

Management of Regulatory Submissions Using eCTD Sequences and Life Cycle Operators

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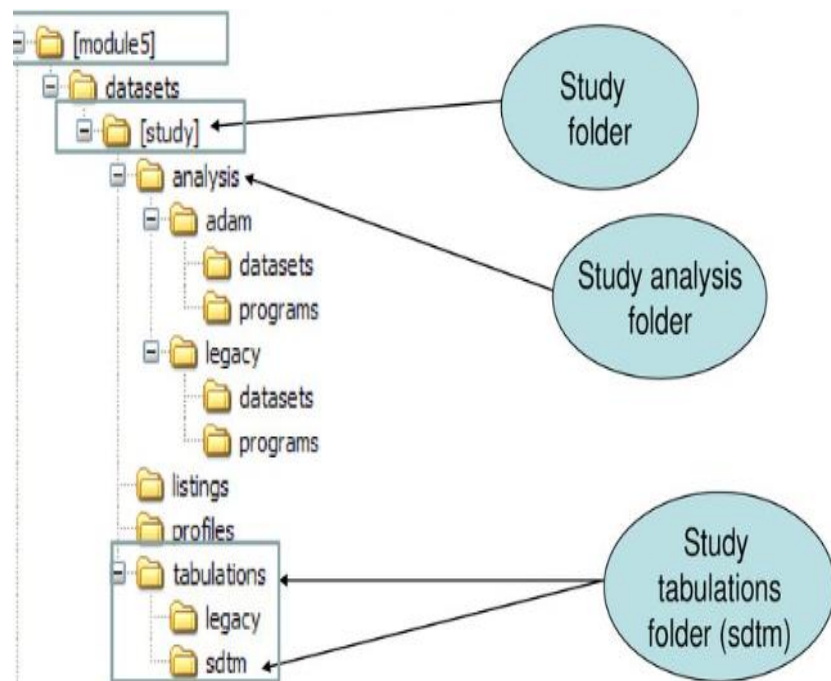
Purpose

- **Present Regulatory Submission Scenarios:**
 - Explore scenarios for Real-Time Oncology Review (RTOR) and Regular Submissions Requiring Updates.
- **Effective Management of Submissions:**
 - Utilize eCTD sequences and lifecycle operators effectively to manage submissions.
 - Include practical examples to illustrate best practices and strategies.
- **Emphasize Collaboration and Collective Review:**
 - Highlight the importance of collaboration between statistical programming and regulatory publishing teams.
 - Discuss the value of thorough collective reviews (Pre-Assembly Reviews and Assembly Reviews) in ensuring compliance.

Agenda

- eCTD format as standard for FDA submissions
- Real-Time Oncology Review (RTOR)
- Preparing the RTOR submission Packages
- Publishing the RTOR Packages in eCTD using
 - Sequence Numbers
 - Life Cycle Operators
- Publishing Regular Submission and Handling the Updates to the Submission
- The eCTD Viewing Tool Capabilities
 - Current View
 - Cumulative View
- Collaboration
- Conclusion
- References
- Acknowledgements

eCTD format as standard for Regulatory submissions



- **Standardized Format:** eCTD is the regulatory submission standard for pharmaceutical and biotechnology companies submitted to authorities like the FDA and EMA.
- **Structured Organization:** Comprises five primary modules (m1 to m5) that facilitate systematic compilation and presentation of data related to drug quality, safety, and efficacy.
- **Lifecycle Management:** Supports efficient management of updates and amendments throughout the product lifecycle, ensuring up-to-date submissions.
- **Element Identification:** Each module contains distinct elements with unique identifiers, ensuring clarity and traceability of submitted documents.
- **Facilitates Regulatory Review:** Streamlines the regulatory review process

Real-Time Oncology Review (RTOR) Initiative

- **Aim:** RTOR aims to expedite the review process for oncology treatments, facilitating faster patient access to effective therapies.
- **Established by:** The initiative was launched by the Oncology Center of Excellence within the FDA.
- **Topline Data Submission:** Allows submission of topline efficacy and safety data before the complete application is submitted.
- **Rollover Deliveries:** Permits other components of the application to be submitted in stages, enhancing efficiency in the review process.
- **Early Evaluation:** Enables the FDA to begin its evaluation sooner, significantly reducing the time from submission to approval.

Preparing RTOR Submission Packages

Submission Organization: The RTOR submission process involved organizing materials into three distinct packages.

RTOR Package 1 Components:

- Key analysis datasets
- Define.xml/define.pdf
- Stylesheet (define2-0-0.xsl)
- RTOR Review Statistical report with topline results
- RTOR Reviewer Guide 1

RTOR Package 2 Components:

- ADLBGRD Dataset
- UpdatedDefine.xml/define.pdf
- Stylesheet (define2-0-0.xsl)
- RTOR Reviewer Guide 2
- Complete SDTM Package

RTOR Package 3 Components:

- Remaining Analysis Datasets
- Updated Define.xml/define.pdf
- Stylesheet (define2-0-0.xsl)
- ADRG
- Analysis Results Metadata

RTOR Package-1

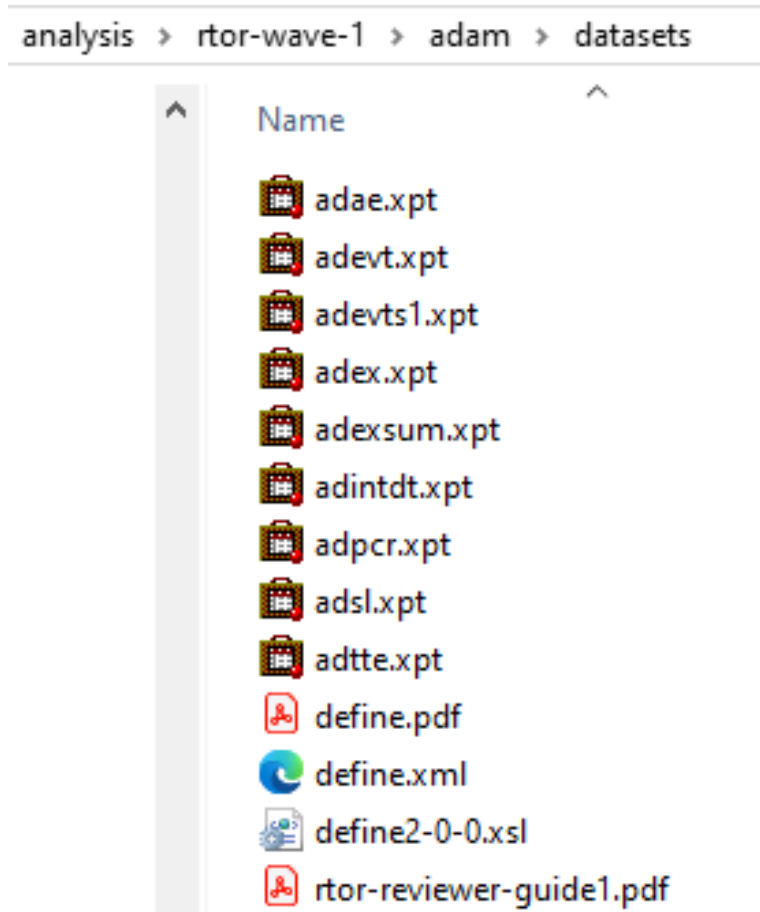


Fig.1. RTOR Package 1 - e-submission components: Key analysis datasets, define.xml/define.pdf, stylesheet (define2-0-0.xsl), and RTOR Reviewer Guide 1.

RTOR Package-2

ADaM Package:

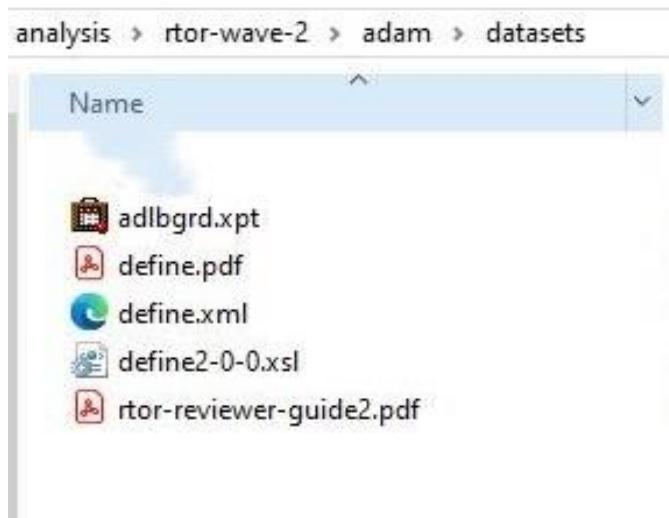


Fig.2. RTOR Package 2- ADaM esub components: adlbgrd dataset, updated define.xml/define.pdf, stylesheet(define2-0-0.xsl), and the RTOR Reviewer Guide 2.

SDTM Package:

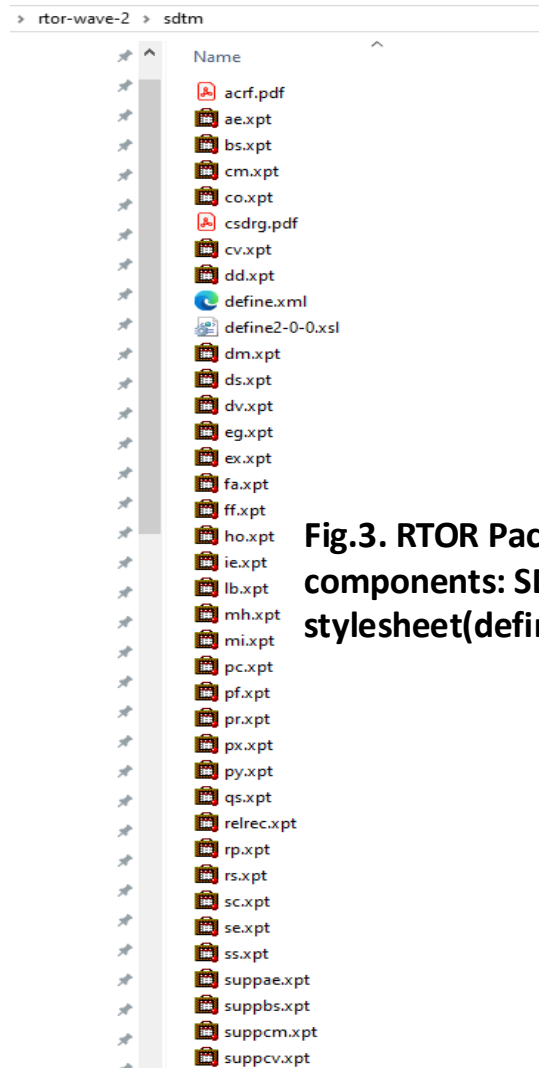


Fig.3. RTOR Package 2- SDTM esub components: SDTM datasets, define.xml, stylesheet(define2-0-0.xsl), csdrg, and acrf.

RTOR Package-3

ADaM Package:

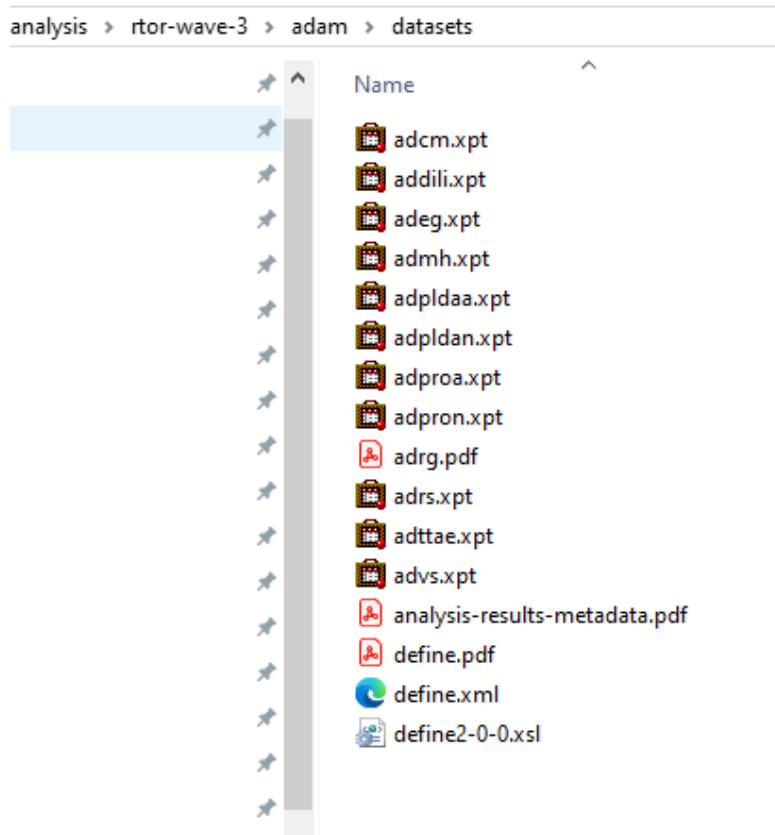


Fig.4: RTOR Package 3-esub components: All remaining analysis datasets, adrg, analysis results metadata, updated define.xml/define.pdf, and stylesheet (define2-0-0.xsl).

Publishing The RTOR Packages in eCTD

Sequence Numbers:

- Serve as unique identifiers for distinguishing various submissions within the same application throughout the product lifecycle.
- Allow regulatory authorities to track the history and progression of the application.
- Establish clear traceability from the initial submission to subsequent updates through chronological organization.

Life Cycle Operators:

- **NEW:** Indicates that the leaf element is not related to any previously submitted leaf elements.
- **REPLACE:** Signifies that the existing leaf element is replaced by the newly submitted leaf element.
- **DELETE:** Indicates that no new file is submitted, and a previous leaf element is no longer relevant.
- **APPEND:** Denotes that a new leaf element is associated with an existing leaf element.

RTOR Packages and Sequence Numbers

Application folder name	Sequence number	Type of submission
ONC510V01	2567	RTOR Package-1
ONC510V01	2649	RTOR Package-2
ONC510V01	2706	RTOR Package-3

Table 1. The RTOR packages and the corresponding Sequence Numbers of the Application ONC510V01.

RTOR Package-1 eCTD Publishing

- **First Submission Overview:** In the initial submission of RTOR Package-1 (Sequence#2567), all leaf elements were submitted for the first time, each defined with the lifecycle operator "NEW."
- **Significance of "NEW" Operator:** The "NEW" operation indicates that the documents had no prior submissions, representing the initial collection of datasets and related files associated with the application.
- **Highlighted Leaf Element:** The Analysis Data Definition for Study (XML VERSION) was highlighted, featuring the leaf title, file name as define.xml, and operation marked as "NEW"

The screenshot displays the RTOR Package-1 eCTD publishing interface. On the left, the 'Submission Sequence' tree shows the hierarchy of documents. The 'Analysis Data Definition for Study ONC510V01 (XML VERSION) (2567, NEW)' is highlighted. On the right, the 'Leaf Attributes' panel shows the details for this selected element.

Submission Sequence:

- 2567 Submission Sequence
 - 1 Administrative Information
 - 5 Clinical Study Reports
 - 5.3 Clinical Study Reports
 - 5.3.5 Reports of Efficacy and Safety Studies
 - 5.3.5.1 Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
 - ONC510V01- Double blind randomized trial evaluating ONC510 vs SOC
 - 06D5QJ ONC510V01 Statistical Report: (2567, NEW)
 - Appendices
 - Individual Patient Data Listings
 - Analysis (ADaM)
 - Programs
 - Datasets
 - Analysis Data Definition for Study ONC510V01 (PDF Version) (2567, NEW)
 - Analysis Data Definition for Study ONC510V01 (XML VERSION) (2567, NEW)**
 - Analysis Data Definition Stylesheet for Study ONC510V01 (2567, NEW)
 - RTOR Reviewer's Guide (2567, NEW)
 - adae.xpt (2567, NEW)
 - adevt.xpt (2567, NEW)
 - adevts1.xpt (2567, NEW)
 - adex.xpt (2567, NEW)

Leaf Attributes:

- Extension : Study Report
- Last Repository Data Retrieval : 24-May-2021
- Creation Date : 24-May-2021
- Name : Analysis Data Definition for Study ONC510V01 (XML VERSION)
- Abbreviated Name : Analysis Data Definition for Study ONC510V01 (XML VERSION)
- Title : Analysis Data Definition for Study ONC510V01 (XML VERSION)
- Leaf ID : a52ac3be5bcb0114382205e568140f644
- Number :
- Owner :
- Leaf Status : Published
- Modified Leaf :
- Modified Leaf Submission :
- Modified File Override :
- Operation : NEW
- Output File : define.xml
- Published Output Location :
- Language :
- Application Version :
- Font Library :
- Role :
- Actuate :
- Show :
- Use Native File : Yes
- Link Text :
- Keywords :

Fig. 5. RTOR Package-1 eCTD publishing with sequence number 2567.

RTOR Package-2 eCTD Publishing

- **ADLBGRD Dataset** : With Operation “NEW”
- **Updated Define**: With Operation “REPLACE”
- **Stylesheet (define2-0-0.xml)**: With Operation “REPLACE”
- **RTOR Reviewer Guide** : With Operation “NEW”
- **Complete SDTM Package**: With Operation “NEW”

| Submission Sequence # | File name | Operation | File Being Modified |
|-----------------------|----------------------|-----------|---------------------|
| 2567 | 2567\...\define.xml | NEW | |
| 2649 | 2649\...\ define.xml | REPLACE | 2567\...\define.xml |

Table 2. Second submission -Sequence#2649 replaces the previously submitted define.xml file from -Sequence#2567 with the updated version.

RTOR Package-2 eCTD Publishing-Continued

- **Define.xml:** With an operation of “REPLACE.”
- **Modified Leaf Attribute:** The leaf element has a “modified leaf” attribute that specifies the title
- **Modified Leaf Submission Attribute:** The “modified leaf submission” attribute provides the prior Sequence#2567
- **New Dataset Annotations:** Annotations for the newly added file adlbgrd.xpt are noted with the operation of “NEW”

The screenshot displays the RTOR-2 eCTD Submission Sequence#2649 interface. The left pane shows the Submission Sequence tree with folders like Administrative Information, Clinical Study Reports, and Appendices. The right pane shows the Leaf Attributes for the selected file 'Analysis Data Definition for Study ONC510V01 (XML VERSION) (2649, REPLACE)'. The attributes include Extension (Study Report), Creation Date (14-Jun-2021), Name, Abbreviated Name, Title, Leaf ID, Number, Owner, Leaf Status (Planned), Modified Leaf (Analysis Data Definition for Study ONC510V01 (XML VERSION) Modified File), Modified Leaf Submission (2567 Modified Sequence), Modified File Override, Operation (REPLACE Operation), Output File (define.xml File name), Published Output Location, Language, Application Version, Version, Font Library, Role, Actuate, Show, Use Native File (Yes), Due Date, and Link Text.

Fig. 6. RTOR-2 eCTD Submission Sequence#2649.

RTOR Package-3 eCTD Publishing

New leaf elements: With Operation “NEW”

- adcm.xpt
- addili.xpt
- adeg.xpt
- admh.xpt
- Analysis Data Review’s Guide (ADRG)
- Analysis Results Metadata (ARM)

Updated Define.xml: With Operation “REPLACE”

Stylesheet (define2-0-0.xsl): With Operation “REPLACE”

- Sequence#2649 introduced define.xml as a replacement for the original file submitted in Sequence#2567.
- Sequence#2706 replaces the define.xml from Sequence#2649.

| Submission Sequence # | File name | Operation | File Being Modified |
|-----------------------|---------------------|-----------|---------------------|
| 2567 | 2567\...\define.xml | NEW | |
| 2649 | 2649\...\define.xml | REPLACE | 2567\...\define.xml |
| 2706 | 2706\...\define.xml | REPLACE | 2649\...\define.xml |

Table 1. The RTOR packages and the corresponding Sequence Numbers of the Application ONC510V01.

RTOR Package-3 eCTD Publishing-Continued

- **Define.xml** with Operation “NEW”
- **Modified Leaf Attribute:** the title of the replaced leaf
- **Modified Leaf Submission Attribute:** This attribute provides the Prior Sequence #**2649**.
- **New Dataset Annotations:** Annotations for the newly added files are noted with the Operation of “NEW”

The screenshot displays the RTOR-3 interface. On the left, the 'Submission Sequence' tree shows the hierarchy for Sequence Number #2706. The tree includes folders for Administrative Information, Clinical Study Reports, and Clinical Study Reports. Under Clinical Study Reports, there is a folder for Reports of Efficacy and Safety Studies, which contains a folder for Reports of Controlled Clinical Studies Pertinent to the Claimed Indication. This folder contains a submission titled 'ONC510V01- Double blind randomized trial evaluating ONC510 vs SOC'. Under this submission, there are folders for Appendices, Individual Patient Data Listings, Analysis (ADaM), Programs, and Datasets. The Datasets folder is expanded, showing a list of files. The file 'Analysis Data Definition for Study ONC510V01 (XML VERSION) (2706, REPLACE)' is highlighted. A red annotation 'All New datasets and documents with Operation "NEW"' points to the 'NEW' status of several files in the Datasets folder.

On the right, the 'Leaf Attributes' panel is displayed. It shows the following information:

- Extension : Study Report
- Last Repository Data Retrieval : 26-Jun-2021
- Creation Date : 26-Jun-2021
- Name : Analysis Data Definition for Study ONC510V01 (XML VERSION)
- Abbreviated Name : Analysis Data Definition for Study ONC510V01 (XML VERSION)
- Title : Analysis Data Definition for Study ONC510V01 (XML VERSION)
- Leaf ID : a823f49c903710951319ff245fb6565c3
- Number :
- Owner :
- Leaf Status : Published
- Modified Leaf : Analysis Data Definition for Study ONC510V01 (XML VERSION) Modified File
- Modified Leaf Submission : 2649 Modified Sequence
- Modified File Override :
- Operation : REPLACE Operation
- Output File : define.xml File name
- Published Output Location :
- Language :
- Application Version :
- Version :
- Font Library :
- Role :
- Actuate :
- Show :
- Use Native File : Yes
- Due Date :
- Link Text :

A red annotation 'Leaf Title Corresponding The File:define.xml' points to the 'Output File' field.

Fig.8. The RTOR-3 with Sequence Number #2706

Regular Packages Requiring Updates

- In the context of regular submissions requiring updates, we must apply the appropriate lifecycle operators—New, Replace, Append, and Delete—carefully during the submission process.
- While we can use the "APPEND" operator to add supplementary information to existing documents, we should avoid using it for study data that require updates; instead, we must submit those using the "REPLACE" operator.
- Additionally, the "DELETE" operator is applied when a document is irrelevant and should be removed from review.
- Sequence #0000, the file “nausea-sr15.pdf” is initially submitted, and in Sequence #0001, the applicant requests its deletion, instructing the reviewer to disregard its contents

| Submission Sequence # | File name | Operation | File Being Modified |
|-----------------------|-------------------------|-----------|---------------------------|
| 0000 | 0000\...\nauseasr15.pdf | NEW | |
| 0001 | | DELETE | 0000\...\ nausea-sr15.pdf |

Table 4. DELETE Operation : The leaf element has the operation of “DELETE” and the “modified-leaf” attribute identifies the leaf element in a previous sequence that is no longer relevant to the review.

eCTD Viewing Tool Capabilities

Current View

- **Access to Latest Files:**
 - Allows reviewers to access the most up-to-date files associated with an application.
- **Efficiency in Evaluation:**
 - Streamlines the review process by presenting the latest document submissions for quick evaluation.

Cumulative View

- **Comprehensive Overview:**
 - Displays the entire application, highlighting all historical sequence numbers and lifecycle operators.
- **Change Traceability:**
 - Details all modifications such as newly added, replaced, appended, or deleted documents.
 - Aids reviewers in understanding the evolution of the application over time.

Collaborations

- **Importance of Collaboration:**

- Effective collaboration between statistical programming and regulatory publishing is essential for successful submission management.

- **Submission Plan:**

- Consider lifecycle management details upfront when authoring documents to streamline the submission process.
- Implement a submission tracker (e.g., Excel or specialized tool) to outline content in each submission, including submission dates, document components, and lifecycle operators.

- **Collaborative Review Processes:**

- **Pre-Assembly Review (PAR):**

- ❖ Conducted before the Assembly Review to verify content within each eCTD module.
- ❖ Ensures accuracy of each element, its attributes, and hyperlinks within documents.

- **Assembly Review (AR):**

- ❖ Final review to ensure the accurate inclusion of documents and appropriate use of sequences and lifecycle operators.
- ❖ Provides the last opportunity to present a complete and organized submission before it is sent to regulatory authorities.

Conclusion

- Effective management of regulatory submissions using eCTD sequences and lifecycle operators is crucial.
- Presented practical examples with snapshots demonstrating the use of sequences and lifecycle operators for streamlined submission for RTOR.
- Discussed approaches for managing regular submissions that require updates
- Highlighted the importance of collaboration between statistical programming and regulatory publishing teams in planning submissions.
- Stressed the role of thoroughness in the publishing dossier through Pre-Assembly Reviews (PAR) and Assembly Reviews (AR).
- Examples and methodologies provided serve as a valuable reference for addressing complex submission challenges.

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Thank You!

