand better collaboration and access

R&D outsourcing continues to rise sharply to meet the demands of life sciences organisations' growing pipelines, but CROs have to keep evolving or more nimble competitors will take their place. Regulatory pressures are also growing to improve the Trial Master File (TMF) inspection process. Many CROs are still stuck in the pre-digital age, but some are now using electronic TMFs to provide real-time visibility, increased control and improved compliance to stakeholders. The onus is on CROs to play a more strategic role in order to develop long-term, trusted partnerships and deliver and facilitate faster time-to-market for sponsors.

By Rik Van Mol

**34**It's no secret that competitive pressures are mounting for contract research organisations (CROs). Life sciences companies need to get to market faster and do so more efficiently, and that means working with strategic partners that are able to enhance rather than hinder this process. As a result, the stakes for CROs are high.

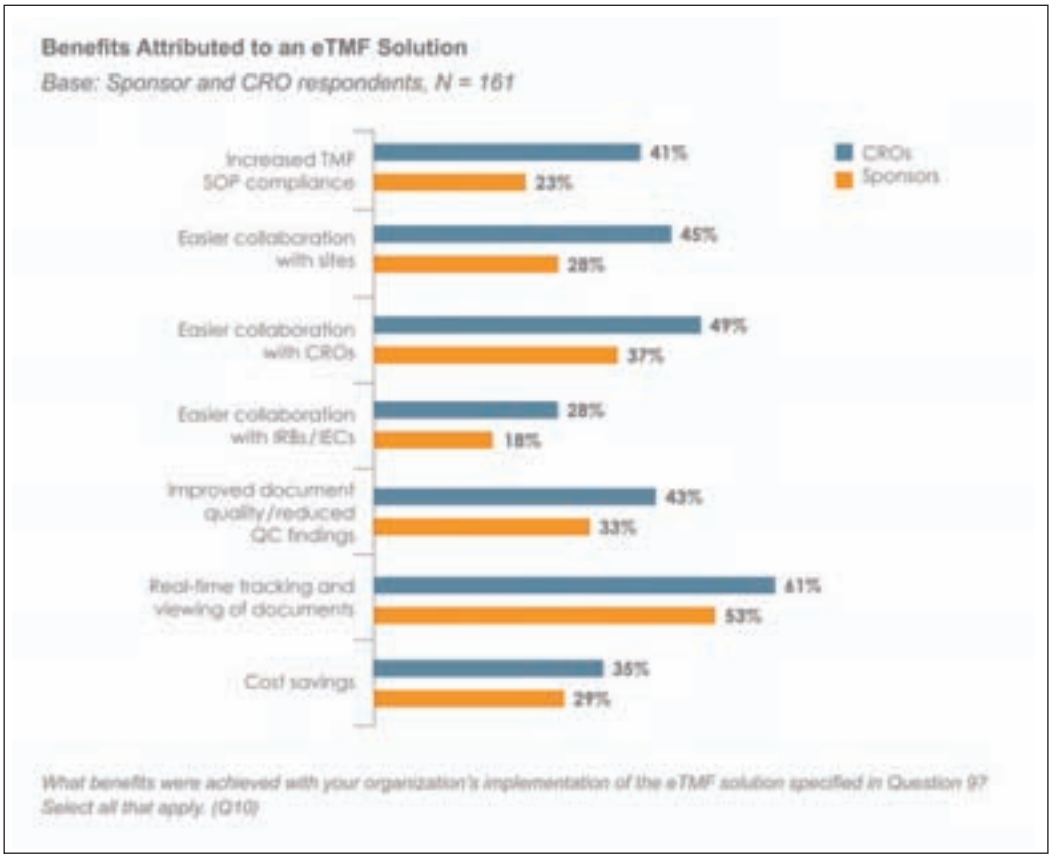
One of the key components in enabling relationships with sponsors to prosper is the quality of the Trial Master File (TMF) system. Many CROs are still stuck in the pre-digital age, tabulating clinical data in a paper-based format that makes it challenging for both sponsors and health authorities to access relevant information as and when they need it. However, some organisations have embraced the opportunities that technology offers to improve this state of affairs.

Enter advanced electronic Trial Master File (eTMF) applications. These cloud-based eTMF applications give CROs the technology foundation needed to provide real-time visibility, increased control and improved compliance to all stakeholders, including sponsors, sites and investigators, throughout the clinical trial process. By eliminating the paper-based and file-share systems that lead to costly delays, errors and inefficiencies, CROs can establish a foundation for sustainable collaboration with sponsors moving forward.

According to the Veeva 2014 Paperless TMF Survey: The State of CRO TMFs, one in five CROs is now using a purpose-built eTMF application to manage the mass of documentation in clinical trials. These forward-looking CROs have experienced major benefits (**Figure 1**), including increased inspection readiness, higher-quality TMFs and improved collaboration with external partners.

However, this research shows the majority of

Figure 1




CROs are still using paper-based or simple file-share systems to manage TMF documents. These outdated technologies hinder collaboration and limit sponsors' visibility and control over the clinical process.

## Facing today's TMF challenges

Traditional paper and file-share systems are time-consuming and resource intensive, requiring an inordinate amount of manual effort to maintain TMF quality and completeness, which can seriously affect relationships with sponsors. Documents are typically stored in both paper and electronic format (making version control difficult), and are often siloed by functional area or organisational boundary. This inevitably leads to process redundancies and duplicate documents, not to mention unnecessary compliance risk, all of which require time and effort to reconcile. When a typical Phase III study can generate many thousands of documents, this is no trivial matter. Add to this the increasing complexity of study protocols, the global nature of clinical development, and the growing number of trial stakeholders (CROs, sites, agencies, committees, etc), and it is no wonder that the act of simply compiling multiple trial documents into a coherent and readily accessible TMF has become a massive headache and organisational nightmare for CROs and sponsors alike.

Yet technology exists that can radically improve this process. For example, using a collaborative eTMF application in the cloud can provide a single source of truth during the entire study. All stakeholders – whether investigators, monitors or even inspectors – can access the same documents and associated workflows, which helps to increase visibility, compliance and efficiency, and ultimately encourage a trusted and lasting partnership between CRO and sponsor.

## Creating a single source of the truth

eTMF systems that are easily and securely accessible by all remove barriers between sponsors and CROs. This fosters trust and creates an environment conducive to real-time information sharing throughout the entire trial process. Strategic collaboration also improves dramatically when technology removes internal and external silos. According to the Veeva 2014 Paperless TMF Survey, CROs using purpose-built eTMF systems report significant improvements in collaboration with sponsors, while almost half of

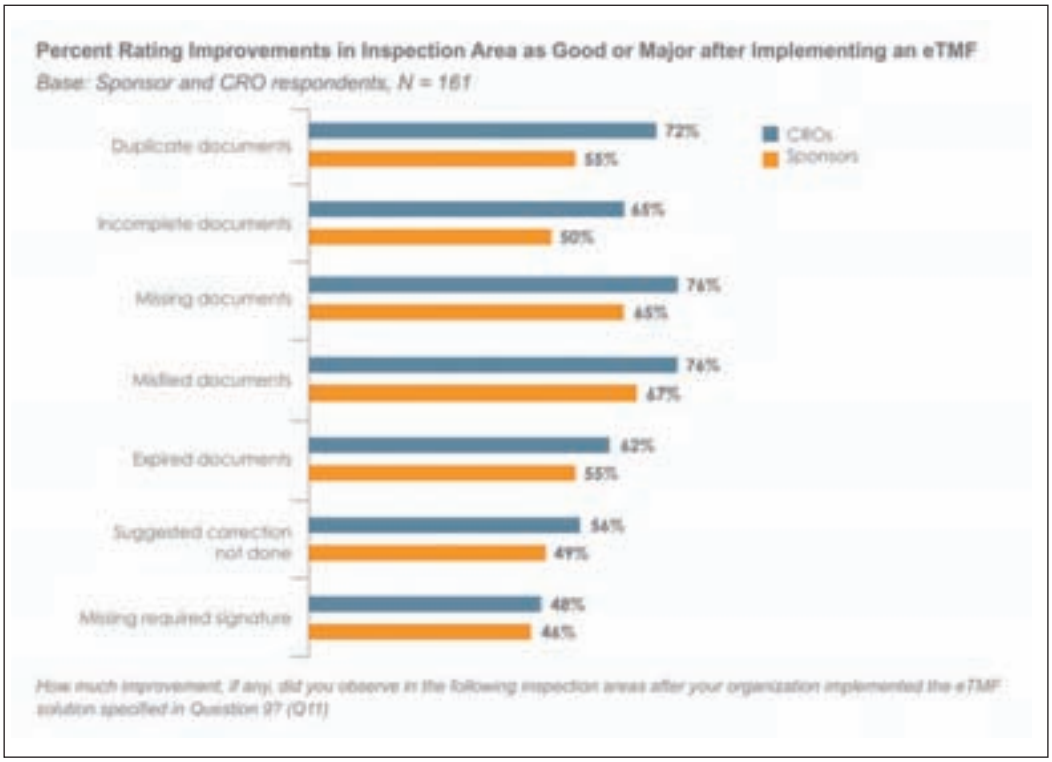
the CROs surveyed report easier collaboration with sites (45%) and other CROs (49%).

The results also demonstrate that many CROs report improvements in real-time tracking and viewing of documents (61%) and increased document quality (43%). Jessica Vicari, Director of Regulatory Support Services and Document Management at global CRO Advanced Clinical, said: "The Veeva TMF survey results are eye-opening, yet point towards a clear-cut way for all CROs to step up their level of support to sponsors. We invested in a cloud eTMF 12 months ago and almost immediately began collaborating more efficiently with sponsors."

Using an eTMF application provides a single point of access for both CROs and sponsors throughout the clinical trial – from site feasibility to study start-up and through database lock – so everyone is always working with the most up-to-date versions of documents. With better visibility, sponsors have more control over content and grow increasingly more secure in the relationship. Sponsors can collaborate with CROs in real time and still maintain a single source of the truth. "With a cloud-based eTMF, we can provide sponsors with total transparency of trial data and enable a richer, more collaborative partnership for improved trial results… including faster time-to-market," said Gregg Dearhammer, COO at inVentiv Health Clinical, a top eight CRO.

PharmaStart, another global CRO, has been able to provide increased visibility and control to its clients since implementing a cloud-based eTMF globally across more than 75 investigator sites. Rebecca Moraris, Director of Clinical Operations at PharmaStart, said: "Securely accessible in the cloud and as easy to use as Amazon, our new eTMF ensures both external and internal teams can fully leverage the system. Everyone can work in parallel, so we don't wait, for example, while documents are shipped to sites or a wet signature is captured via courier from locations all around the globe. It also provides total transparency and a better vantage point for sponsors, sites and internal groups to identify problems early and fix them quickly."

Figure 2




## Improving inspection readiness

It isn't just sponsors that want better levels of transparency. While paperless technology can improve visibility, collaboration and control between CROs and sponsors, it also enables inspection readiness – a top concern of life sciences companies. CROs using advanced eTMF applications report improvements in many inspection areas, including reduction of missing (76%), misfiled (76%), duplicate (72%), incomplete (65%) and expired (62%) documents (**Figure 2**).

Health authorities are increasingly seeking electronic access to TMFs. In April 2014, the Medicines and Healthcare Products Regulatory Agency (MHRA) updated its definition of a critical good clinical practice (GCP) finding to include TMFs that are incomplete and inaccessible. Specifically, the MHRA says the TMF is not compliant if it "…is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection..."

Incomplete TMFs are a common problem when the TMF is predominantly paper-based. With no single source of truth, documents may be in different boxes or filing cabinets, or even geographically dispersed. Adding hours to the audit process just to assemble the right content can influence the auditor's and inspector's perception of the sponsor's compliance efforts. Paper can also be easily damaged or even destroyed during the trial process, which can also result in an incomplete TMF.

The MHRA tightened its parameters on TMFs after repeated inspection delays. In 2013, 33% of sponsor inspections required extra days due to an incomplete TMF or lack of accessibility. Now, adding fuel to the fire, nearly 30% of inspectors in the UK are refusing to use paper, requiring access to an eTMF instead, according to the Drug Information Association's (DIA's) 2014 TMF survey. With other regulatory authorities likely to follow the precedent set by the MHRA, TMFs worldwide will come under increasing pressure to address these issues.

Cloud-based eTMFs can mitigate this challenge and greatly improve inspection readiness because they are always available and accessible, supporting sponsor compliance objectives by enabling rapid responses to health authority inquiries. Inspectors can quickly search across an entire TMF in a matter of seconds to access and view relevant content. Eldin Rammell, a clinical records management expert and Managing Director at Rammell Consulting, said: "In the face of MHRA's updated definition for critical findings, it is encouraging that organisations utilising eTMF applications are experiencing significant benefits in inspection readiness and business efficiency gains."

The Veeva 2014 Paperless TMF Survey reveals

an increase in the number of clinical trial sponsors that plan to provide auditors with remote access to their eTMFs. More than 32% of TMF owners surveyed report that they will grant auditors remote access to their eTMFs by early 2015, versus the 16% who provide them with access today – a jump of 100%. An additional 12% of survey respondents indicate they will give remote access to their eTMFs "as soon as they have the technology to support it".

## Going paperless and changing perceptions

According to the Veeva 2014 Paperless TMF Survey, CROs are swamped in paper, using more than their sponsors across all functional areas. Contracts and clinical operations teams are the most paper dependent, with 59% of all contracts (52% for sponsors) and 47% of all clinical operations documents (41% for sponsors) still in paper format.

In addition, 80% of CRO survey respondents reported using email and 65% still rely upon paper-based methods, to share TMF documentation, whereas the number of sponsors exchanging TMF documents via email (64%) and paper (52%) is lower. Although email is technically electronic, it offers few advantages over manual paper-exchange methods. It is faster, but it is still unstructured communication that is highly insecure and not integrated with the TMF, which inevitably creates version control issues.

One explanation for CROs' continued reliance on paper is an outdated perception that institutional review boards and ethics committees require wet ink signatures on all physical documents. However, since the major health authorities in the US and Europe now accept electronic signatures on the majority of TMF documents, this is a perception that quickly needs to change. Kythera, a clinical-stage biopharmaceutical company that can now capture electronic signatures, is building new procedures to take full advantage of this time-saving convenience. "Historically, we collected many more signatures than the government requires, adding a lot of inefficiency to the process because

everything gets stalled while we wait on those signatures," said Renee Fate, Kythera's Senior Manager of Document Management. "Electronic signatures will prevent needless delays in creating submission-ready documents."

Going paperless enables CROs to eliminate slow, risk-prone manual hand-offs, and create new efficiencies they can pass on to their cost-conscious sponsors. Any CRO which can demonstrate improvements here – swapping one type of paper for the kind that pays for new research – provides a tremendous competitive advantage. Unsurprisingly, 63% of CROs surveyed said that cost savings were a top driver of eTMF adoption. Another significant benefit of cloud eTMF systems is that, once defined, they can easily be reused from study to study, speeding start-up on all future studies.

Improving efficiency, collaboration, control and compliance by breaking the paper chain enables CROs to maintain stronger, more collaborative relationships with sponsors. But in order to reap these benefits, CROs need to take the initiative and drive change by going electronic.

## CROs gain the most from a streamlined model

While both sponsors and CROs stand to benefit from driving industry-wide transformation with new eTMF technology, CROs have the greatest opportunity to positively impact the most products in development. One CRO can be involved with many different studies and their corresponding sponsors, whereas a sponsor generally influences just its own products. In an industry where the top eight CROs account for more than 66% of all clinical trials, their position as agents of change is a significant one.

As sponsors increasingly outsource clinical operations, including TMF management and oversight, it is CROs that can gain the most from more automated and streamlined clinical processes. While sponsors benefit from real-time status updates, improved trial quality and inspection readiness, CROs benefit from a more efficient, scalable model that enables them to leverage technology across hundreds of trials and thousands of sites. The TMF survey shows that CROs report large improvements in SOP compliance (41%) and improved document quality, with fewer QC findings with their eTMF applications than their sponsors (23% and 43%, respectively).

IDDI, a biostatistical and eClinical services provider headquartered in Belgium, has not looked back since it transitioned to a cloud-based eTMF application. "We were looking to move from our hybrid system (part paper and part online file share) to a single, digital solution for improved quality, efficiency, and control, while allowing our colleagues and clients to easily access data through the cloud," said Linda Danielson, COO. IDDI migrated most of its active studies to a cloud eTMF in 2013, followed by 40 new studies in 2014, and reports improved partnerships. "Our eTMF enables effective collaboration since sponsors can review, edit, and approve documents in real time."

## Part of the problem or part of the solution?

R&D outsourcing continues to rise sharply to meet the demands of life sciences organisations' growing pipelines, with CROs contributing to the development of all of the top 20 selling drugs in 2013. But CROs have to keep evolving or more nimble competitors will take their place. And increasingly, the TMF is becoming a solution to distinguish themselves as trusted partners.

Life sciences companies themselves are moving away from what have been largely manual TMF processes and simple file shares, towards advanced eTMF technologies, to enable paperless trials. In fact, the number of TMF owners actively building or evaluating eTMF applications to support more efficient collaboration throughout clinical trial studies is up from 17% in 2010 to 34% today, according to a 2014 DIA TMF Reference Model survey. In the industry's big push forward, CROs cannot afford to lag behind. There's too much to lose and much more to gain by embracing e-collaboration.

Sponsors may already be embracing cloud-based collaboration, but CROs are in an important position to drive wider industry acceptance and use. "CROs have a tremendous opportunity to distinguish themselves from the pack and position their organisations as long-term partners," said Ken Getz, Director of Sponsored Research Programs and Professor at Tufts CSDD. "There's a lot at stake for all parties, so it's vital that CROs urgently build the modern infrastructure, top talent and compliant processes that will lead to efficient and safe drug development."

In conclusion, CROs need to critically review their operational processes. Are they using technology to provide better insight and improve collaboration with sponsors, partners, regulators and review boards? Or are they still reliant on outmoded ways of information sharing that complicate relationships, and critically, increase time-to-market? In other words, are they part of the problem, or part of the solution?

Early adopters of eTMF systems have already reaped significant benefits, including streamlined operations, increased visibility and access and improved collaboration across the clinical ecosystem. These forward-looking CROs are well positioned to establish themselves as long-term partners, critical to the success of their study sponsors. Having anticipated the demand for eTMF systems, they are in the best position to help companies meet the challenges of the life sciences industry going forward. DDW

***Rik Van Mol*** *is Vice-President of R&D strategy for Veeva Systems.*

*The Veeva 2014 Paperless TMF Survey: The State of CRO TMFs examines the current state of eTMF adoption among sponsors and CROs, as well as the benefits, drivers, and barriers to implementing electronic processes. This research builds upon respected surveys conducted by the TMF Reference Model group by providing additional insight into the remaining sources of paper and the types of eTMFs utilised. The full Veeva 2014 Paperless TMF Survey showed that advanced eTMF solutions, in particular, deliver greater visibility, inspection readiness, SOP compliance and cost savings over local or cloud file systems. Process-driven functionality and easy, secure cloud access to eTMFs enables CROs, sponsors, investigator sites and other partners to more effectively and efficiently work together. All parties benefit from greater visibility throughout the trial, plus sponsors are better prepared for remote or on-site inspection. Additionally, health authority inspectors are easily granted access to an eTMF in the cloud without elaborate training or complicated provisioning.*