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Submission Survival Guidelines for Statistical Programmers

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ABSTRACT

With accelerated cycle times whether it is *PRIME, RTOR or SAKIGAKE, submission processes are being redesigned in major markets. As a result, pharmaceutical companies must expedite drug approval through streamlined submission activities. This makes the statistical programming function a key stakeholder who needs to focus on a consistent approach across the portfolio in creating high quality submission deliverables, while maintaining speed and efficiency. This can only be accomplished through proactive planning, education, and awareness of submission requirements at every programming milestone. The intent of this poster is to provide a visualization of the programming life cycle for a successful submission. This will serve as a one-stop shop, consolidating guidelines from multiple sources and simplistically explaining each submission component. These guidelines, in the form of a flowchart, will cover industry best practices, link to external resources, and include implications of upfront planning and ongoing risk assessment, all targeting a successful submission package. This poster will illustrate the details of the submission survival guidelines a programming team will need to plan programming deliverables and execute an efficient submission.

*PRIME, RTOR, SAKIGAKE are accelerated pathways across major markets in EU, US, and Japan.

INTRODUCTION

This paper describes an easy-to-navigate flowchart. It walks through several of the key components, programming milestones and dependencies that contribute to a fast and successful submission. The focus is to provide flexibility and ease as programmers navigate the complex regulatory landscape and provide the best solutions to their companies in their goal to create a healthy electronic data submission (eSUB) package. The paper also touches upon early preparation for accelerated pathways and other often overlooked submission related activities.

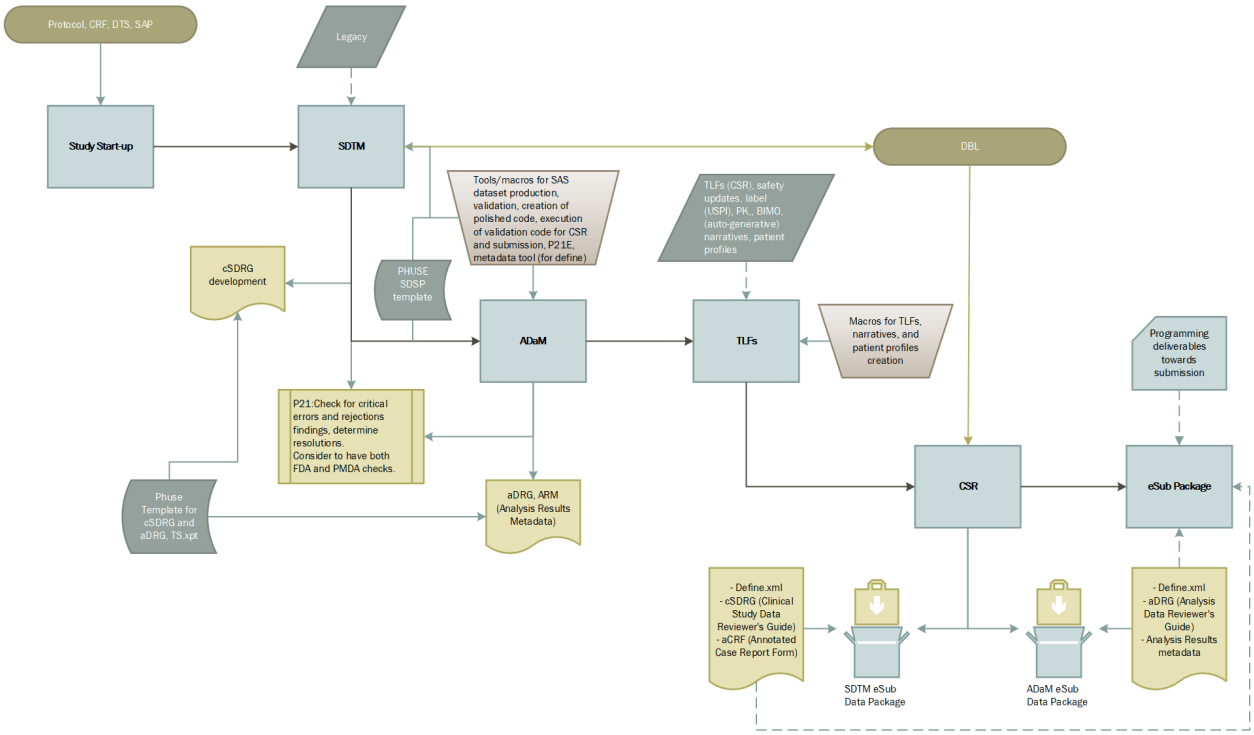

Figure 1 Study Life cycle from a Programming perspective

STUDY MILESTONES

The Study Life Cycle and all its components are captured from the programmer's perspective in Figure 1 Study Life cycle from a Programming perspective. Each Checkpoint, whether it is the Study Startup, the Database Lock or the eSUB package development, requires appropriate assessment and proactive planning from programmers to enable a successful submission. Each of the checkpoints should be planned in advance, making sure resources and delivery model are identified as early as possible.

As shown in Figure 2 Study Milestones below, the programmer can easily visualize, in a left to right flow, when and which milestones should occur during the conduct of a study in preparation for a submission, starting with the Protocol Synopsis and ending with the CSR Tables, Listings and Figures (TLFs). All milestones relevant to statistical programming are included regardless of direct involvement. For example, the programmer may not be crucial to the development of the Protocol but should be aware of its status and timing. First Subject First Visit (FSFV) is called out as this is not only a crucial milestone for a study, but sponsors may also choose to time deliverables based on when FSFV occurred (for example, SDTM within 3 months of FSFV, etc.).

Monthly SDTM is displayed as spanning a large timeframe to demonstrate that monthly SDTM production will likely be ongoing starting shortly after FSFV up until Database Lock (DBL) to support data cleaning and review activities. This allows the team to run Pinnacle 21 (P21) periodically to check for compliance issues.

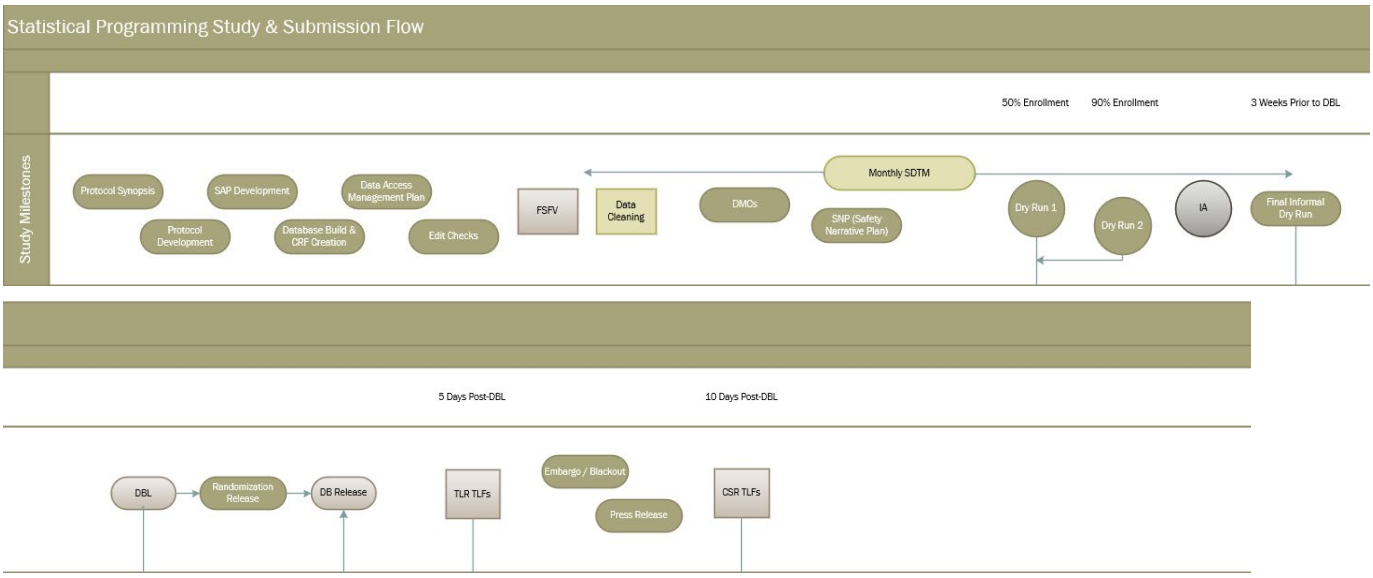

Figure 2 Study Milestones

In this figure you can also see general timing recommendations such as two TLF Dry Runs each at around 50% and 90% enrollment, and Top Line and CSR TLFs completion at 5 days and 10 days post-database lock, respectively. Sponsors may choose to update these to reflect their own guidelines, but to make sure that end-to-end data processes are included.

Similarly, sponsors may choose to update the language to reflect their own conventions. For example, they may use FSI rather than FSFV, or use another term besides Dry Run.

PROGRAMMING DELIVERABLES

This section focuses on the portions of the flowchart that demonstrate the timing and scope of programming activities and deliverables, both during the conduct of the study and for submission. Each deliverable is aligned under the study milestones timelines to help the statistical programmer to better visualize when generally the activity should be performed.

STUDY DELIVERABLES

Figure 3 Start-up Programming Deliverables below displays the portion of the flowchart focused on the programming activities conducted towards the beginning of the study, including development of the SDTM specifications and SDTM-annotated CRF. After the SAP is developed, the programmer or designee can begin to develop the Table of Contents necessary for the CSR, DMC, etc. From the TOC, the TLF mock shells and ultimately the ADaM Specifications can be produced.

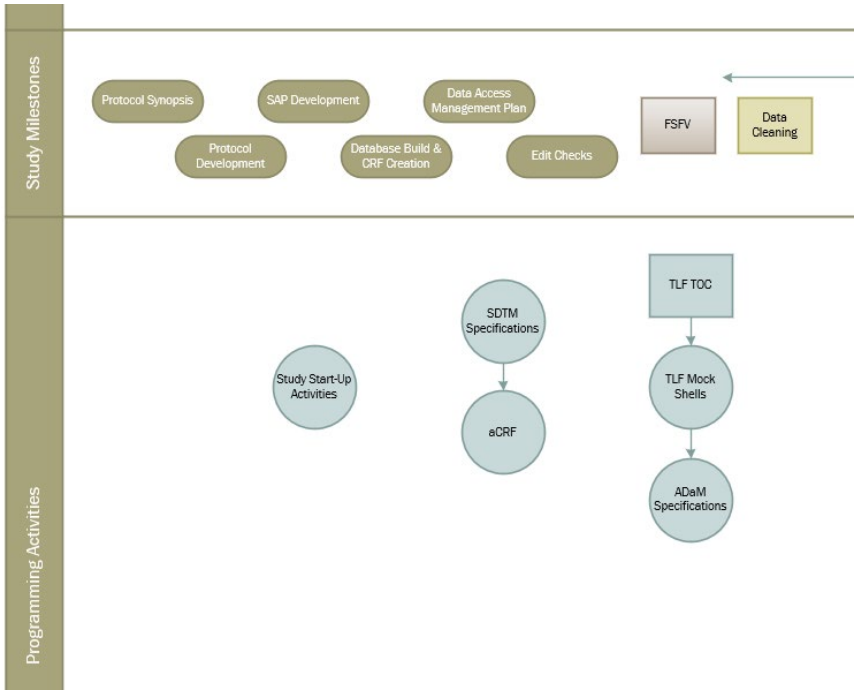

Figure 3 Start-up Programming Deliverables

Moving further along to the right in the flowchart, you encounter the programming deliverables associated with Dry Run activities as shown in Figure 4 Dry Run Data and TLF Deliverables below. Both Dry Runs 1 and 2 are displayed as having the same tasks, starting with SDTM production, QC, and Pinnacle 21 validation, followed by the same for ADaM, and ending with TLF production and QC, and finally the Dry Run Review. P21 reports should be generated for every SDTM run and fallouts addressed as early as possible. For ADaM datasets, the recommendation is to run the P21 at targeted Dry Runs and errors addressed as early as possible.

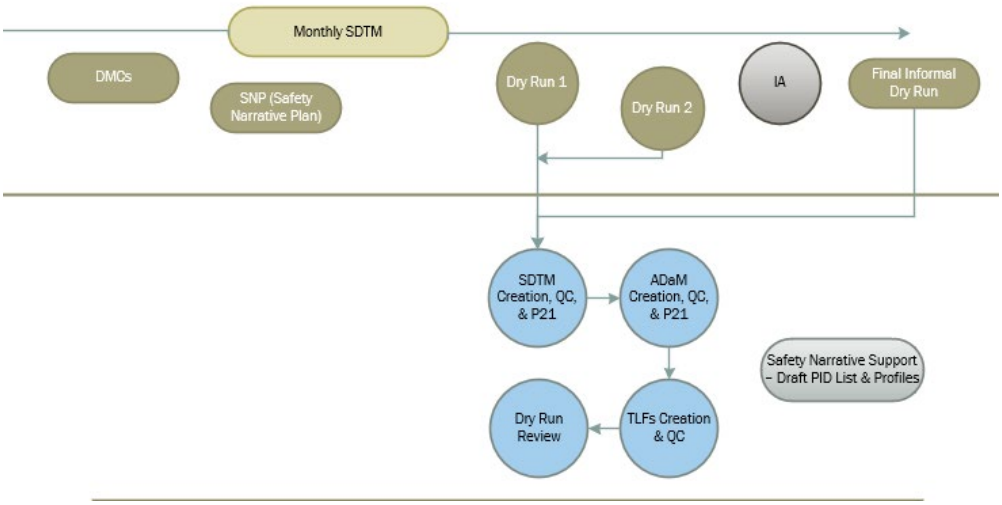

Figure 4 Dry Run Data and TLF Deliverables

Figure 5 Final Data and TLF Deliverables displays similar steps as for the Dry Runs but for the final creation of data and TLFs for the Top Line Report and CSR. Note that the flow for SDTM shown below is in alignment with a definition of database hard lock (or “release”) on SDTM, though certain sponsors may define this on raw data instead.

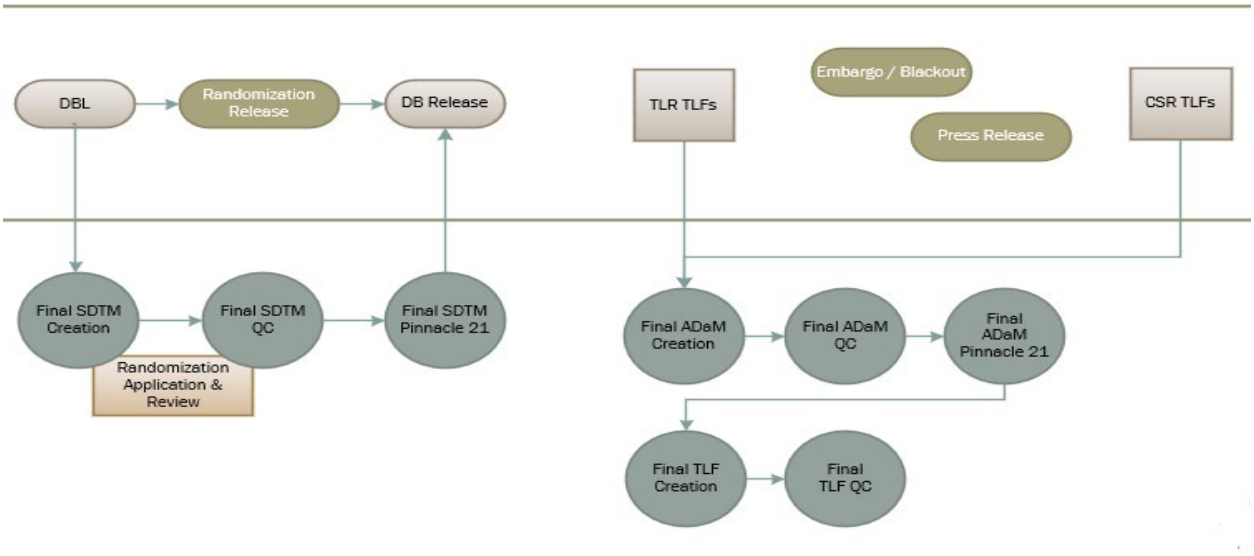

Figure 5 Final Data and TLF Deliverables

SUBMISSION DELIVERABLES

Submission deliverables for both FDA and PMDA are displayed in the section of the flowchart shown in

Figure 7 FDA vs. PMDA Submission Deliverables further summarizes the submission deliverables to each of the two regulatory agencies, as well as the commonalities between them. Both include submissions of SDTM and ADaM data and defines, the aCRF, and ADaM programs. Differences include the naming convention for the ADaM Data Reviewer’s Guide as well as the inclusion of the Analysis Results Metadata (ARM), which is optional for submission to the FDA but strongly recommended for PMDA.

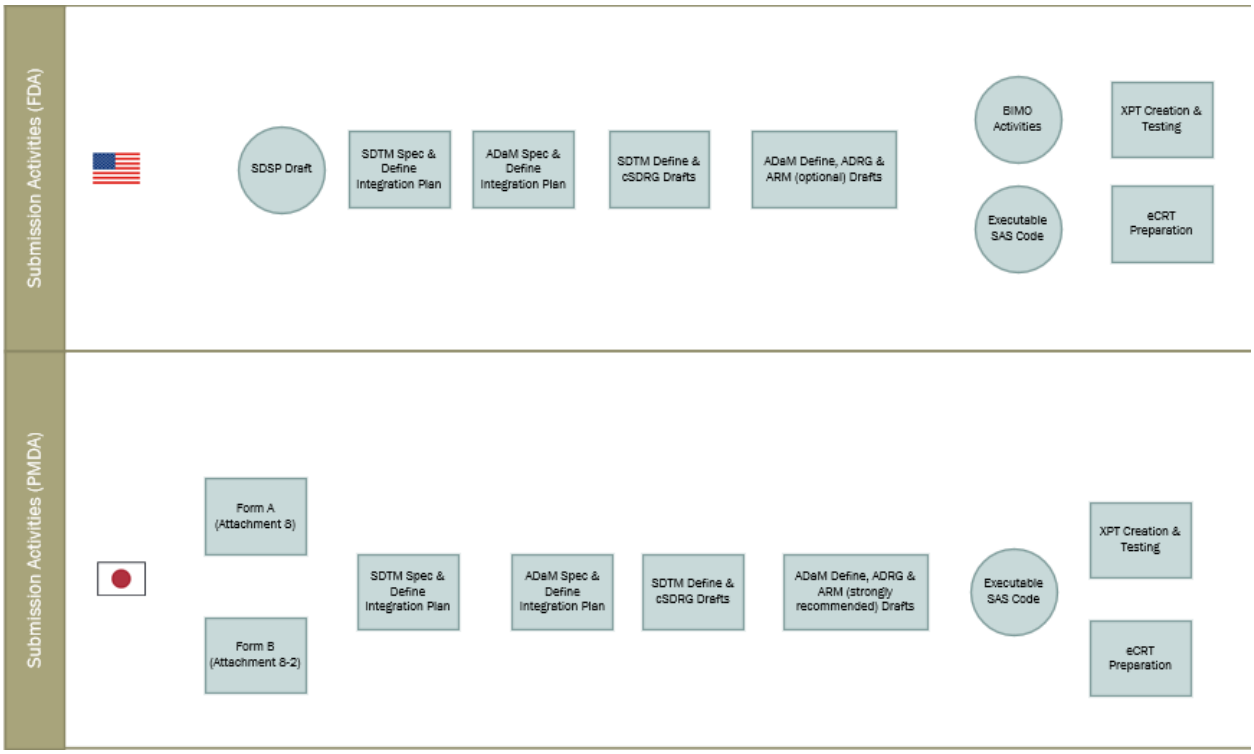

Figure 6 Submission Deliverables for FDA and the PMDA

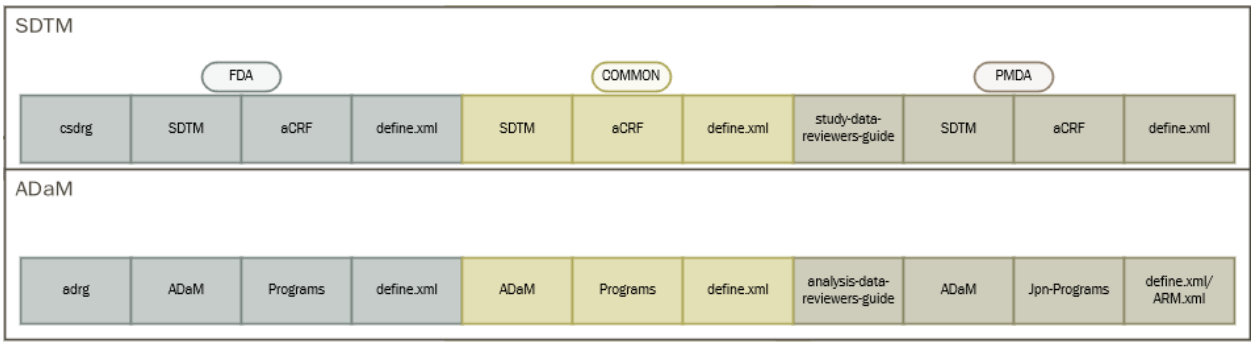

Figure 7 FDA vs. PMDA Submission Deliverables

SUBMISSION DELIVERABLES AND ASSOCIATED ACTIVITIES

The keys deliverables for submission includes P21 report, define.xml and the reviewer's guide. This supportive documentation should be in draft stage at least 8-12 weeks before DBL. The P21 report should be at least 90% compliant by that timeframe, and Bioresearch Monitoring (BIMO) outputs (only needed for the FDA) should be available for review. All submissions whether it's for the FDA or the PMDA are fraught with strategic changes. Regardless, the final goal is a successful submission. Figure 8 Submission Deliverables and Associated Activities below describes how programmers can contribute to key pieces of the submission discussion including inspections and meetings with regulatory agencies. A few components of the post-submission activities are also captured keeping in mind that not all submissions have a similar pre-submission series of activities.

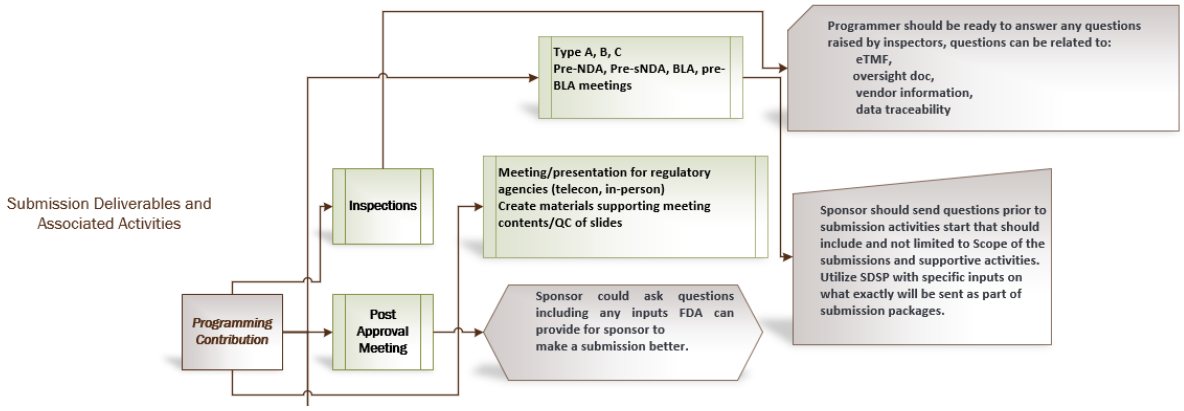

Figure 8 Submission Deliverables and Associated Activities

ACCLERATED SUBMISSION PATHWAYS

Often certain drugs and biologics with promising early results are identified for an accelerated submission pathway. They are used to accelerate the approval of drugs to shorten the consultation and review time. These include RTOR, PRIME and Sakigake. As a result, there are several downstream implications such as increased resources to front-load the submission activities and preparation, mature data and >1 eCTD package for early review of the submission package.

CONSIDERATIONS FOR RTOR

RTOR or Real Time Oncology Review is for the FDA and provides earlier access to topline safety and efficacy data and data packages. It also provides patients earlier access to therapies. The Submission teams need to strategize their process of submission and the speed with which they produce the deliverables.

Statistical Programmer Contribution for RTOR

There should be earlier preparation of data packages and validation to address issues. Proactive planning and early communication with the regulatory team and statisticians help in the review of the early submission package. The goal should be to submit a complete data package instead of just TLFs as part of the early submission package. The focus should be on early identification and interpretation of ad-hoc analyses. Figure 9 RTOR Overview presents a high-level overview of an accelerated pathway in the US. This requires best practices for batch submission of ADaM datasets with minimal resubmission of new or updated datasets for early and easy review by the agency.

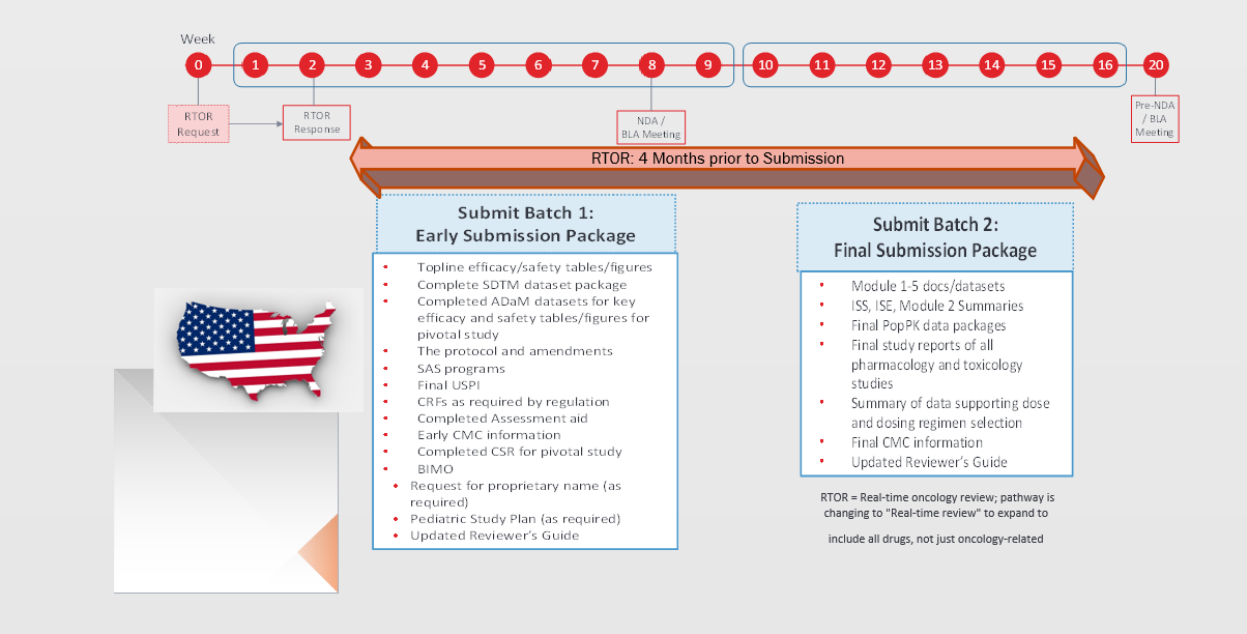

Figure 9 RTOR Overview

CONSIDERATIONS FOR SAKIGAKE

Sakigake is for the PMDA and reduces the time for PMDA consultations. These are targeted for drugs that are of high public interest and meet an unmet medical need. The Submission teams need to strategize their process of submission due to prioritized consultation timeline, pre-application review of the draft eCTD and prioritized NDA review.

Statistical Programmer Contribution for Sakigake

The team needs to understand the chronology of the two different eSUB packages before NDA and at the time of the NDA submission. There should be earlier preparation of data packages based on specific requirements and timeline considerations. Figure 10 Sakigake Overview presents a high-level overview of an accelerated pathway in Japan, which requires upfront planning on how to manage the multiple data packages.

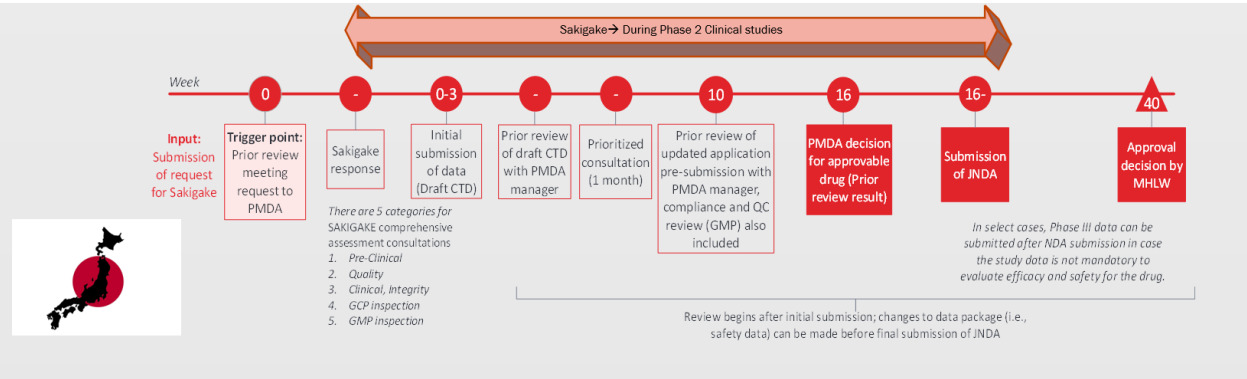

Figure 10 Sakigake Overview

CONCLUSION

The paper is written keeping in mind the programming role in submission. All components of the study must align to create a successful eCTD package, from study start to final eSUB creation. Programmers need to navigate a complex changing regulatory landscape with region-specific guidance. In addition, regulatory agencies offer options for accelerated approvals. This paper covers two such scenarios. In addition, the ePoster has several links to external resources which serve as a one-stop shop for consolidated guidance from various agencies.

CONTACT INFORMATION

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