PharmaSUG 2022 - Paper SS-039

Real Time Oncology Review Readiness from Programming Perspective

Binal Mehta, Mukesh Patel, Merck & Co., Inc., Rahway NJ USA

ABSTRACT

The US Food & Drug Administration (FDA) Oncology Center for Excellence (OCE) has introduced a pilot program Real Time Oncology Review (RTOR) to enhance their review process for Oncology treatments, aiming to provide treatments safely and effectively as early as possible to patients. Another objective for this pilot project is to maintain and improve review quality as well as maintain the reviewer's workload through data and analysis standardization while allowing early meaningful engagement with applicant. The RTOR program was initially begun to support Supplemental Drug Applications that added new dosing regimens, new indications, or any new clinical information to the label for prescribing medications, but later this program was expanded to include original new drug applications and biological license applications for new molecular entities (NME).

Applicants require careful planning and resource management due to multiple package transfers (RTOR & Final Submission) and interactions with FDA. The FDA received RTOR submissions a median of 5.7 weeks prior to final submission application and the median time frame for an FDA approval from time of application submission is 3.3 months in an RTOR review. The approval time savings in an RTOR review over a standard or priority application submission review is not guaranteed as other parts of review may influence the overall timelines. A quality RTOR submission package plays a critical role for an applicant to get a timeline advantage and stay ahead in getting an approval or meaningful interaction with FDA. The statistical programmer plays an important and crucial role working on key components of the RTOR package and eventual final submission application. This paper will walk through some of the key components of an RTOR package and cover the logistics of preparing them, from a statistical programmer point of view.

INTRODUCTION

This paper will cover the steps for preparing an RTOR submission for an oncology study from the statistical programmer's perspective. It will describe which components are submitted as part of the RTOR package and when the statistical programmer should kick off preparation for these components. Figure 1 provides an overview of the expected submission activities and components that a statistical programmer is responsible for working on. Timelines for the components in RTOR versus the final submission will be highlighted and how to plan for parallel activities on blinded and unblinded data and their impact on preparation for the final submission. Various challenges faced by the statistical programmer will be presented along with steps to take to achieve meaningful resolution of these challenges. Lastly, this paper will also provide insight into coordinating activities between cross functional teams.

RTOR SUBMISSION PACKAGE:

The key components of a RTOR submission package are the SDTM package and the ADaM RTOR package.

SDTM Package:

The SDTM RTOR submission package includes the SDTM dataset SAS® transport files (xpt), the data definition file (define.xml v2.0) and stylesheet (define2-0-0.xls), the Annotated Blank CRF (acrf.pdf) and the Clinical Study Data User Guide (csdrg.pdf).

SDTM xpt files: SDTM datasets are submitted in the SAS® Transport Format (XPORT) Version 5. SAS® transport files (.xpt) are created from SDTM datasets using the XPORT engine and PROC COPY procedure or the XPORT engine and a SAS® data step. There should be one dataset per transport file, and the dataset in the transport file should be named the same as the transport file and these files should not be

compressed. Datasets greater than 5 gigabytes (GB) in size should be split into smaller datasets, no larger than 5 GB.

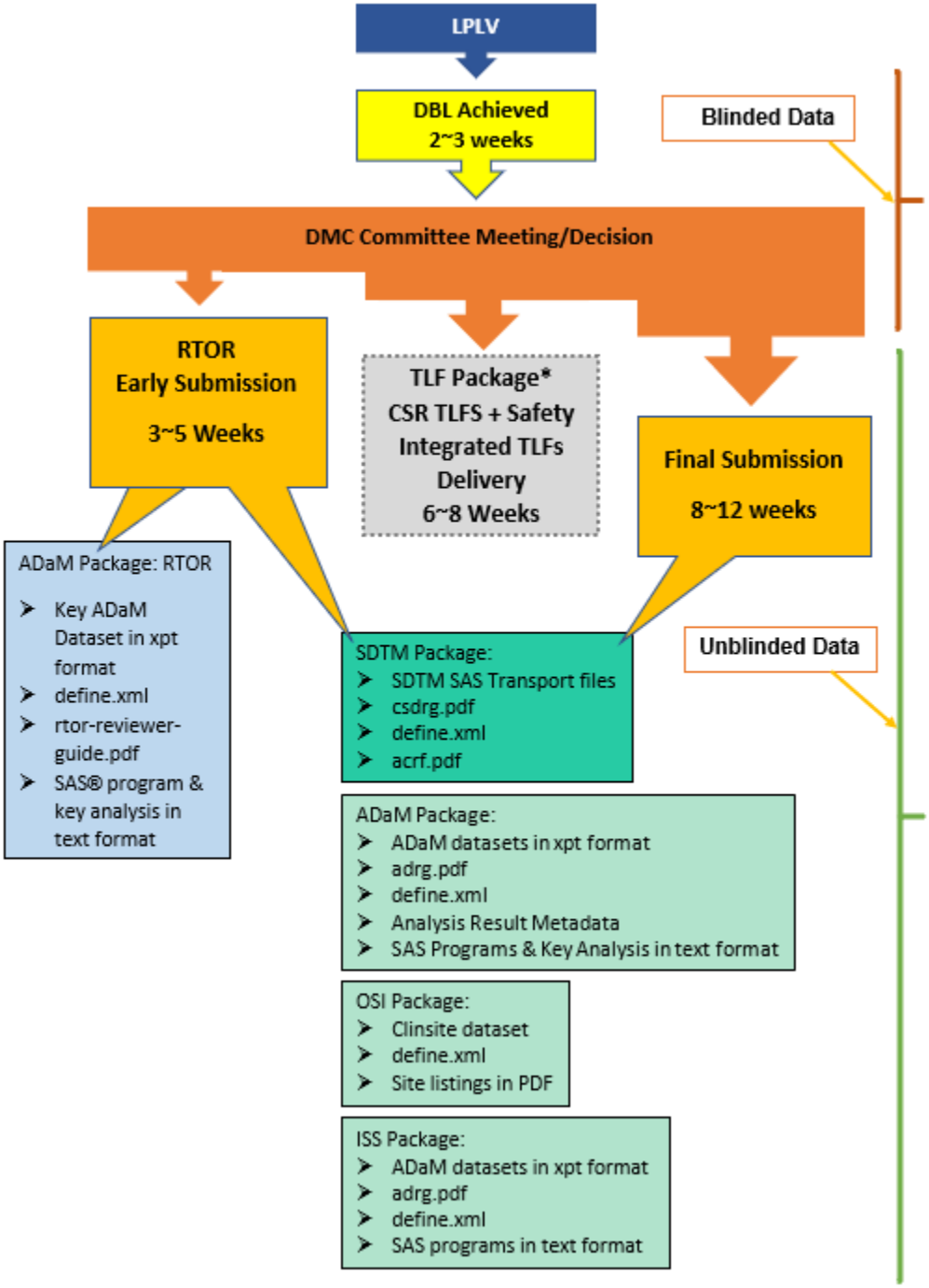

Figure 1. Overview of Submission Activities

*Note: eSubmission components exclude the TLFs development performed by the Statistical Programmer for the CSR.

Define.xml: The define.xml is a crucial document in communicating the structure and content of the study SDTM package. It should be complete and describe Study information/header section, Tabulation Datasets Lists, Dataset Section, Value Level Metadata, Controlled Terminology, Computational Algorithms and Comments sections and externally linked files.

Clinical Study Data Reviewer's Guide (cSDRG): The preparation of the Clinical Study Data Reviewer's Guide is recommended as an integral part of a standards-compliant study data submission. It should describe any special considerations, derivations or conformance issues that may facilitate an FDA (Food and Drug Administration) reviewer's use of the submitted data. It should help the reviewer understand the relationships between the study report and the data. It must include the study protocol title/number/version, study design, standards, formats, and terminologies implemented and their versions, a description of the study datasets, and the data standards validation issues and explanations.

Annotated Blank CRF: An annotated case report form (aCRF) is a PDF (Portable Document Format) document that maps the clinical data collection fields used to capture subject data to the corresponding variables or discrete variable. The aCRF is provided as a PDF with the file name "acrf.pdf". When data are recorded on the CRF but are not submitted, the CRF fields should be annotated with the text "NOT SUBMITTED" and an explanation should be documented in the cSDRG on why these data have not been submitted. The aCRF should include treatment assignment forms, when applicable, and should map each variable on the CRF to the corresponding variables in the datasets (or database). The aCRF should include the variable names and coding for each CRF item.

ADaM RTOR Package: The key components of ADaM RTOR submission package are the ADaM dataset SAS® transport files (xpt), the data definition file (define.xml v2.0) and stylesheet (define2-0-0.xls), the RTOR reviewer's guide (rtor-reviewers-guide.pdf) and key SAS® programs to produce submitted SAS datasets and key analysis programs in text format (.txt files).

ADaM xpt files: ADaM datasets are submitted as SAS® V5 transport files in an electronic submission. There should be one dataset per transport file. In oncology studies, the RTOR ADaM package usually includes key ADaM datasets ADSL, ADAE, ADEX, ADEXSUM, ADLB, ADRS, ADINTDT, and ADTTE. Individual study teams can decide which datasets should be included in this package. A RTOR submission requires certain variables in ADaM datasets recommended by Pilot Office on Oncology Diseases (OOD) Safety Team Standard Data Requests as shown in figure 2.

ADSL	ADAE	ADLB
SAFFL (Safety population flag)	WRSBLFL (Worsening of Baseline AE Flag)	BASE (Baseline Value)
DCTREASP (Reason for Disc from Treat Due to COVID)	TREMzzFL(Treatment Emergent Analysis zzFlag)	CHG (Change from Baseline)
DTH30TFL	AACNSD01 (Analysis Action Taken with Study Drug 01)	PCHG (Percent Change from Baseline)
DTHA30FL (Death After 30 Days of Last Treatment)	AACNSDzz(Analysis Action Taken with Study Drug zz)	LBSTRESN (Numeric Result/Finding in Standard Units)
DTHB30FL (Death After 30 Days of Last Treatment)	DOSR01FL (Dose Reduced Study Drug 01 Flag)	LBSTRESC (Character Result/Finding in Std Format)
DTHDY (Study Day of Death)	DOSRzzFL(Dose Reduced Study Drug zzFlag)	LBSTRESU (Standard Units)
LSTALVDT (Date Last Known Alive)		LBSTNRLO (Reference Range Lower Limit-Std Units)
DCTDT (Treatment Discontinuation Date)		LBSTNRHI (Reference Range Upper Limit-Std Units)
CUTOFFDT (Data Cutoff Date)		

Figure 2. An excerpt from the Pilot Oncology Diseases (OOD) Safety Team Standard Data Requests.

Define.xml: It provides metadata for the ADaM datasets. This is the most important document the ADaM RTOR submission package. It describes the dataset structure and provide information about datasets, variables, controlled terms, and other specified metadata. This document lists the datasets included in the submission and provides a detailed description of the contents of each dataset. All ADaM datasets should have a define.xml document and a corresponding define.xls (stylesheet). In a RTOR submission, the define.xml will be trimmed to provide information only for key ADaM datasets submitted early instead of information for all the study ADaM datasets.

RTOR-reviewers-guide: This document serves as an alternative to the Analysis Results Metadata (ARM) document. It provides information for the SAS® programs supporting the top line safety and efficacy tables, listings, and figures (TLFs) included in the RTOR package and is provided as a PDF file.

Program Text files: For a RTOR submission, only key ADaM dataset programs and top line safety and efficacy TLFs report macros are provided in text format. The programs should be able to replicate analysis datasets and TLF results.

RTOR PACKAGE PREPARATION:

As outlined in Figure 1, the timelines to prepare a RTOR package are noticeably short, once a study has a positive DMC decision, so it is recommended that the preparation of the package start at least four to five weeks before the database lock. To add, the statistical programmer will remain blinded after database lock allowing them to have three to four weeks of additional time till the DMC decision to work on preparing submission deliverables giving the statistical programmer a total of eight to ten weeks to get ready using blinded data. The statistical programmer can start preparing the package components on blinded data and eventually complete all the remaining activities on unblinded data once the study has a positive outcome and moves forward to submission. We explain which activities can occur on blinded and unblinded data in detail as follows.

SDTM Package Preparation using Blinded Study Data:

Define.xml: Prior to four to five weeks before database lock, the SDTM specification should be completed so the statistical programmer can start the development of the define file. This is the time the statistical programmer should review all the variable derivations, mappings, formats, and control terminology to streamline glitches in the specifications. Wider team meetings at this stage are encouraged to have prompt decision and resolution on any outstanding issues.

SDTM xpt files: Development of all the SDTM datasets should be completed including development of the SDTM Trial Summary (TS) dataset. The TS specification should be thoroughly reviewed and approved by the project statistician and lead programmer. The statistical programmer can convert the SDTM datasets into xpt files and ensure the size of each file is less than 5GB.

Datasets and Define Validation: It is expected that SDTM datasets are validated using the Pinnacle 21 tool throughout the life cycle of data flow (i.e., from the start of the data flow to database lock). Continual review allows enough time for resolution of data collection and entries issues, CRF collection or modifications during the study. These discrepancies may result in the opening of queries for trial sites, and some may take a considerable amount of time for resolution and correction. Since the SDTM data package is one of the first deliverables in a RTOR submission, periodic P21 runs are absolutely needed prior to database lock to ensure high-quality compliant CDISC SDTM data. Then after creating the define, it is necessary to do Pinnacle 21 validation along with the SDTM xpt files to identify any conformance issues. Doing this in advance of the database lock helps the team to have enough time to resolve any conformance issues.

Clinical Study Data Reviewer's Guide (cSDRG): Prior to four to five weeks before database lock, the statistical programmer should start gathering information required for Clinical Study Data User Guide (cSDRG). It includes acronyms, various terminology used in the trials, specific data collections, detailed

conformance section, mapping decisions, sponsor-defined domains, study specific implementation, and sponsor extensions to CDISC controlled terminology. It is understandable that not all explanations and resolutions can be finished for all conformance issues, but every effort should be made to have a draft cSDRG completed using blinded data.

Annotated Blank CRF: During the life cycle of the trial, multiple versions of the case report form (eCRF) may exist. The statistical programmer must ensure that the most current version is used for annotation. All quality checks should be performed to ensure correctness of aCRF.

PK (Pharmacokinetics) Data: If the study involves PK analysis, the programming team should clarify if the SDTM PC domain is available and document details for cSDRG in collaboration with the PK analysis team.

ADaM RTOR Package Preparation using Blinded Study Data:

Define.xml: The statistical programmer can start working on cleaning the ADaM specifications for spelling errors, cross checking formats, code lists, methods, removing any strike through comments, removing any programming language, and simplifying define derivations. The statistical programmer can then use the Pinnacle 21 tool to create a quality define file in xml format.

ADaM xpt files: The statistical programmer can test run the conversion of the ADaM datasets into xpt files. This step ensures most of the issues in creating xpt files can be addressed promptly on blinded study data.

Datasets and Define Validation: It is expected that ADaM datasets must have been validated through the Pinnacle 21 tool. The statistical programmer should validate the define.xml with ADaM xpt files for ADaM compliance, controlled terminology, regulatory conformance, metadata, data quality, and analysis support. This step allows the statistical programmer to cross verify the define file and ADaM datasets for CDISC compliance and make any necessary modifications in define file and ADaM datasets algorithms before getting unblinded.

RTOR-reviewers-guide: The statistical programmer can start preparing this document two to three weeks before database lock. They can start gathering information from the statistician about which key safety and efficacy TLFs are expected to be submitted to FDA early.

Programs text files: The statistical programmer can work on ADaM macro programs and key analysis for TLFs and convert them into text files. The statistical programmer should ensure that all text files are executable and can replicate analysis datasets and TLF results.

SDTM Package Preparation using Unblinded Study Data:

Define.xml: Comments from the review of define file on blinded data must be incorporated at this stage in the SDTM specifications. The statistical programmer should use these specifications to create the define file on unblinded data. Once the define file is developed, the statistical programmer can send it for final team review.

SDTM xpt files: Once unblinded SDTM datasets are available, the statistical programmer should convert them into xpt files. Any issue in converting SDTM datasets to xpt files should have been resolved on blinded data hence this step should be straightforward.

Datasets and Define Validation: During the validation process, the statistical programmer should re-check the issues that were unresolved on blinded data and evaluate any new issues that arise on unblinded data. The statistical programmer should work on resolving any remaining issues. If issues cannot be resolved by this time, then an explanation must be provided in cSDRG document.

Clinical Study Data Reviewer's Guide (cSDRG): Use the cSDRG document developed on blinded data. Address all conformance explanations and implement all comments from the reviews. If it requires adding or updating information due to unblinded data, the statistical programmer should work on it.

Annotated Blank CRF: Since there is no blinding or masking on a CRF, the annotated blank CRF should be a copy of the one developed using blinded data unless there is any specific update to the collected fields after it has been created.

ADaM RTOR Package Preparation using Unblinded Study Data:

Define.xml: The comments from the review of define file on blinded data must be incorporated at this stage in the ADaM specifications. The statistical programmer should use these specifications to create a final define file on unblinded data. For the RTOR package, the statistical programmer should trim the ADaM specification for the key required analysis datasets, if not already done on blinded study data. This can be done manually or by using a utility macro. Next, the statistical programmer can use these trimmed ADaM specifications to create a define file. Once define file is developed, the statistical programmer can send it for team review.

ADaM xpt files: The statistical programmer should ensure that only key analysis datasets have been converted to xpt files.

Datasets and Define Validation: The statistical programmer should validate the define.xml with ADaM xpt files using the Pinnacle 21 tool. Conformance issues that arise from this validation should be either resolved or a detailed explanation about the unresolved issue should be documented in ADRG document. Please note that the ADRG is not submitted early in a RTOR submission.

RTOR-reviewers-guide: The statistical programmer can finalize the drafted version of the guide developed based on blinded data. If this document is not completed earlier, the statistical programmer should complete it now. Attention is required when there is any addition or removal of TLFs from the earlier version of the document.

Programs text files: The statistical programmer should copy program text files to production and ensure that all text files can replicate analysis datasets and TLFs results on unblinded data.

SDTM AND ADaM RTOR PACKAGE REVIEWS:

Reviews of the SDTM and ADaM package components for RTOR are important and can catch issues that may not be found by automated macros or utility check tools. The statistical programmer can reach out to a Subject Matter Expert (SME) and management in advance, discuss timelines for review of these documents. Figure 3 displays the review process implemented for RTOR.

Package Review on Blinded Data: A peer programmer and study statistician can review submission components developed using blinded data. The statistical programmer should reach out to the SME for review of components in advanced of the database lock. This will save time while working on unblind data since many of the comments can be addressed prior to database lock.

Package Review on Unblinded Data: As outlined in Figure 3, the statistical programmer should plan for multiple reviews by team members, SMEs, and management. Package reviews done prior to database lock can help to accelerate preparation of packages post database lock developed on unblinded data. Multiple rounds of review help in improving the quality of submission packages.

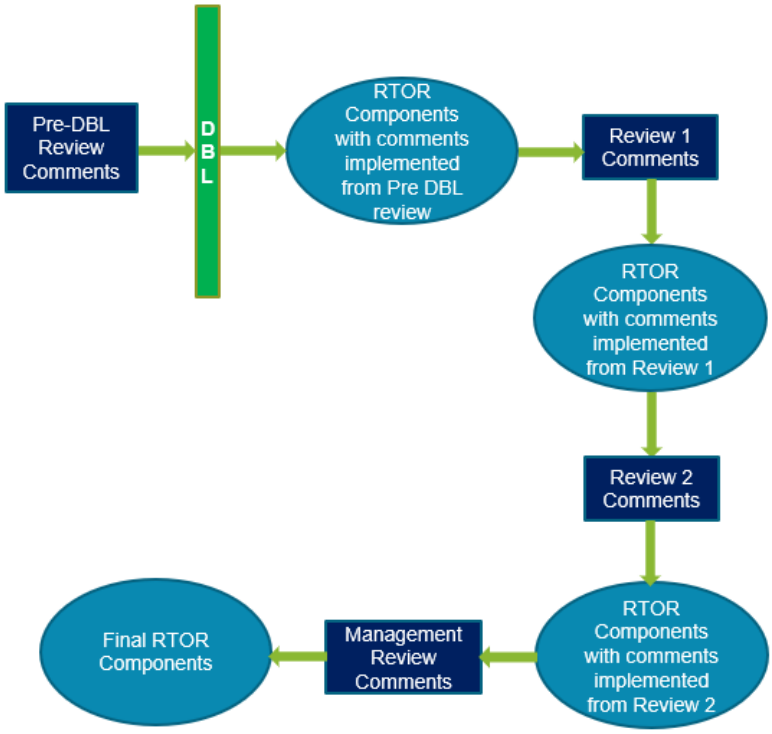

Figure 3. RTOR component review process

FINAL SUBMISSION PACKAGE: The key components of the final submission package are the SDTM package, ADaM package and OSI package.

SDTM Package: The FDA does not require the SDTM package to be re-submitted with final submission package as it has been submitted with RTOR submission package unless there is a post database lock critical change. If a critical change impacts the content or structure of the SDTM package, then a re-submit of the package may be required otherwise, no SDTM package is needed.

ADaM Package:

Define.xml: The statistical programmer should create a complete define file including all ADaM analysis datasets on unblinded data. To do this, the statistical programmer can use the define file from RTOR ADaM submission package and add any remaining ADaM dataset specifications. The FDA recommends providing a define file with all ADaM datasets even though key ADaM datasets specifications were already submitted during the RTOR submission. This complete define file will replace the prior RTOR define file in the final submission.

ADaM xpt files: FDA requires to submit all remaining study ADaM xpt files which were not previously submitted with the RTOR submission package.

Analysis Data Reviewer's Guide (adrg.pdf): This document is recommended as an important part of analysis data submission for clinical trials. Although this document holds some duplicate information that can be found on other submission documents, the content is designed to help the reviewer better understand the ADaM datasets, key derivations information and its terminology, explanation of any unusual data points, summary, and explanation of conformance findings. This document will help the reviewer to understand data and reproduce the primary data analysis and endpoints.

Since the ADRG is not part of RTOR submission package, the statistical programmer should start gathering information while the study is blinded but can complete this document using unblinded data once the RTOR submission package has been dropped off to FDA.

Analysis Results Metadata (arm.pdf): This document holds key information for all the ADaM analysis data used to create the safety, efficacy, and other clinical study tables, listings, and figures. This document will have a one-to-one relationship between the analysis data and variables used to create clinical study reports.

Like the adrg.pdf, this document can be prepared once the RTOR submission package has been dropped off to FDA.

Programs text files: The statistical programmer should prepare programs for the remaining ADaM dataset and safety and efficacy TLFs mentioned in the analysis results metadata in text format.

OSI (Office of Scientific Investigation) Package: The key components of OSI package, also known as Bioresearch Monitoring (BIMO), are the Summary Level Clinical Site dataset (clinsite.xpt), define.xml and the Subject Level Data Line Listings by Clinical Site in pdf format. The statistical programmer can start preparing this package once the RTOR submission package has been dropped off to FDA.

ISS (Integrated Safety Summary) Package: This package includes the ISS ADaM analysis datasets in xpt format, the ISS adrg.pdf, the define.xml and define.xls (stylesheet) and SAS programs for key analysis in text format (.txt files). The statistical programmer can start preparing for this package once the RTOR submission package has been dropped off to FDA.

TLF PACKAGE: Although this programming work is not formally considered part of the eSubmission deliverables to be produced for the submission, the programming to develop the content and tables for the CSR needs to happen in parallel with all the other concurrent submission activities after DMC decision. This paper doesn't focus on this component of TLF development but instead focuses on the key data deliverables for inclusion in the submission and how to efficiently prepare them for RTOR.

CHALLENGES AND RESOLUTION:

Competing Activities: RTOR package activities begin four to five weeks before database lock, while other analysis and reporting activities to generate the CSR deliverables occur in parallel with it. The statistical programmer should be aware of and closely track both timelines ahead of time and allocate appropriate resources so that both activities can progress without issues.

Continuous updates in Specifications: In an ideal scenario, the specifications should have been finalized three to four weeks before database lock, but in practical scenarios, there are always updates happening in the specifications up to database lock. The challenge for the statistical programmer is to create the define file with continuously updated specifications. The statistical programmer should ensure that these last minutes updates are accommodated in the define file by keeping track of all these updates in specifications hence carrying those to the define file is easy.

Delayed response from stakeholders: Many times, the statistical programmer does not get response on queries, questions, and input specifications in time from clinical and statistician teams and this leads to delays in generating RTOR components. The statistical programmer should schedule meetings and clearly specify the problems and their effects on timelines.

Review of RTOR submission package: No matter how much planning and preparation is done by the statistical programmer to provide RTOR package promptly to management/SME for review, there is possibility it may be delayed due to unforeseen reasons. There is also a possibility that the statistical

programmer provides the RTOR package on time for management/SME review. However, their availability may be impacted due to multiple tasks on their hand, so your package review may get delayed. In such scenarios, the statistical programmer should be ready for this challenge and may extend working hours to accommodate comments from the review.

COORDINATION BETWEEN CROSS FUNCTIONAL TEAMS:

During the life cycle of clinical trial, the statistical programmer is responsible for and must coordinate with various teams such as data management, clinical, statistician, PKPD team, medical writers, regulatory, and external vendors. The statistical programmer should schedule meetings with team members based on requirements and incorporate suggested input from them during various times in the trial, as needed. This will help in producing quality data, specifications, and overall submission packages in a timely manner.

CONCLUSION:

The Real Time Oncology Review (RTOR) program is designed to allow the FDA to review data ahead of time. As explained in this paper, well established planning prior to database lock, and proper execution of all the submission activities are key to successfully rolling out high-quality submission components rapidly after database lock and DMC decision. It is important to collaborate with various stakeholders and have meaningful decision-oriented communication to resolve all issues early on as this will lead to quality submission components. With proper advanced planning, the statistical programmer should be prepared to work quickly with tight timelines once a decision to file is made and be ready overcome all challenges swiftly to create a high quality and compliant RTOR submission package.

ACKNOWLEDGEMENT:

The authors would like to thank management team Lisa Pyle, Sapan Patel, and Amy Gillespie for their time in reviewing the paper and providing valuable comments.

REFERENCES:

U.S. Food and Drug Administration: Initial Experience with the Real-Time Oncology Review Program
U.S. Food and Drug Administration: Initial Experience with the Real-Time Oncology Review Program - PubMed (nih.gov)

Analysis of the Real-Time Oncology Review (RTOR) Pilot Program for Approvals of New Molecular Entities
https://pubmed.ncbi.nlm.nih.gov/33913098/

Real-Time Oncology Review
https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review

Food and Drug Administration. “Study Data Technical Conformance Guide” Oct 2019
https://www.fda.gov/media/131872/download

Analysis Package e-Submission – Planning and Execution
https://www.lexjansen.com/pharmasug/2020/SS/PharmaSUG-2020-SS-156.pdf

CONTACT INFORMATION:

Name: Binal Mehta
Enterprise: Merck & Co., Inc.
Address: 126 E. Lincoln Ave
City, State & Zip: Rahway, NJ 07065-4607
Phone: (732) 594-3383
E-mail: binal.mehta@merck.com
Web: www.merck.com

Name: Mukesh Patel
Enterprise: Merck & Co., Inc.
Address: 126 E. Lincoln Ave
City, State & Zip: Rahway, NJ 07065-4607
Phone: (732) 594-3057
E-mail: mukesh.patel1@merck.com
Web: www.merck.com