Phone: +1 833 366 6887
Email: contact-us@ennov.com
Website: en.ennov.com

White Paper

Unified CTMS and eTMF

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Taken together, CTMS and eTMF contain the body of documents and data necessary to plan, manage and document a clinical trial. Historically, these have been two separate systems, often loosely integrated using vendor tools (APIs).

In the latest generation of eClinical infrastructure, these formerly disparate systems are merged. The result is that users no longer work in "CTMS" or "eTMF", but in a harmonized clinical infrastructure where a single source of truth is a given, and changes and additions automatically impact the appropriate data, documents and processes.

The impact of a unified CTMS and eTMF can be dramatic. Benefits include:

- Elimination of the need to plan, implement, validate and maintain integrations
- Single source of truth for information about studies, sites, milestones, documents, and much more – eliminating discrepancies or time lags for updates
- Increased efficiency through automation, for example automating the planning of TMF, production of key documents, and more
- Increased insight through the production of harmonized reports and dashboards interpreting a richer body of data
- Improved risk management based on a greater knowledge of risk triggers

This paper provides concrete recommendations for key areas where a unified CTMS and eTMF can result in the greatest benefit.

1. Automate planning of the contents of the TMF using CTMS data

Your CTMS holds the master data about a study – protocol information, countries and sites of conduct, investigator information, and more. If this information doesn't exactly match what is used for eTMF, there's a problem somewhere.

In a unified CTMS and eTMF, information only exists once, so this common problem can be eliminated. As a study is set up (in what is traditionally thought of as CTMS), information should drive the initial planning of the TMF, and trigger changes to the TMF when the plan changes.

When the trial is initially planned, there are many aspects that will drive the documents needed in the TMF. In most cases, this will result in creating of planned documents (placeholders) in eTMF, but information can also be used to drive security, metrics, and more.

CTMS Information	TMF Impact
Study information: ID, protocol title, therapeutic area, indication, phase, sponsor and/or CRO, etc.	• Used to create backbone of TMF • Used to tag documents for metrics analysis (e.g., completeness by CRO or for a given therapeutic area or phase) • Triggers planning of core documents for the study • Controls security access to the TMF (for specific sponsor or CRO)
Protocol design: randomization, blinding, etc.	• Determines the need for specific artifacts such as IP Unblinding Plan, End of Trial or Interim Unblinding, and various Randomization documents • Governs the need to handle unblinded documents in a specific TMF
Countries of conduct	• Triggers planning of core documents for the country • Drives the need for specific country level documents such as Health Authority (HA) submissions and approvals, registries, etc. based on the country's requirements (ideally in conjunction with Regulatory Intelligence) • Impacts the need for translations
Sites of conduct and associated site personnel	• Triggers planning of core documents for the country, plus any site documents required in the country of conduct • Triggers the planning of documents for each team member based role (Principal Investigator, Sub-Investigator, etc.)
Monitoring Visit Schedule	• Triggers planning/due dates of documents related to each visit
Committees	• Drives the need for documents for each committee (charter, member list, output, etc.)
Labs and other facilities	• Drives the need for documents for each lab (certification or accreditation, normal ranges, head of facility CV, etc.)
Training Plan	• Defines the list of training materials needed for the trial and the evidence of training needed per individual or site

All this planning can be automated. For example:

- The monitoring visit schedule should trigger the creation of placeholders for documents such as the confirmation letter, monitoring visit report, and follow-up letter for each visit. Each placeholder should be clearly named with the document type and visit ID, and should be assigned a due date based on an offset from the visit date.
- The creation of a new sub-investigator for a site should create placeholders for that sub-I's documents, such as CV, medical license, and training documents. (Just creating a batch of these based on an expected number of sub-Is, without identifying by name, is not helpful.) For bonus points, existing documents for that person could be linked in automatically. However, that approach should be used with caution as multiple investigators with the same name could exist, or CVs might need adjustment to cover qualifications for a specific trial.
- Placeholders for lab and committee documents can be created and tagged with the specific lab or committee name, giving greatly increased insight into TMF completeness.

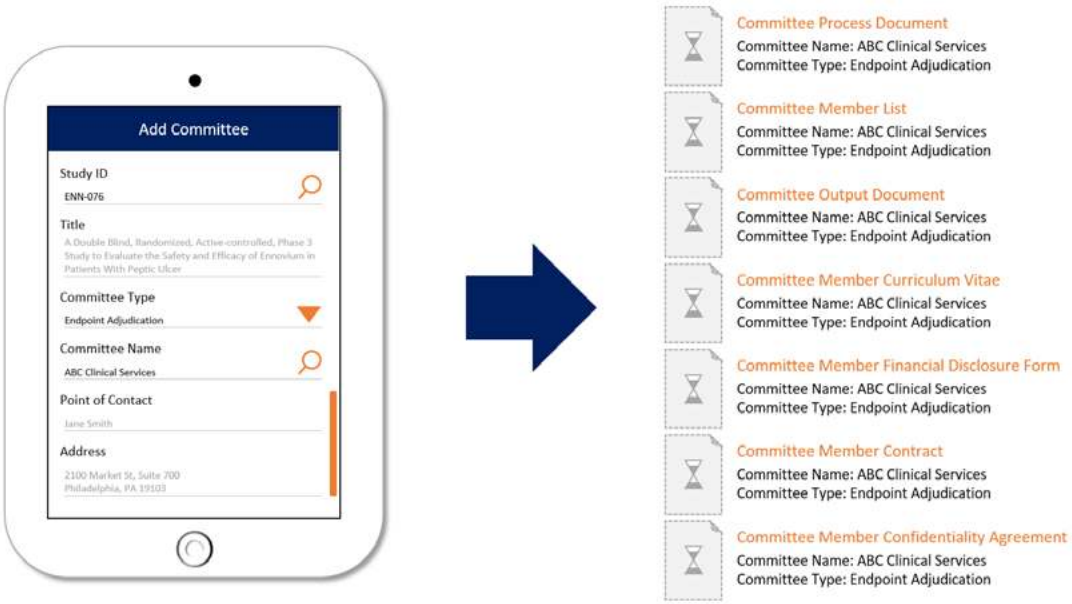

Figure 1 shows an example of how document placeholders can be automatically created for a new Endpoint Adjudication committee.

As the trial evolves over time, changes may occur. For example, additional sites could be added, or a new lab could be selected, and CTMS updated accordingly. This should trigger the automatic creation of appropriate placeholders in eTMF. Other events may also be useful, such as flagging the need to update a signature log when new site personnel are added.

2. Monitor progress using a consolidated view of the trial

CTMS milestones and events are associated with planned and actual dates, and sometimes related to sets of documents. For example:

- Drug Shipment / IP greenlight for each site requires a set of final documents such as IRB approvals, protocol signature pages, and many more.
- IRB/IEC submissions require the protocol, IB, informed consent, investigator CV, advertisements, financial disclosures, etc.
- Site Closeout requires the receipt of all expected documents from a site

The unified CTMS and eTMF allow milestone tracking to include both these documents and non-document tasks (often found in checklists) to be monitored in a single view to determine when a milestone is truly complete. For example, a site initiation milestone might require a set of documents to be received and finalized, but also require the monitor to complete a series of questions confirming what was discussed with the site.

Using a unified CTMS and eTMF, the milestone can be represented holistically as a collection of data, documents and processes, allowing tracking and close-out in a single location. This approach also provides a more complete picture of incomplete and overdue activities, and provides a user with the ability to prioritize his or her workload to concentrate on what is needed immediately.

3. Create documents from data

A CTMS excels at collecting structured data. In some cases, this can almost entirely automate the creation and filing of documents. For example, data collected in CTMS can trigger the creation of monitoring visit documents such as confirmation letters, monitoring visit reports, and follow-up letters. Timely filing of these documents is critical – the MHRA notes "Monitoring visits rely on the information in the previous report, so the previous report should be completed and filed in the TMF prior to the next visit."[1] Automation should assist in timely and accurate report filing, although the ability to add supplementary information to reports is still needed.

Another area that benefits greatly from automation is the Note to File (NTF). In this case, timely filing is not the issue, since these are not planned documents. The real benefit is the ability to evaluate whether NTFs are being used appropriately. In the article **Use, abuse and misuse of notes to file**, the author notes: "The misuse of NTFs has been cited in warning letters issued by the US-FDA. In these cases, the inspectors from the US-FDA Department of Scientific Investigations (DSI) have admonished sponsors for documenting important events in a clinical trial simply by generating a "Memo-to-File". " [2]

If the information used to create NTFs is standardized and structured, reports and metrics can be used to determine whether usage is appropriate. Some examples might be to evaluate whether the information in the NTF is or should be held elsewhere, whether repeated protocol deviations are occurring but aren't being detected, or when NTFs are being used for purposes that are best managed elsewhere, such as action item closeout.

When documents are created from data, accurate TMF filing is automated as well, since users will provide key filing information (study, site, document type) as an integral part of the creation of the document.

4. Use TMF intelligence to aid in study management

Filing of certain documents in eTMF should trigger an alert visible on CTMF dashboards. For example, the appearance of a protocol deviation document should trigger a process to evaluate the deviation and initiate corrective and/or preventative actions.

Another example would be the appearance of a protocol amendment. If this amendment had not already been planned in CTMS, it should prompt a set of actions to ensure that its impact is properly assessed and communicated, as discussed in the next section on study events.

5. Handle study events

Certain events that occur during a trial may result in a set of documents and activities. The most common example is a protocol amendment. Consider the actions that may be triggered when a protocol amendment occurs:

- Assessment of impact on other documents (informed consent, case report form…); update of documents
- Distribution of documents to sites; collection of signature pages
- Notification of site personnel; updated training
- Notification of IRB/IEC and/or Health Authorities (depending on the nature of the amendment)
- Possible need to inform or re-consent subjects

Figure 2 shows the workflow for a typical protocol amendment involving new safety information and updated inclusion criteria.

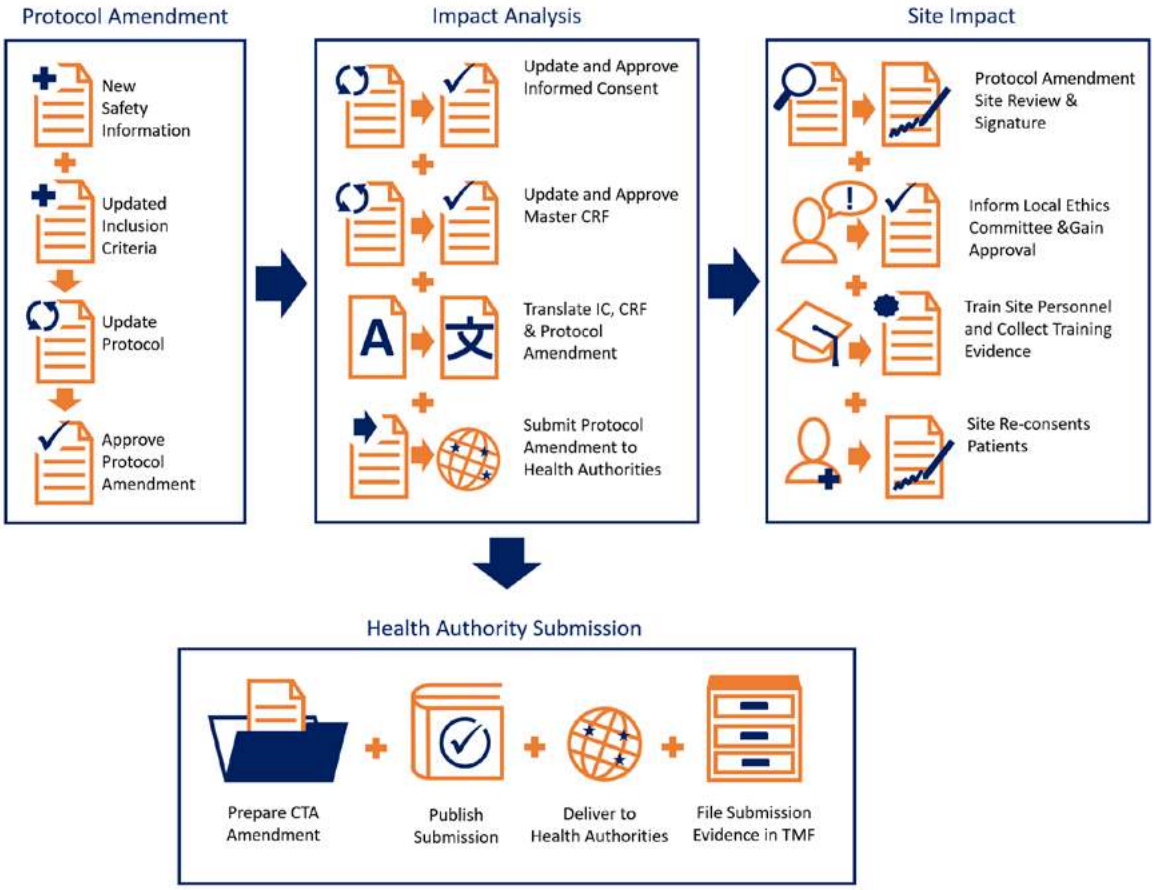

Figure 2- Managing Protocol Amendments

According to Tufts CSDD, biopharmaceutical companies report making an average of 3 amendments to phase 1 protocols and 7 amendments to phase 2 and 3 protocols.[3] Therefore, the ability to handle amendments efficiently while maintaining compliance is critical.

A unified CTMS and eTMF can handle all aspects of this process in a holistic manner, again by automating the generation of tasks along with the planning and collection of documents. By treating the amendment as a unified process with its own dashboards and reports, compliance tracking can be done with a single click instead of by consolidating multiple reports and spreadsheets.

Conclusions

In examining the integral relationship between CTMS and eTMF, it's hard to escape the conclusion that they originally developed as separate systems solely due to technology limitations going back many years – with CTMS originating as a database and eTMF as a document management system.

Operating CTMS and eTMF as separate systems inevitably results in disjointed workflows, manual processes, incomplete information and increased risk. It's time to unite the technology and reap the benefit.

References

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[2] *Hazra A. Use, abuse and misuse of notes to file. Perspect Clin Res. 2011;2(1):38-40. doi:10.4103/2229-3485.76289*

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