Paper AD06

Semi-Autogenerated Narratives

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ABSTRACT

As part of a regulatory submission, individual patient narratives are required. To reduce the workload for the medical writers and to shorten the time from database lock to submission, in some cases, we can utilize fully auto-generated narratives produced directly from the clinical database (ADaM). Though, not all narratives can be fully auto-generated, e.g. narratives covering serious adverse events often require input from a medical writer, apart from the data coming through the clinical database. However, the production of these narratives can still be automated to certain extent and we refer to these as semi auto-generated narratives. While fully auto-generated narratives are relatively easy to produce, semi auto-generated narratives pose a more challenging task.

In this paper, we present a process that utilizes the Tata Consultancy Services (TCS) Auto Narrative Writing (ANW) Platform, which allows the production of semi auto-generated narratives during an ongoing trial. This improves data accuracy ensuring a consistent high quality and reduces the time from database lock to the availability of submission-ready narratives. By removing the narratives from the critical path, medical writers can focus on clinical trial reports and integrated summaries, which are often time critical and cannot be produced during an ongoing trial.

INTRODUCTION

As a programming team we should always look for efficiency gains that will ensure high quality and shorten timelines – ultimately reducing the time to market. Using the CDISC standards has led to a high degree of automatization with respect to the traditional end-of-text and in-text deliverables for clinical trial reports. We are therefore in a position where the programming team is ready to take on new challenges adding more value and/or streamlining production of new deliverables.

In this paper, we give an example where cross-functional and cross-company collaboration resulted in the use of less resources and reduced timelines while maintaining high quality. We hope that this case study can serve as inspiration for other programming teams looking out for new challenges. It also serves as an example that adding more resources in one function to solve a given task is not always the optimal solution – combining the expertise across functions may often be a better strategy.

THE CASE

During interactions with a regulatory agency Ferring was requested to produce narratives for all subjects with a positive outcome related to the primary endpoint. It was estimated that approximately 800 narratives would be needed. These narratives should include data from the clinical database like demographic information, treatment allocation and actual exposure, efficacy outcomes and details on medical history, adverse events and concomitant medications. Since information on randomized treatment and actual exposure was to be included in the narratives, it was considered most efficient to start working on the individual narratives after the database had been unblinded, i.e. after database lock.

Since clinical data was to be included in the narratives, a full QC against data listings and/or patient profiles was required. Taking this into consideration it was estimated that it would take approximately 2-3 hours to write and QC each narrative, i.e. one medical writer would be able to produce 3-4 narratives per day. A very optimistic estimate was that one medical writer would be able to complete this work within one year if he/she did absolutely nothing else than work on these narratives.

THE CONCERN

The trial with requirement of these narrative was a part of project with ambitious timelines: The plan was to have the full submission package ready for the eSubmission team only 4 months after database lock. Not only did this imply

that the narratives were a heavy task on the critical path, it also blocked medical writing resources that was needed for writing the clinical trial report and the integrated summaries. Clearly the narratives could not be written by only one medical writer within the given timeframe. The traditional solution would be to add more resources, i.e. more medical writers to complete this task within 4 months. However, having multiple medical writers working on these narratives raised the concern of ensuring consistency.

To address this concern, different scenarios were analyzed, and it was concluded that the narratives could be grouped into different categories depending on the patient's status at the end of the trial. For each of these categories a template was designed. Consistency would then be ensured by having the medical writers using the correct template when writing the narratives. At Ferring the Medical Writing team and Global Biometrics team have a very tight collaboration since Global Biometrics produce most of the in-text tables used for the clinical trial reports and integrated summaries. Therefore, the lead programmer on the trial became aware of this challenge. By having a programmer evaluating the templates it became clear that these could be populated directly from the clinical database (ADaM). This is illustrated in Figure 1

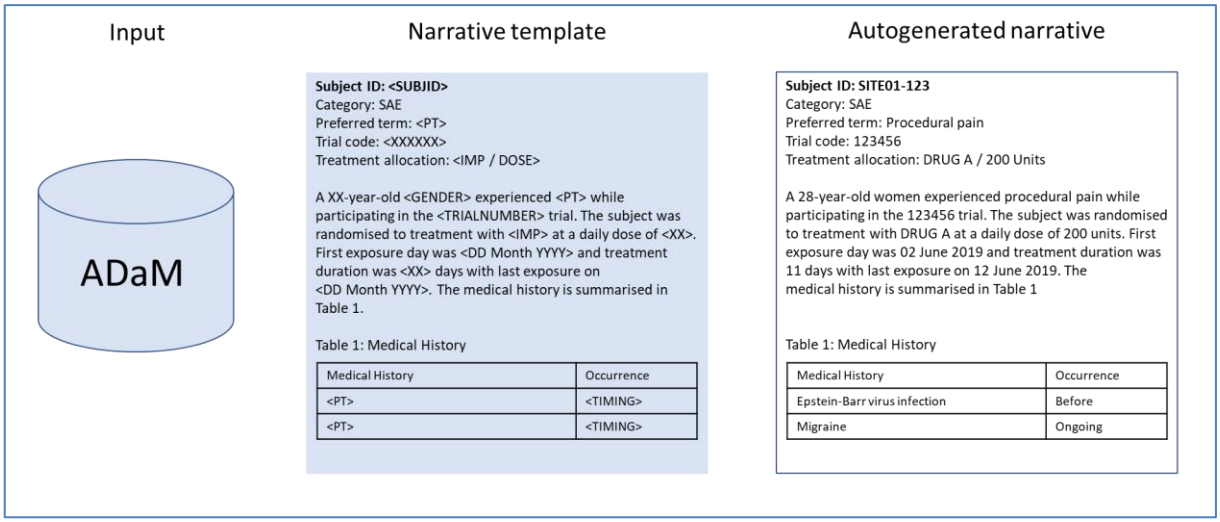

Figure 1: Illustration of the fully autogenerated narrative. Based on a template the final narrative is autogenerated by mapping from the ADaM database to the template.

At this stage you can probably envision a fully auto-generated narrative that could be produced within a few days of programming: Simply writing a SAS program that would loop over the patient population, identify the patients where a narrative was needed, identify which template should be used for each patient and then populate the relevant template with data from the clinical database. While this would to some extend have solved the case at hand it did not provide the full solution. Not all narratives can be automatically generated – some will require input from a medical writer and subsequent approval by the medical responsible for the trial.

THE COMPLEXITY

While the case above could be solved directly using SAS programming, the general case turned out to be more complex. Thorough discussions with medics and medical writers were conducted to identify the requirements for an ideal solution. During these discussions the participants were encouraged to envision the ideal narrative, i.e. not to limit themselves to what is technically possible to achieve using SAS alone or how narratives usually looked.

Obviously, the narratives should contain auto-generated text. Further, the requirements included the option to include tables/figures and entering manual text to further describe a given case. In addition, requirements on traceability through e.g. track changes and version control were also included. Last, but not least, it was required that the solution must have a user-friendly interface both with respect to getting an overview of the status of each narrative and for working with the narrative when adding manual text.

When writing narratives for serious adverse events it is sometimes necessary to get further clarification from the investigator to fully understand and describe the case. Ideally this correspondence with the investigator should be done shortly after the serious adverse event has ended. It should therefore be possible to write the narratives while the trial is ongoing. Since some of the information needed in the narrative is only available after database lock it should be possible to update the autogenerated part and the manual part independently. To secure full traceability of the narratives this update should be traceable via version control and track changes. Writing the narratives while the trial is ongoing further minimize the work needed after database lock.

In summary the following high-level requirements were identified:

- Auto-generated text
- Auto-generated tables for instance showing medical history
- Auto-generated plots showing for instance an overview of adverse events relative to IMP exposure
- It should be possible to enter manual text to further describe a case for a subject if needed
- The interface for entering manual text should be very close to Word
- It should be possible to work with different templates depending on the type of narrative needed
- It should be possible to update the manual part and the auto-generated part independently
- The data flow both with respect to the clinical data and the manual input should be tightly controlled
- Following a refresh of the clinical data, it should be possible to track if a narrative has changed

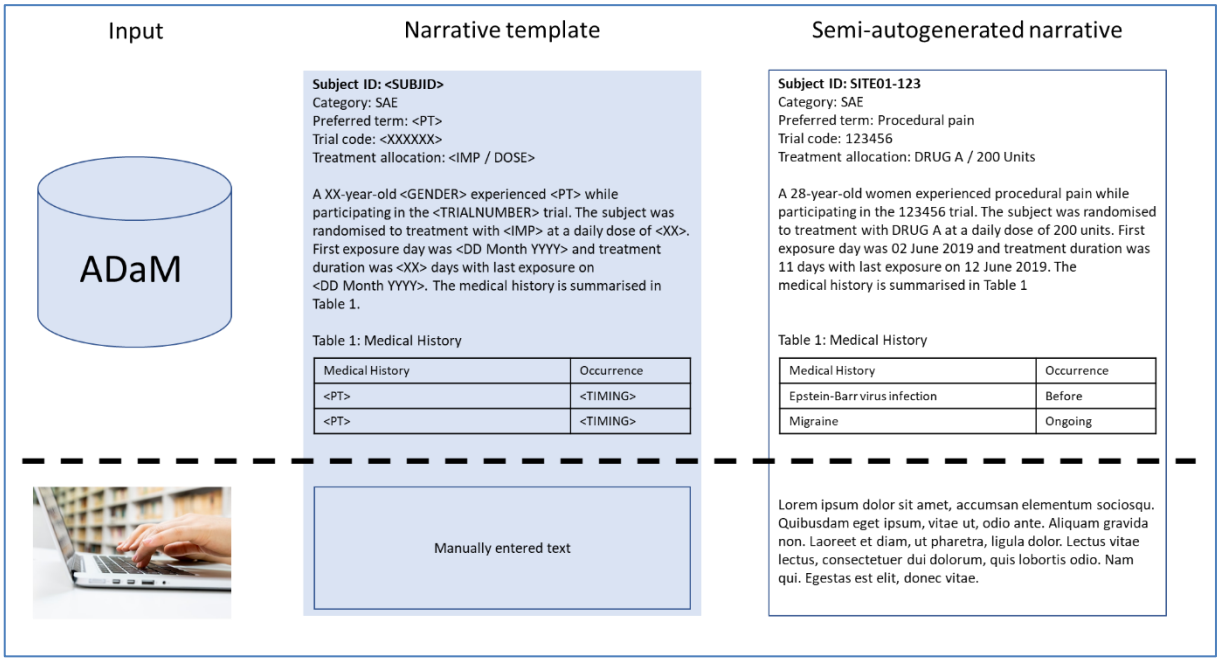

Figure 2: Illustration of the Semi-autogenerated narrative. This poses a more challenging task since it combines mapping from the ADaM database and manual input. A further level of complexity is added by the requirement that it should be possible to update the two parts independently including maintaining version history and control.

The full complexity of a semi-autogenerated narrative is illustrated in Figure 2. Based on the complexity of these requirements – especially the ones related to user friendliness and version control – it was decided to search for a tool that could solve this. Based on an evaluation of different vendors it was concluded the TCS Auto Narrative Writing Platform was the one that came closest to meeting all requirements. Ferring entered into a good collaboration with the TCS team developing the platform and they adapted the platform to meet all requirements.

THE COMPLETE SOLUTION

TCS Advanced Drug Development (ADD) is a suite of platforms covering the entire clinical R&D value chain. The platforms harness new digital technologies such as automation, AI, and IoT – to bring about disruption in clinical research.

The TCS ADD Auto Narrative Writing (ANW) Platform enables clinical data variables to flow directly from clinical datasets (e.g. SDTM / ADaM), patient listings and Patient Profiles into narratives. Additionally, the platform can be integrated with the existing Clinical databases / repositories or EDC systems.

The system allows the user to setup a Global Library with for instance therapeutic area relevant templates which are then ready to use in studies. These global templates will have auto mapping with standard datasets (e.g. SDTM / ADaM datasets). In case additional mapping is required specific for a particular study, templates can be configured / updated accordingly.

Following are some of the salient features of the platform.

- ✓ One study can use multiple templates covering different categories like e.g. SAE, death, discontinuation etc.
- ✓ Narrative templates can be customized as per study requirement
- ✓ Narrative templates can be reused for narratives for the same compound / similar study
- ✓ FastTrack Study Setup
- ✓ Minimal QC review needed for data accuracy
- ✓ Consistency in formatting and language of narratives
- ✓ Editing features like MS Word
- ✓ Audit trail of changes and version control
- ✓ Project status dashboard available real time for management review
- ✓ Online project activity status for narrative team
- ✓ Inbuilt online review workflow
- ✓ Auto update of narratives post database lock/ for periodic IDMC (independent data monitoring committee) meetings
- ✓ Post database lock data refresh of narratives
- ✓ Patient profile generation out of datasets

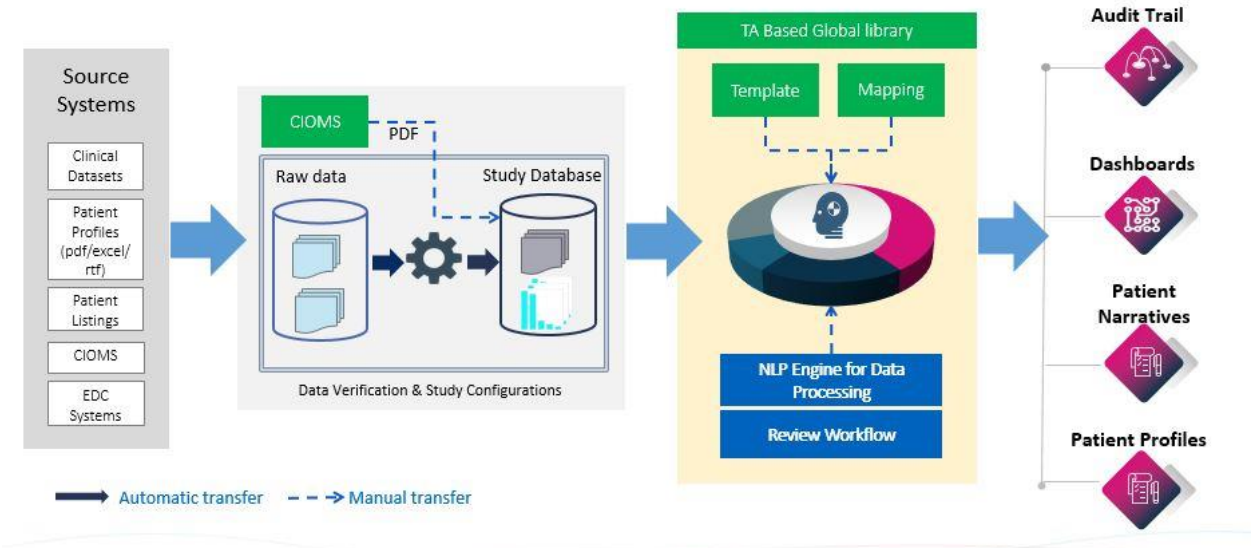

Figure 3: Illustration of high-level solution architecture of Auto Narrative Writing Platform.

Since the information flows directly into the narrative template from the clinical datasets, data accuracy is ensured implying high-quality narratives are produced with minimum QC needed. The narrative template has static (constant) fields and dynamic fields (patient specific values). This helps to ensure consistency in narratives for a specific study

and across the studies for a compound. The platform has an intuitive and easy to use interface making it very easy for users to add a new template and do the mapping to the data.

A customized template is prepared by the Medical writer and configured in the platform by the ANW administrator. The narrative template can be amended in the middle of a study in case of any protocol or CRF amendment. The template can further be customized and reused for the subsequent studies based on the sponsor or therapeutic area specifications. This allows reusability of the content and minimize the study set-up time for future studies. The graphic/ tabular representation of the trend in patient data values is available. In addition to the narratives for clinical study reports, the platform solution is useful for IDMC narratives as well.

After the initial data setup and mapping variables with study templates the platform generates the narratives for all available patients as per defined categories. After this step the Author can take control of the narratives and update if required (Figure 4). Once Author is done with the changes, further workflow can be initiated for e.g. review by a clinician before finalization of narratives. The platform gives the capability to have inline comments and to edit / update the narratives with real time track changes mode with MS Word like features. During all these reviews, the platform keeps all versions in the system including an audit trail of all changes being made in the individual narratives.

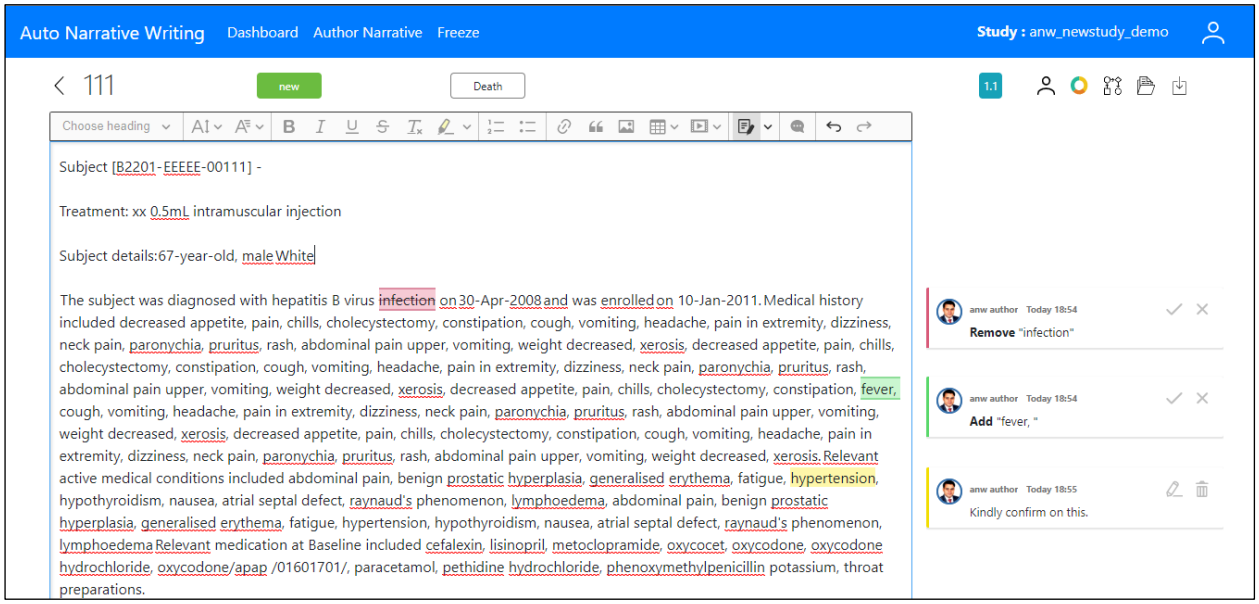

Figure 4: Example of use MS Word like user interface for updating the autogenerated narrative if required.

Following database lock the platform has the capability to keep all changes at the patient level and only data changes will be updated in the narratives. This will again reduce the time taken to update the narratives post database lock.

Finally, for tracking the study progress the platform gives the capability to configure dashboards and reports within the system.

TCS and Ferring collaborated and leveraged the TCS Auto Narrative Writing Platform to meet all requirements. Ferring medical writers provided the narrative templates. A Ferring statistical programmer having good understanding of the study data provided the data needed for the narrative from the ADaM database and shared a data mapping document. The TCS ANW team then configured the template, data and data mapping in the platform and Ferring medical writer started using the ANW platform via a web link.

The Ferring medical writer added subject specific comments in each subject narrative and these comments were later reviewed by another Ferring medical writer in the Platform itself in real-time via a workflow. After the DBL, the Ferring

statistical programmer provided unblinded study data which was uploaded in the platform and all the data fields in the narratives were refreshed.

Once the workflow for all narratives were finalized by the Ferring medical writers, the TCS ANW team extracted all the narratives as .doc files and shared with the Ferring statistical programmer. The programmer then compiled the narratives into a submission-ready word document with the narratives arranged in sections according to the categories. This document as well as the individual narratives was then shared the Ferring medical writers.

The table below describes how Ferring's requirements was met by using the TCS ANW Platform:

Ferring's requirement	Implementation in TCS ANW platform
Auto-generated text	Built in feature
Auto-generated tables for instance showing medical history	Built in feature
Auto-generated plots showing for instance an overview of adverse events relative to IMP exposure	Built in feature
It should be possible to enter manual text to further describe a case for a subject if needed	Built in feature, CIOMS data can be preloaded in the manual text field
The interface for entering manual text should be very close to MS Word	Built in feature
It should be possible to work with different templates depending on the type of narrative needed	Built in feature, configurable based on the study context
It should be possible to update the manual part and the auto-generated part independently	Built in feature
The data flow both with respect to the clinical data and the manual input should be tightly controlled	Data flow from clinical data to TCS ANW Platform is controlled via a process where FTP server was used to share the data. Manually added data was tracked and reviewed via the platform itself
Following a refresh of the clinical data, it should be possible to track if a narrative has changed	Each data load was shared by the Ferring statistical programmer so changes in clinical data was tracked during the data exchange process

CONCLUSION

Combining expertise across functions within Ferring and a good collaboration between Ferring and TCS resulted in a more efficient process that allowed faster production of narratives while maintaining the required level of quality. Among different options the TCS Auto Narrative Writing Platform was chosen for producing semi auto-generated narratives. The Platform had both the required functionality and flexibility and provided full traceability from draft to final narrative via a build in customizable workflow.

The investment in terms of resources needed from the Ferring programming team to set up the TCS Auto Narrative Writing Platform is negligible when compared to the resources saved at the medical writing team. The resources freed in the medical writing team can then be utilized adding more value to the clinical trial reports and integrated summaries.

The ability to independently update the sections based directly on the clinical database and the sections requiring medical writing input allows the narratives to be written while the trial is running. The blinded information can then be automatically inserted when the database is locked, and the randomization and exposure information is released. We are at Ferring currently investigating if the platform can be set up to cover production of serious adverse events narratives across all ongoing trials, i.e. be the main platform for producing these narratives.

Finally, returning to the original case: Since the data was coming directly from the ADaM database no QC was needed. However, since it was the first use of auto-generated text it was decided to do a high-level read-through of all narratives to secure that all was as expected. This took approximately. 5 min per narrative, i.e. a medical writer could finalize 60 narratives per day implying that the full set of 800 submission ready narratives was ready in less than 3 weeks. An enormous saving in resources compared to the estimated full years' work for one medical writer.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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