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The Last Time? Efficiently Scheduling the Pieces of your Submission Deliverables

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ABSTRACT

For clinical trial submission deliverables, timing is everything: the key to efficiency, cost savings, and sanity. Keeping a close eye on item dependency and stakeholder needs ensures that you will make timely deliveries while leaving reasonable padding for the inevitable timeline crunch.

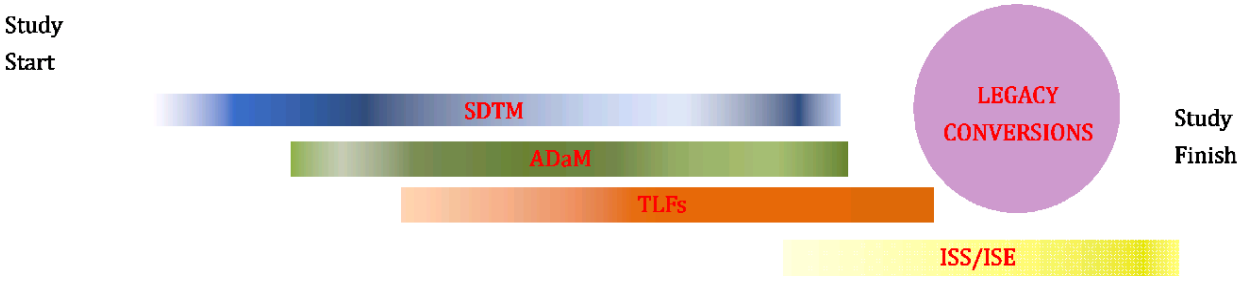
Quality standardized submission data comes with an added cost, which can be exacerbated by starting an expensive task too early and making continual updates throughout the length of the trial. On the flip side, waiting and identifying problems with key elements too late in the process will lead to expensive emergency re-work. When should you start working on the Study Data Reviewer's Guide? During what stage of SDTM development should ADaM ideally begin? When should you start running conformance checks on your data? No two clinical trials are the same, but submission-specific relational timeline metrics can provide useful anchors for all stakeholders in a clinical trial.

INTRODUCTION

A successful submission timeline consists of a few key steps. The first step is to clearly define what overall study deliverables will be expected, and list the individual pieces needed for those deliverables. After that, you will need to plan your timeline for each deliverable working backwards from the planned submission date or other project endpoint. We will outline a "best practice" recommended timeline for each deliverable, but you should create your timeline based on what is needed for your project. The last step to a successfully-planned timeline is to consider the impacted customers and the budget, and then make adjustments where needed. Understanding who is using your deliverables and the budget you have to work with will help determine how many drafts you have and when you should start work on these deliverables, changing the shape of your planned timeline.

DEFINE YOUR DELIVERABLES

Defining what deliverables are needed is the foundation of timeline planning. If you don't know what you need, you can't plan for it. Maybe you will need to plan for an ISS with a few legacy data conversions, or perhaps a Phase III study consisting of SDTM, ADaM, and TLFs. The Phase III study may also have several DMC meetings, central monitoring, and a blinded data review by the sponsor; these are all deliverables as well. Your timeline should include a horizontal bar for each deliverable, as illustrated below:



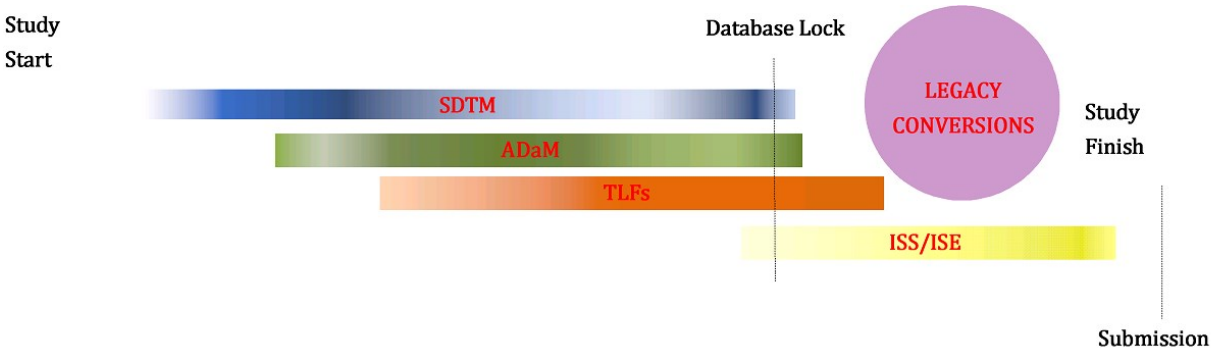
The lines above represent deliverables in a standard clinical trial scenario: SDTM, ADaM, TLFs, an Integration, and Legacy Conversions to include in the integration. The shading represents a typical pattern of effort expended, with darker shades representing peak work times. Peak work times usually coincide with both external and internal deliveries,

but there may be other factors to account for that are more specific to your project or organization. Also, these deliverables have specific expected components contained within them. Refer to the chart below for the most common deliverable components for CDISC study submissions. You should add in any additional items that will be needed for your work.

SDTM	ADaM	TLFs	(ISS or ISE)	Legacy Conversion	Other Considerations
SDTM data	ADaM data	CSR displays	Integrated data and displays	Components vary but may include limited CDISC domains and legacy reviewer's guide.	SDSP
annotated crf	Program delivery prep	Program delivery prep	Program delivery prep		Analysis Results Metadata
csdrg	adrg	QC/Review	QC/Review		BIMO
conformance checks	conformance checks		conformance checks		Test Submission
QC/Review	QC/Review		adrg		upversion coding
define	define		define		

IDENTIFY DELIVERABLE ENDPOINTS

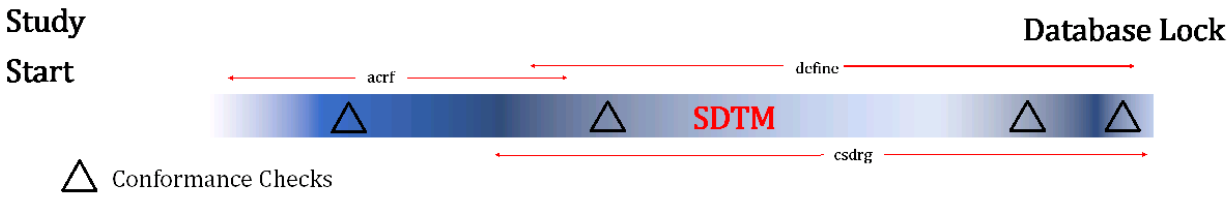
Once you have established what deliverables are needed for your project, next mark the important endpoints for that work. The overarching endpoint for most submission deliverables may be the point in time where all items are sent to publishing or perhaps when all final deliverables are signed off on in some other way. To fully ensure that these hard stops will be met, we would argue that in almost all cases, the most important endpoint for biometrics deliverables that directly involve the study data is database lock. In the case of an integration of several studies, the lock date of the final study to be included in the integration should also be an endpoint anchor. Our recommendation is to plan on having almost all programming activities, define file preparation, and reviewer's guides completed by this time. Note that we said "almost all"—these activities can't be finalized until submission. For example, you can't include data conformance in your reviewer's guide until after your final program run of the data. Submission activities are never "pushbutton", but marking your endpoint and prepping to have a solid delivery at that time will give you a place to work backwards from in order to ultimately determine interim deliverables and a starting date. For the purposes of this paper, the deliverables that we are talking about are the typical ones in the chart above; however, on a smaller scale, the same endpoint strategy should apply to DMC meetings, central monitoring programming, and any other line item deliverable. Having all programming activities completed and tested by the chosen endpoint for these pieces is important as well and will keep things running smoothly.



For the most part, the starting point and the work flow for most standard deliverables will be similar: a strong start to the work, a maintenance phase, and then a flurry of finalization work at the end. As noted above, this is illustrated by the darker shading representing peak work flows.

The individual deliverable components such as the define files and reviewer's guides for CDISC projects and the acrf for SDTM have a recommended work flow and require timeline planning, too. Again, the goal should be to have all these things as close to final as possible by the time you reach the endpoint of your project timeline. As seen below, a typical SDTM deliverable consists of the SDTM data (specification and programming workflow in shaded blue), the annotated

CRF, the define file, the csdrg, and conformance checks.

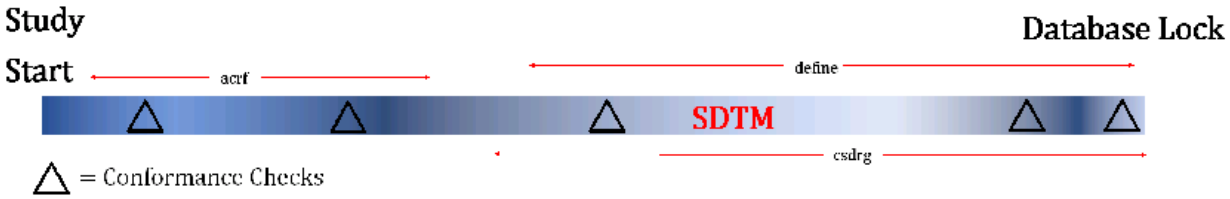


Let's take a closer look at some delivery components as they pertain to SDTM:

1. The SDTM data creation will begin after study start and after the EDC is populated with some subject data. The work peaks at the time that all domains are being programmed, validated, and checked for conformance to P21 or other sponsor standards. The SDTM should go through a maintenance phase after the handoff to ADaM, and the work should at that point revolve around getting new raw data, running SDTM creation programs, and resolving any issues that come along. As expected, another work peak comes at the time of database lock.
2. The annotated crf (acrf) will generally need to be started early since it will serve as the basis for the specifications and programming of the majority or your SDTM deliverable. The annotated crf should slightly precede the creation of SDTM data. Along with annotating your CRF, we also recommend completing several of your Trial Designs datasets at this time: TA – Trial Arms, TE – Trial Elements, and TV – Trial Visits. Not only will this help you to identify any tricky spots that you will need to watch for while working on specifications and programming data, but getting the acrf and trial design data completed early allows time for sponsor buy-in, comments, and updates.
3. The FDA reviewers spend quite a bit of time in the CDISC study data guides and were involved in the template creation by PhUSE. It is clear that the reviewer's guides are very important, so it is best to have a thorough guide. Creation of the clinical study data reviewer's guide (csdrg) should be in progress when the SDTM data are being programmed. Keeping notes about domain-specific oddities and places where the study data will deviate from the model as you spec and program will save you time at the end of the project. Some organizations use tools to populate the csdrg or adrg documents. These can be a big time saver, but they will only be able to populate the technical pieces of the document. Descriptions will need to be done manually and started early to ensure completeness. Once the SDTM data structure is final and in the maintenance phase, you can work on completing the other sections of the guide either manually or with the help of a tool. To ensure that you don't duplicate effort and continually update the csdrg needlessly, leave areas such as the supplemental grids blank until SDTM structure is complete and the data are in the maintenance phase.
4. Like the csdrg, creation of the define file should begin when SDTM is in the programming phase. The creation method of the define does vary widely across the industry. For example, some organizations use P21 to create their define, some tie in the elements of the define with specification creation, and other companies have a home-grown tool that somewhat automates the task. Whichever method applies to your situation, it is still a good idea to work towards having all origins, links, controlled terminologies, and method populated and working before the end of your study. If you have carefully planned for and executed your SDTM, the define can be created before lock and will only need the dependent XPT data, acrf, and csdrg dropped into place.
5. In general, checking your data for conformance should be done "early and often". Over time, data standards have taken on a more rigid framework, and ensuring conformance has become an integral part of study planning. For the most part, our use of the word "conformance" implies running Pinnacle 21 community or enterprise on your study data and updating the data based on the findings, but there may be other sponsor- or study-specific conformance required. Going through an initial cycle of SDTM data creation, conformance findings, and updates to the SDTM data will mean that your ADaM can be built with a higher degree of confidence in the stability of the SDTM. Likewise, checking for conformance early may result in changes to acrf mapping, define file creation, or notes for your csdrg. As the study continues it will be ideal to check for conformance periodically and make any adjustments if they arise. We do recommend a last look at conformance before data lock as a way to identify any outstanding issues that might need a site query and then of course running checks after lock to use in the conformance report sections of the csdrg.

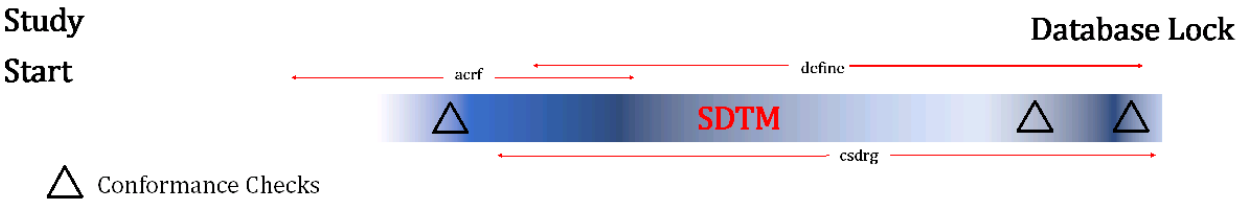
IDENTIFY CUSTOMERS AND BUDGET

Once you have listed your deliveries and planned for each component of those, the final step in timeline planning is using information about customers of your project and budget to make changes to the start date of work and interim deliveries if needed. First, let's take a look at the customers. These are the individuals or groups that will be directly impacted by the timing and quality of the deliverables you have identified. You will need to consider those on your direct team as well as sponsors and vendors. For example, the use of SDTM for central monitoring, risk-based monitoring, or safety reporting has become increasingly common. If your study will be using SDTM for any of these, it is likely that you will be asked, "When can we have SDTM?" and you may also get assurances that the group only needs certain domains. In order to get SDTM completed so early, though, you will need to start the acrf annotation at the time it is finalized and may need to start specifications and programming on test data so that when any subjects enter the study, SDTM can be populated as soon as possible. Your SDTM timeline will need to be adjusted for this earlier starting point.



Another important thing to note is that the customers (internal and external) that you have identified should be given an opportunity to review and comment on the timeline that you have made since the decisions will directly impact their work.

Finally, considering the project budget will help us determine when you can safely start your work and how much effort to devote at various stages of the project. In the example above, your budget should take into account the earlier SDTM start, potential extra deliveries, or loss of efficiency that may come with partitioning out some of the domains and saving the rest for later as a result of the needs of another group. It's possible, though, that the situation for your study is very different. For example, maybe the sponsor has a very limited budget and is only paying for one draft and one final of the SDTM data to be delivered. In this case, you will need to wait as long as possible before beginning SDTM production. Notice a longer space of time between study start and the creation of SDTM in the image below. There is also one less check of study data conformance.



CONCLUSION

While no two clinical trials are exactly the same, there are submission-specific relational timeline metrics that can serve as a basis for timeline planning and study success. Identifying your study-specific deliverables, the major milestones associated with the creation of each of these deliverables, and who the recipients of your deliverables are and what the budget is will ensure that all pieces are accounted for and delivered in a timely, cost-efficient manner. This will minimize stress and ensure the success of all parties involved.

CONTACT INFORMATION

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