Paper DS05

Challenges with Implementation of New Standards and Guidance – A Sponsor's Experience with the April 2018 CBER Vaccine Guidance

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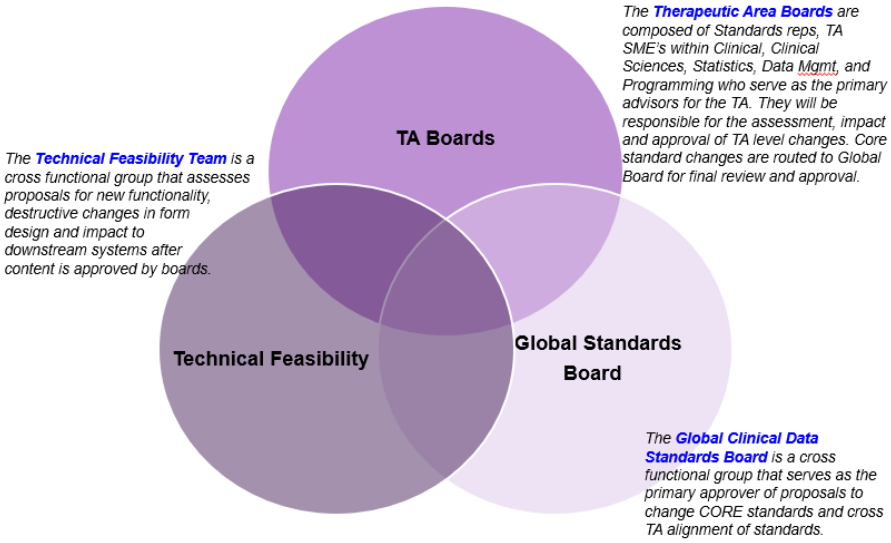
ABSTRACT

For organizations with highly developed data standards, processes, and governance, it can be extremely challenging to keep up with the continuously growing and evolving requirements and guidance published by the various regulatory agencies and standards-developing organizations. Standards are designed to support compliance with some degree of flexibility, but in practice, making timely changes to standards which are actively being utilized in clinical trials can present multiple challenges which need to be assessed and addressed. This paper presents Pfizer's experience with implementation of CBER's April 2018 Guidance for Industry "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review"[1]: highlighting our process along with some of the challenges and considerations and making some recommendations for organizations when incorporating newly released guidance or standards.

INTRODUCTION

Pfizer utilizes standard data collection instruments, dataset standards, and controlled terminology across therapeutic areas (TAs) and clinical programs. These standards are governed by cross-functional TA and Global boards (see Figure 1), which meet regularly to evaluate requests for new standards or changes to standards. Once a standard is approved, it is rolled out for end-to-end implementation, affecting data collection, data management and cleaning, mapping, analysis, and submission as well as other functional areas within the drug development process. With a goal of automated standard datasets, tables, figures, and listings (TFLs), it is critical to have strict and specific data collection standards which are tightly adhered to in order to successfully generate these outputs with minimal programming effort downstream.

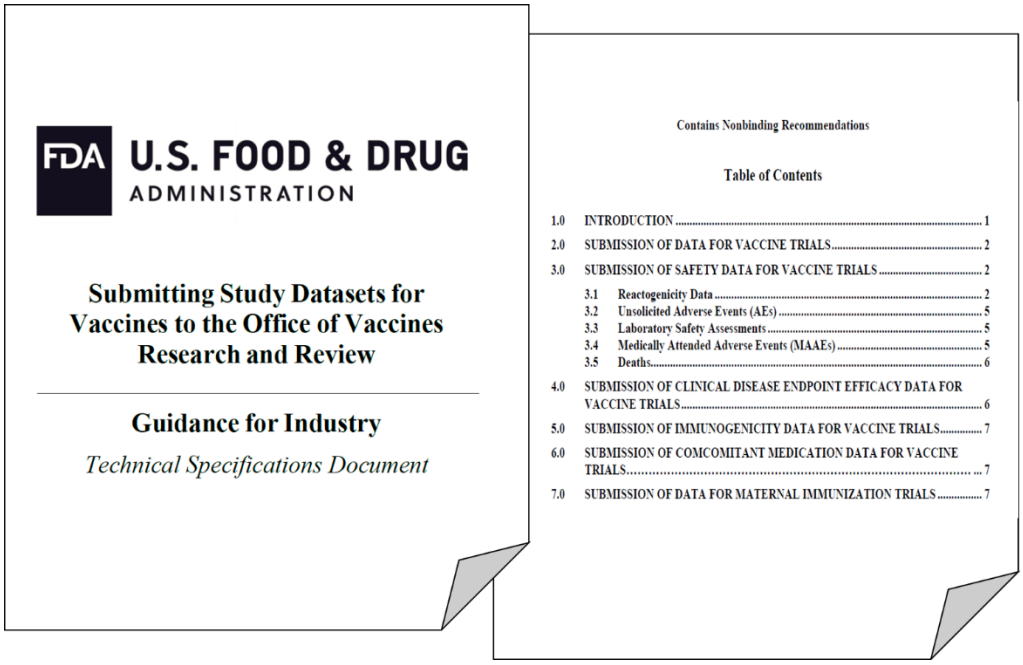
Figure 1 Pfizer Data Standards Governance



Once a standard is in place, it is typically not difficult to add items, such as a field in a CRF or a term in a code list, however anything which requires changes to data structures, or domain or value changes can have a big impact when studies are already using the standards. Depending on the stage of study conduct, it may be difficult to implement changes without affecting the timelines.

In April 2018, CBER released version 1 of "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review – Guidance for Industry" Technical Specifications Document for immediate implementation, with an updated version 2.0 released in October 2019 and version 2.1 (administrative changes) in December 2019. The guidance contains nonbinding recommendations for certain types of data commonly assessed for vaccine studies and how to represent components of this data within CDISC SDTM[2] datasets. Recommendations were included for:

- Reactogenicity data
- Adverse events and deaths
- Laboratory data
- Clinical disease efficacy endpoints
- Immunogenicity data
- Concomitant medications
- Maternal immunization



FDA U.S. FOOD & DRUG ADMINISTRATION

Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review

Guidance for Industry

Technical Specifications Document

Contains Nonbinding Recommendations

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The recommendations touched on most data types collected for a vaccine study and included specific modeling/data structures, inclusion and usage of certain variables, and specific values to be assigned for variables such as –CAT and –SCAT.

As Pfizer already had vaccine data standards in place, a team was assembled to review the guidance against our existing standards and identify gaps and differences. Some of the recommendations varied greatly from our standards or weren't even possible with our current data collection standards. Others would be easier to implement, but still presented a change that would impact our standards at multiple touchpoints and would require decisions be made for ongoing and completed studies. Apart from the general sponsor-level standards implementation challenges and the resulting study-level challenges, the changes could also impact ongoing or future data integration efforts. The changes could not be implemented overnight and would require much analysis and consideration to determine a plan forward.

INITIAL PROCESS AND CHALLENGES

The guidance was first brought to the attention of our Statistical Programming and Analysis (SPA) group by Regulatory since it involved the submission datasets for which SPA was responsible. Our initial step was to thoroughly review the guidance and identify each individual technical specification. The document content was very similar to FDA's Technical Conformance Guide (TCG)[3], addressing certain types of data and how the agency would like it formatted for submission (focused on the SDTM datasets). We extracted a list of specifications from the document (see Figure 2 for example) and then our Programming Standards team, which is responsible for our SDTM standards, compared these requirements to our current standards and assessed for gaps and differences.

Figure 2 Gap Analysis Example

The DS domain should always include the Standardized Disposition Name (DECOD), Reported Term (TERM), Category (CAT), and Start Date/Time of Event (STDTC) variables. If relevant (i.e., multiple doses administered over time), the DS domain should include the use of the Order of Element within Arm (TAETORD) timing variable. The TAETORD timing variable should also be included in other domains when the vaccine is multi-dose.

Section #	Topic	Specification	Standards Updates Needed?	Differences - Details
2	Submission of Data for Vaccine Trials	The DS domain should always include the Standardized Disposition Name (DECOD), Reported Term (TERM), Category (CAT), and Start Date/Time of Event (STDTC) variables.	N	
2	Submission of Data for Vaccine Trials	If relevant (i.e., multiple doses administered over time), the DS domain should include the use of the Order of Element within Arm (TAETORD) timing variable.	Y	TAETORD is not currently included in DS domain.
2	Submission of Data for Vaccine Trials	The TAETORD timing variable should also be included in other domains when the vaccine is multi-dose.	Y	TAETORD is not standard variable for most domains.

Once we had an initial understanding of how our standards compared to what was being requested in the guidance, the Programming team initiated a series of cross-functional meetings to bring awareness of the guidance and the changes that would be necessary for our submission data to be in compliance. The biggest impact would be for the reactogenicity data (comprised of common, expected adverse reactions which occur soon after vaccination) collection and mapping, some of the most critical data for a vaccines study. Several meetings were held during the first couple of months, but it was slow getting any traction let alone forward progress at that point. As we took a break to evaluate our approach, we identified several challenges:

- First, there was not a clear road map to guide us through the changes we would have to address since there was no established process to follow for situations like this. We typically managed standards changes based on study- or program-level requirements or regulatory feedback. In each of those scenarios, there was an assigned project team which would request the changes via our standards ticketing process which would each then be assessed and implemented if approved, but these changes were initiated from an external source and would apply across our entire vaccine portfolio. Who was responsible for implementing them? They had come to the Programming team initially, but the specifications were complex and required a broad understanding of the end-to-end data flow process. Furthermore, the changes involved multiple functional lines, so it was not clear who would play the oversight role to drive the company's effort to implement them. No single person had all the expertise and knowledge across the different functional lines to see an easy and clear resolution.

- Another issue we found early on was that we (programmers) were trying to communicate very technical points concerning data structures, mapping, and terminology which were not always clear to our colleagues in less technical roles or who were less hands-on with the data. Fully understanding the requests and their impact required a broad knowledge across different areas – regulatory and submission requirements, CDISC standards, Pfizer Global and TA standards, and the entire data flow from collection to reporting. The work would impact multiple functional lines, so it was critical to have good communication in order to convey what needed to be done and work to find solutions.

- Then there was a general resistance to change standards that were felt to serve all the various needs and requirements for a vaccine clinical program. Pfizer had been collecting vaccine (and particularly reactogenicity) data the same way for years and it was not only going to be a struggle internally to implement changes (which would affect most functional areas) but also to the sites who were accustomed to our systems and forms. If changes were absolutely necessary, the other functional areas preferred to address them on the back end through the data mapping and programming for the SDTM datasets, however

current data collection standards limited our ability to map completely to the requested structures. It would not be possible to fully address the guidance via programming alone.

- We also had a challenge with making this a priority - everyone had busy calendars and did not always attend the meetings, so it was hard to get a consensus and move forward when we did not have all the decision-makers present.

We then changed course a bit by starting to hold separate meetings of a technical focus with a sub team of Programming, Data Management, and Standards representatives, then putting together a communication plan to share the most viable options with the broader team. We found that it helped to provide a visual representation of the data flow, including sample data collection instruments, flow diagrams, and samples of data, along with text to describe and explain everything. It was important to highlight the changes from our current standards and practices and be prepared to answer questions and discuss the impact. We were fortunate too to have a team member with both clinical and data/technical background who was able to help bridge any communication gaps.

This approach led to more effective conversations, during which we realized that there were several points from the guidance which were not sufficiently detailed to provide a clear understanding of the agency's expectations for the data, conflicted with existing CDASH[4] and/or SDTM implementation guides (IGs), or presented a challenge for collecting, databasing, and/or mapping the data (see Figure 3 for example). At this point, we realized we needed to initiate some discussions with the agency to get a better understanding for how they wanted the data structured and how they intended to review it, as well as to communicate some of our concerns and limitations.

Figure 3 Sample Topic Needing Further Discussion with Agency

Section #	Topic	OVRR Guidance Text	Challenges/Conflicts
3.1	Reactogenicity Data	Reactogenicity data should be represented primarily in the CE domain with the Findings About Clinical Event (FACE) domain and VS domain to provide the specific information for each event…If a reactogenicity event should happen to continue beyond the assessment interval, it should also be represented in the AE domain…The start day/date (--STDY/--STDTC) and the end day/date (--ENDY/--ENDTC) of the reactogenicity event should be identical in both the CE and AE domain; whereas the duration (--DUR) should report the time that the event occurred as part of the assessment interval and as part of the continuance separately (e.g., an event that lasted 6 days in the assessment interval and 3 days beyond the assessment would be reported as Clinical Event Duration (CEDUR) = 6 days and Adverse Event Duration (AEDUR) = 3 days). We recommend one or more check boxes in the CRF, indicating the duration of the reactogenicity event in the assessment period and the duration of the reactogenicity event beyond the assessment period.	• The requested usage of the --DUR variables contradicts the SDTM IG, which notes that the duration is the difference between the start and end dates and is generally only used in lieu of collecting start and end dates. • It may be challenging for sites to accurately determine the duration values to enter for CEDUR/AEDUR. • Standard duration derivations in our data processing are based on stop date minus start date plus 1 day and apply generically across all studies and domains for all duration calculations.

Our first dialogue with the agency was a Request for Comments in which we outlined the challenges and limitations to providing data in the requested structures based on our current data collection instruments and standards and proposed some minimal changes which were possible for us to incorporate without too much disruption to our vaccine trials. The agency responded that, while they appreciated some of our concerns and challenges, they wanted the data submitted according to their specifications. So, the team went back to work, digging deeper into possible ways to meet the agency's requests. We also reached out to other pharmaceutical sponsors with active vaccine programs to get a feel for whether they were experiencing the same challenges. The other companies we had contact with were all experiencing similar challenges, particularly with the reactogenicity. This was reassuring to some degree but highlighted the need for further communication with the agency and suggested to us that a cross-industry effort may be of benefit to sponsors and the agency and may lead to a speedier resolution that works for all parties.

We stretched ourselves to identify alternative strategies for the data mapping. Feeling confident that we had solid data collection practices and could provide the full safety profile for a vaccine, we prepared a proposal which comes quite close to their requirements, but requires a lot of derivation in SDTM, which is not standard practice and creates complications in documenting traceability. This approach would however reduce burden on the investigative sites and Data Management while facilitating the review needs of the agency.

As we prepared to respond back to the agency, a new version of the guidance (v2, October 2019) was released, which added further requirements. Efforts were paused to assess the additions and determine if there was any impact to our proposal. The main points for reactogenicity were unchanged, but there were some additional requirements for adverse events and prior/concomitant medications to discuss internally. We ultimately decided to move forward with the proposal as we continued to work out the details for how to implement the other additions. As of this writing, we are awaiting the agency's response to our proposal.

IMPLEMENTATION CONSIDERATIONS

Once we have reached agreement with the agency, we will complete the standards implementation process by submitting change requests for all affected modules and communicating the changes to all relevant functional lines via awareness sessions prior to formal rollout. In the meantime, we are also formulating an implementation plan for our active vaccine programs, detailing how we plan to address the changes for completed, ongoing, and future studies. This will be a particularly high priority for any programs which have submissions planned this year. Late-stage changes could impact our ability to submit the data on time, especially as it may take extended time to fully implement the more complex changes, and any changes to completed studies would run a risk that the original results could not easily be reproduced. It would also be challenging to have a mix of standards used within a submission, particularly for integrated datasets since the new structures differ from our original structures. Standards for each study had previously been detailed in the Study Data Standardization Plan (SDSP)[5] which was submitted to the agency and new standardization plans following the guidance would need agreement from the agency. With this in mind, we are considering our short- and long-term implementation plans.

If the agency agrees with our proposal, we would begin to implement the changes for all future studies as well as any ongoing studies which can be updated without impacting final reporting timelines. For completed studies, we could provide datasets in the updated mapping structures along with the original datasets used to analyze the data for the Clinical Study Report (CSR). Care would need to be taken to ensure that the original study results could be replicated, or any differences explained in the Clinical Study Data Reviewer's Guide (cSDRG)[6].

Changing the SDTM data structures will necessitate changes to our analysis dataset and TFL processing. It takes time to modify specifications and programs, then test and release the code, so it is unlikely that any studies locking in the next several months would be able to implement the changes. In these cases, we may have to complete our analyses using the old standards but consider providing supplemental datasets using the new standards, to aid in review.

Similarly, for any upcoming data integration efforts, we will need to consider the timing and impact of updating to the new standards. For active programs which have a mix of completed and ongoing studies, there may be a mix of standards used and we will need to decide whether to integrate into the old or new standards. This may depend on timing as well as the number of studies which would need to be converted.

If the agency has further suggestions for us to incorporate, changes may take additional time to implement and any submissions planned this year would need discussion with the agency.

It is also worth considering whether changes resulting from this guidance and related interactions with the agency should be rolled out as one package or separately as they get finalized. Some items from the guidance are more straightforward to implement while others may need additional time or require further discussion before they can be implemented. If moving forward in a piecemeal fashion, there may be differences across studies within a program which would need to be factored in for data integration and potentially noted within the data reviewer's guides.

LESSONS LEARNED AND RECOMMENDATIONS

These sorts of "technical specifications" are often seen as purely to be applied to the programming of the CDISC datasets, but if utilizing an end-to-end data standards approach, then data collection should ultimately align with the submission data structures, including terminology. This then impacts data management and monitoring and everything downstream, as well as related or interacting systems. Thus, we need to encourage taking a "big picture" approach to implementing these types of requests and collaborative cross-functional efforts. For example, Clinical or

Data Management lines may feel it is not necessary to add an extra field in a CRF, however if information is not available somewhere in the database, it may not be possible to include in the CDISC datasets since there has to be a complete audit trail (traceability) for each data point. At the same time, we need to assess the full impact of adding that field (or any other type of change) – considering the following questions for the end-to-end study data flow, for example (but not limited to):

- Does it necessitate any changes to the protocol?
- Will this be extra work for the sites?
- Is it feasible to collect the data?
- Can it be implemented in the database as requested?
- Will it require extra data cleaning?
- Does it need to be reconciled with other data and can that be automated, or would it be a manual effort?
- Is there a clear mapping to SDTM and ADaM and does it appropriately fit into the standard data structures as outlined in the IGs?
- Does it conflict with other standards which are already in place?
- How will it be used in analysis and reporting?
- Does it impact any standard reports that were already developed, or other systems which may use the data (e.g. for safety review/reporting)?
- Do the costs of the change far outweigh the benefits?

With the technical nature of this guidance and multiple functional lines being involved in the discussions and implementation, we needed to be able to communicate the proposals in both technical and non-technical terms. Certain groups needed to understand how to program for the data and other groups needed a descriptive (words and pictures) summary. We also needed to be able to provide tracking and high-level summaries for management. We found that we had faster progress when those with the technical data/programming skills worked together first to brainstorm potential solutions along with their impact and pros and cons, then made a recommendation to move forward with and pulled in other functional lines to get their feedback. This saved us from putting excessive time and effort into options which were ultimately not going to be feasible to implement and allowed us to focus on the most viable options instead.

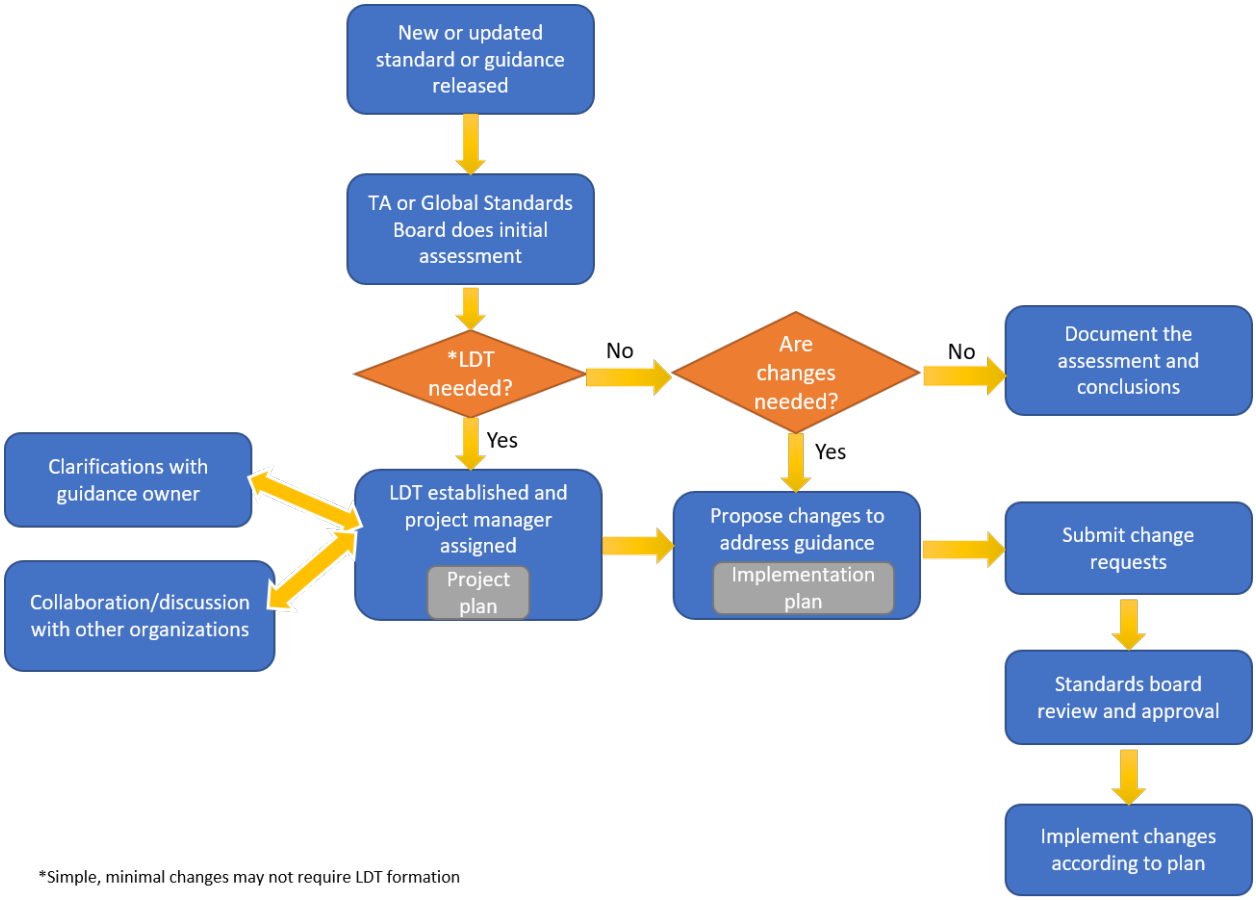
In some cases, the agency's guidance/requests were not fully aligned with CDISC standards or other regulatory guidance. Additionally, some of the requests may not be feasible given our database structures or other limitations, or may be open to interpretation. It is important to be able to collaborate with the agency to ensure understanding of the requirements as well as bring awareness of the challenges and work with them to find alternate solutions which will address their needs or concerns. Industry feedback will be critical to ensure that the guidance can be followed if it becomes binding. Currently, cross-industry meetings are underway to collaborate on addressing some of the challenges multiple sponsors are facing in implementing the guidance. We are hopeful that a dialogue can be initiated with the agency to share feedback and work together to come to an effective solution that can be applied across sponsors for all vaccine submissions.

Probably the biggest lesson learned through this effort was that we needed a more formal process internally to address these requests in the future and someone assigned to oversee the work. We have already experienced two updates while addressing this guidance and the agency will likely continue to make updates as they receive more submissions and work with industry to determine an optimal mapping specification which serves their review needs while also meeting the needs of sponsors and investigative sites. Furthermore, regular updates to the TCG and releases of new versions of the CDISC standards and Therapeutic Area User Guides (TAUGs)[7] will continue to impact standards implementation, and other reviewing divisions at FDA or at other regulatory agencies may release their own technical specifications for different therapeutic areas and indications as well. With this in mind, we worked with cross-functional leadership teams and our standards governance groups to formulate a charter for limited duration teams (LDTs) to be established to address any future standards, guidance, or specifications of this nature.

The LDTs are to be comprised of representatives from multiple functional lines and roles from the relevant therapeutic area(s), including Clinical, Data Management, Programming and Statistics, Regulatory, Quality, and Data Standards. Other roles or functional lines may be brought in as applicable. The LDT will coordinate with our data standards governance boards and a project manager will be assigned to oversee tasks and timelines and track progress. The LDT's remit is to assess the guidance to confirm our data standards are in alignment or work out a proposal to address the requests, communicating with the requestor and/or other organizations as needed to get a full understanding and come to an effective solution. A project plan will be generated with timelines, decision owners, and priorities, as well as an escalation path. The team will also generate an implementation plan to detail how the changes will be rolled out or deviations will be documented, particularly for completed and ongoing studies. Once a

solution is reached, the team is then responsible to submit the standards updates requests for implementation and assist with communicating the changes throughout our organization.

Figure 4 LDT Process Flow



CONCLUSION

This paper is written based on Pfizer's Statistical Programming and Analysis group's experience, but there are multiple functional lines and roles involved with implementation of this guidance and it is taking cooperation and collaboration between these groups to make decisions and carry them out. We feel it is vital to have an established process to be able to handle these types of external specifications, clearly outlining everyone's roles and responsibilities. Communication amongst the team members from the different functional areas is critical to making decisions and progress. While it is important to try to see things from others' perspectives, it is also necessary to consider the big picture for how the changes fit into and impact the entire data flow, to then determine where and how best to apply the changes. Additionally, support is needed from leadership to resource and prioritize this work.

When there are questions or concerns with the requests, it is best to initiate external discussions early so as not to waste excessive time on items which may later be clarified or possibly eliminated or revised. If the agency is not aware of the challenges sponsors are facing, they cannot address them. Proactively holding honest conversations can benefit all the parties involved.

Although these efforts were focused on vaccine data standards, we believe that the process and recommendations can be applied to other TAs/indications and types of guidance. We have also focused on data submissions to the FDA, but these suggestions could be applied to guidance, specifications, or feedback from other regulatory agencies as well.

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