Paper SA03

# Management of Regulatory Submissions Using eCTD Sequences and Life Cycle Operators: Lessons from Real-Time Oncology Review (RTOR) and Regular Submissions

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## ABSTRACT

The eCTD format has become the standard for regulatory submissions by the FDA, resulting in a streamlined and efficient review process. This paper aims to provide practical examples of effectively utilizing eCTD sequences and lifecycle operators in two scenarios: Real-Time Oncology Review (RTOR) submissions, including rolling submissions, and regular submissions requiring updates. The eCTD structure organizes submission content into five modules (m1 – m5), with leaf elements representing individual files or documents within these modules. Each submission is assigned a unique sequence number at a specific time point, which encompasses a collection of modules and leaf elements. Throughout the submission lifecycle, lifecycle operators, like 'new,' 'replace,' 'delete,' and 'append' facilitate the management of file status and updates. The paper provides comprehensive examples that demonstrate the practical use of eCTD sequences and lifecycle operators in both RTOR and regular submissions with update requirements. We believe these examples will serve as valuable reference when tackling complex submission challenges.

## INTRODUCTION

The electronic Common Technical Document (eCTD) serves as a standardized format widely utilized by pharmaceutical and biotechnology companies when submitting regulatory applications to health authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). This electronic submission format offers a structured and efficient approach to compiling and presenting experimental data regarding quality, safety, and efficacy. Additionally, this format provides the ability to manage updates and amendments to the submission throughout product lifecycle. The eCTD consists of five primary modules (1):

- m1: Administrative Information and Prescribing Information
- m2: Common Technical Document Summaries
- m3: Quality
- m4: Nonclinical Study Reports
- m5: Clinical Study Reports

Files pertaining to each module must be placed in the appropriate folder (e.g., m1 – m5). Furthermore, each of the five modules is further subdivided into one or more elements, each with a distinct element identifier.

On the other hand, The Real-Time Oncology Review (RTOR) initiative (2), established by the Oncology Center of Excellence, aims to expedite the review process to bring effective oncology treatments to patients quickly. By allowing the submission of topline efficacy and safety data prior to the full application and permitting other components as rollover deliveries, RTOR enables the FDA to initiate its evaluation sooner, thereby expediting the review process.

## PREPARING RTOR SUBMISSION PACKAGES

In this section, we share our experiences with the RTOR submission process. Once our study was selected for RTOR submission, we organized the submission materials into three distinct packages, which were subsequently delivered to the FDA in a sequential manner. To maintain confidentiality, we will use a dummy study ID (ONC510V01) throughout this paper to outlining our submission approaches

### RTOR PACKAGE-1

This package includes key ADaM analysis datasets that support the topline results, along with the define.xml file, the stylesheet (define2-0-0.xsl), a statistical report featuring the topline results, and an RTOR Reviewer Guide 1. To provide a visual representation of the e-submission components for this package, please refer to the snapshot below (Fig. 1).

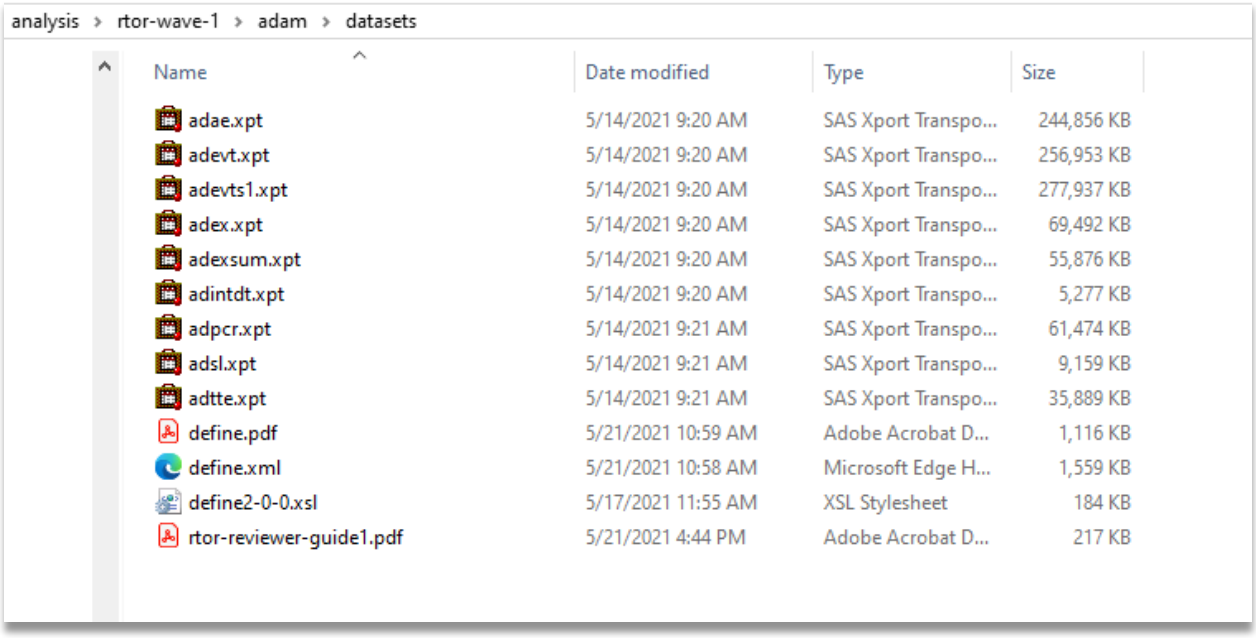


**Fig. 1.** RTOR Package 1 - e-submission components: Key analysis datasets, define.xml/define.pdf, stylesheet (define2-0-0.xsl), and RTOR Reviewer Guide 1**.**

**RTOR PACKAGE-2**

This second package includes an additional ADaM dataset, adlbgrd dataset, an updated define.xml/define.pdf, stylesheet (define2-0-0.xsl), and a new RTOR Reviewer Guide 2 that describes the additional dataset in the ADaM package (Fig. 2), in addition to the complete SDTM package (Fig. 3).

**ADaM Package:**

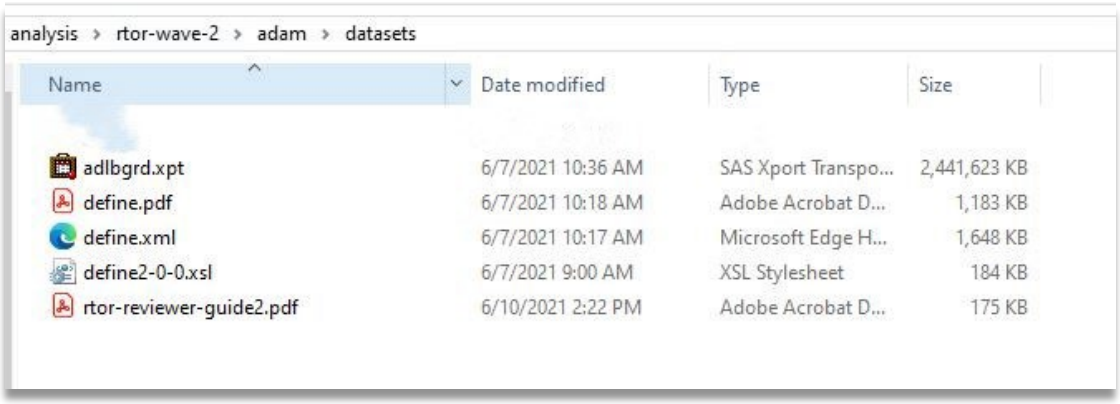


**Fig. 2.** RTOR Package 2- ADaM esub components: adlbgrd dataset, updated define.xml/define.pdf, stylesheet(define2-0-0.xsl), and the RTOR Reviewer Guide 2.

**SDTM Package:**

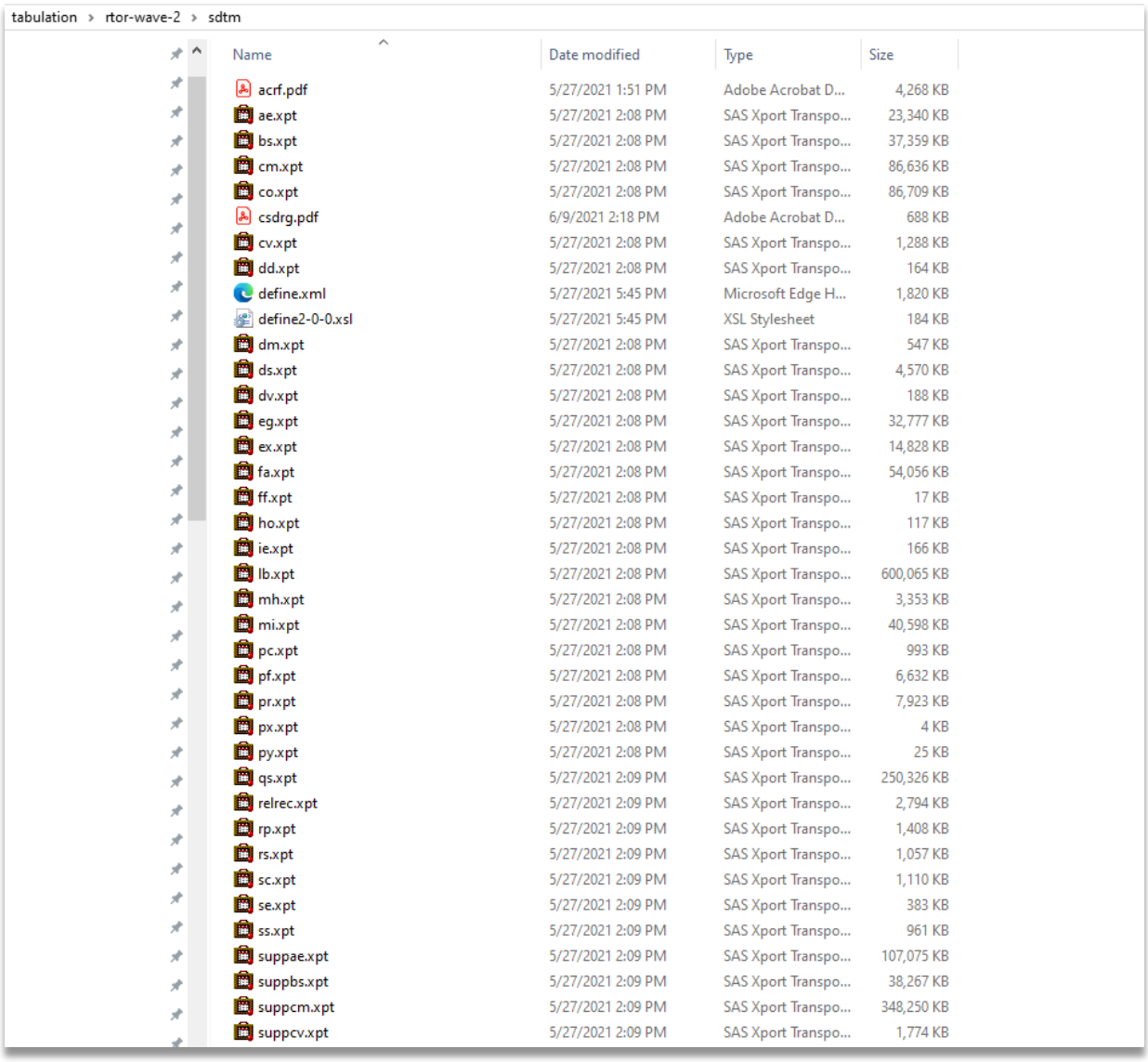


**Fig. 3.** RTOR Package 2- SDTM esub components: SDTM datasets, define.xml, stylesheet(define2-0-0.xsl), csdrg, and acrf.

**RTOR PACKAGE-3:**

The final package includes all remaining ADaM analysis datasets, Analysis Data Review's Guide (ADRG), analysis results metadata, and an updated define.xml/define.pdf that contains all the metadata for the ADaM analysis datasets submitted across the three packages for this submission (Fig.4).

**ADaM Package:**

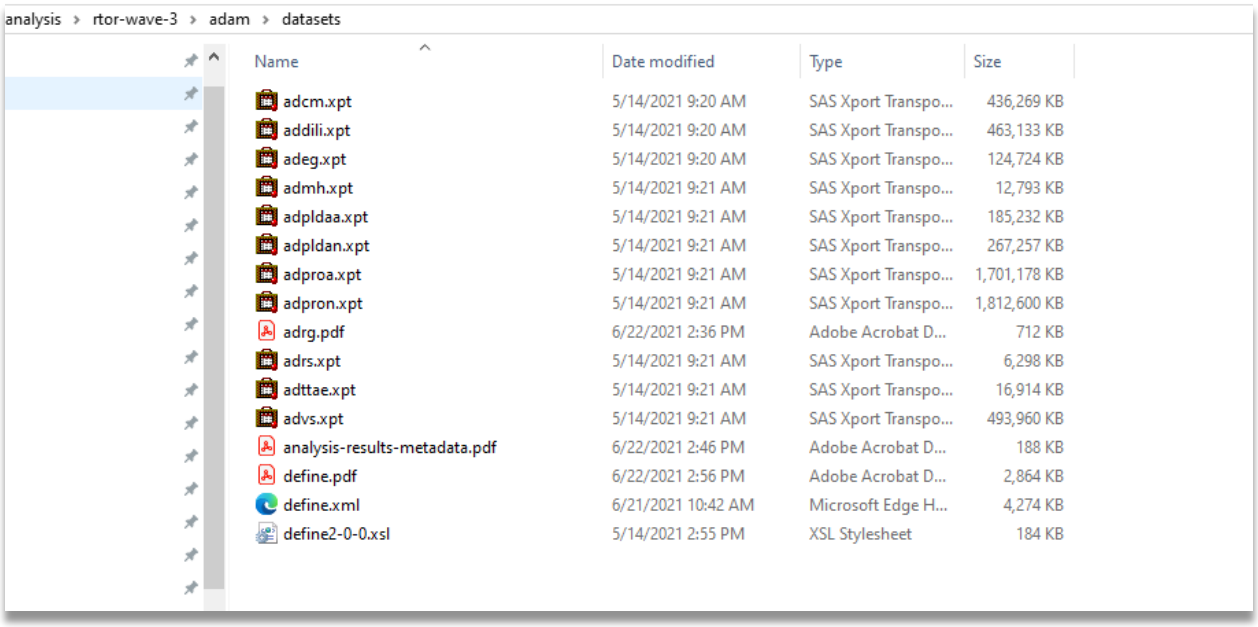


**Fig. 4.** RTOR Package 3-esub components: All remaining analysis datasets, ADRG, analysis results metadata, updated define.xml/define.pdf, and stylesheet (define2-0-0.xsl).

## PUBLISHING THE RTOR PACKAGES IN eCTD

In this section, we discuss the publishing aspects of the RTOR packages using the eCTD backbone. Before detailing the publishing process for the three outlined packages, we will clarify important concepts such as sequence numbers and lifecycle operators that are used in the management of the submission.

**SEQUENCE NUMBERS:** In the context of eCTD (electronic Common Technical Document), sequence numbers are unique identifiers that differentiate various submissions for the same application throughout the product lifecycle. Each submission is assigned with a specific sequence number, allowing regulatory authorities to track the history and progression of the application. By organizing submissions with chronological sequence numbers, clear traceability is established from the initial submission to the subsequent updates.

**LIFE CYCLE OPERATORS:** The life cycle operators describe how a particular document or file (referred to as a "leaf element") relates to previously submitted documents or files in a submission. These operators communicate the intended action for each leaf element within the application

- **NEW:** The leaf element has no relationship with previously submitted leaf elements.
- **REPLACE**: An existing leaf element is replaced by the new leaf element.
- **DELETE:** No new file is submitted; instead, this indicates that a previous leaf element is no longer relevant.
- **APPEND:** This means that a new leaf element is associated with an existing leaf element.

**RTOR PACKAGES AND SEQUENCE NUMBERS:** The details of the sequence numbers employed for each RTOR package are as follows (Table 1.).

| 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.

The following case examples from our RTOR submission demonstrate how we applied sequence numbers and lifecycle operators, specifically the values “NEW” and “REPLACE.” These examples illustrate the practical use of the life cycle operators in managing the submission, although they do not cover all operations.

**RTOR PACKAGE-1 eCTD PUBLISHING:**
For the initial submission of RTOR Package-1 (Sequence#2567), we submitted all leaf elements for the first time, defining each element with the lifecycle operator "NEW." This operation "NEW" indicates that these documents had no prior submissions and comprise the initial collection of datasets and related files. We highlighted the leaf element: Analysis Data Definition for Study (XML VERSION) showing the leaf title, file name as define.xml, with operation "NEW" (Fig. 5.).

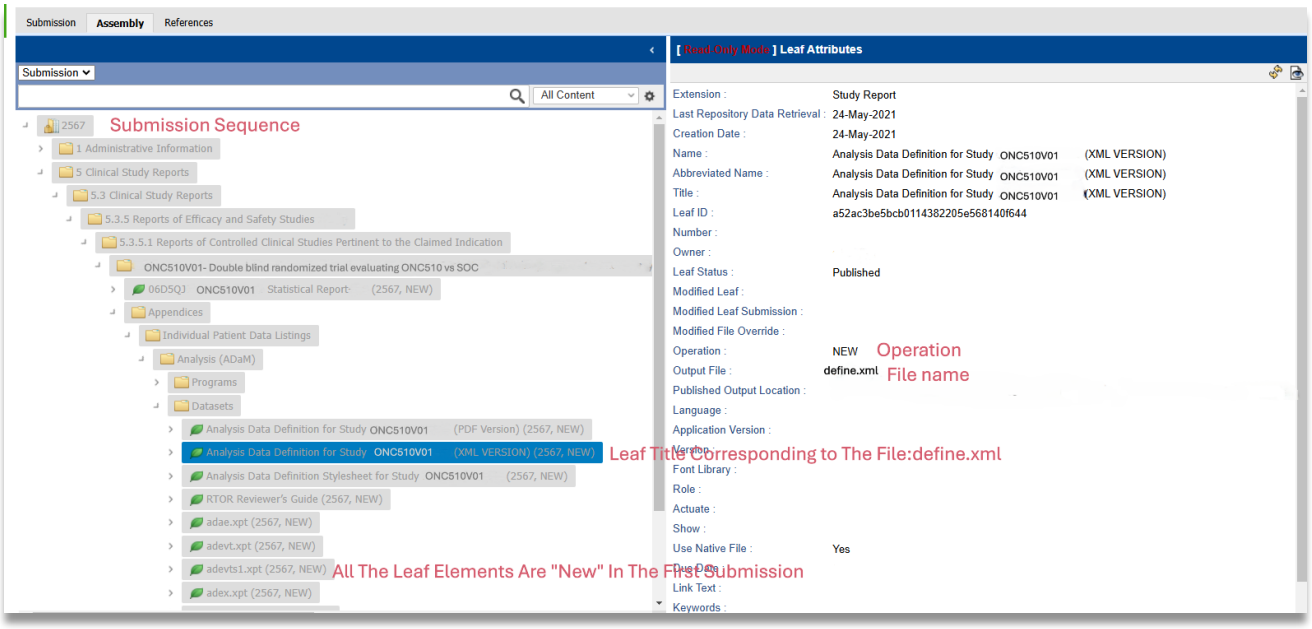


**Fig. 5.** RTOR Package-1 eCTD publishing with sequence number 2567. Analysis Data Definition for Study (XML VERSION) was highlighted showing file name as define.xml, leaf title and operation "NEW". Each leaf element has a sequence number and a life cycle operator "NEW".

**RTOR PACKAGE-2- eCTD PUBLISHING:**
In the second submission, RTOR Package-2 (Sequence#2649), we replaced the previously submitted define.xml from Sequence#2567 with an updated version (Table 2). Additionally, we submitted a new dataset, adlbgrd.xpt, as part of the ADaM package and included the complete SDTM package in this new sequence. While the original define.xml from Sequence#2567 is retained for traceability, the updated version in Sequence#2649 will be utilized for the review.

| 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.

We provide additional annotations in the eCTD backbone specific to the file define.xml with an operation "REPLACE". The leaf element includes a "modified leaf" attribute that denotes the title of the replaced leaf-"Analysis Data Definition for Study (XML VERSION)" from prior sequence, while the "modified leaf submission" attribute gives the prior Sequence#2567. This allows a reviewer to trace the original leaf elements and understand the current updates. Furthermore, we provide annotations for the newly added file for adlbgrd.xpt, noted with the operation of "NEW" (Fig. 6). It is important to note that the eCTD "APPEND" operator should not be used when we submit updated data files, but instead use "REPLACE" operator for any updated files (3).

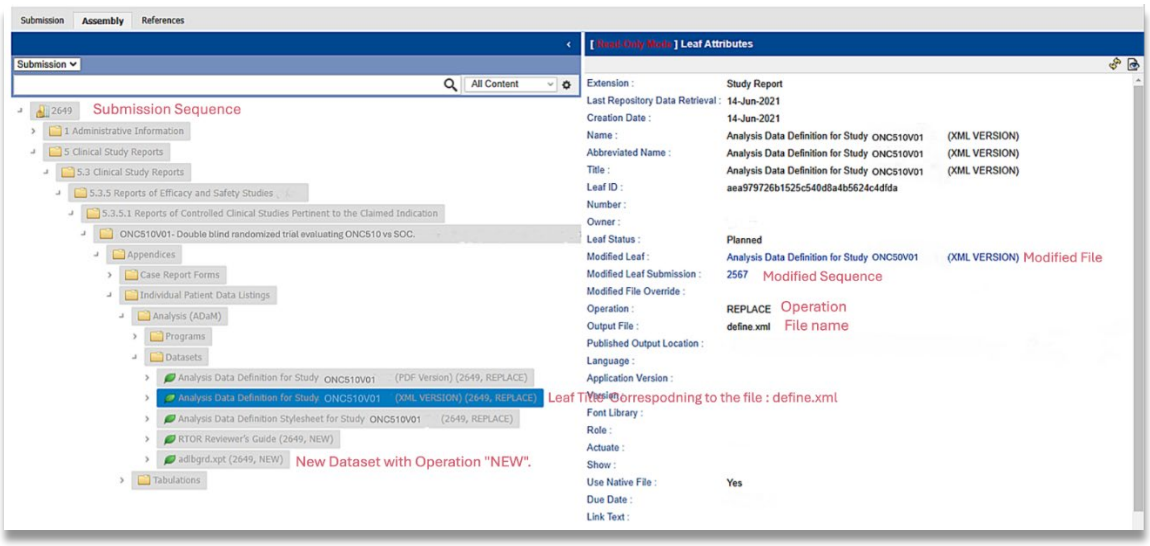


**Fig. 6.** RTOR-2 eCTD Submission Sequence#2649 highlights the file define.xml with the operation "REPLACE." The leaf element includes a "modified leaf" attribute that denotes the title of the replaced leaf-"Analysis Data Definition for Study (XML VERSION)" from prior sequence, while the "modified leaf submission" attribute gives the prior Sequence#2567. New leaf elements are noted with the operation "NEW."

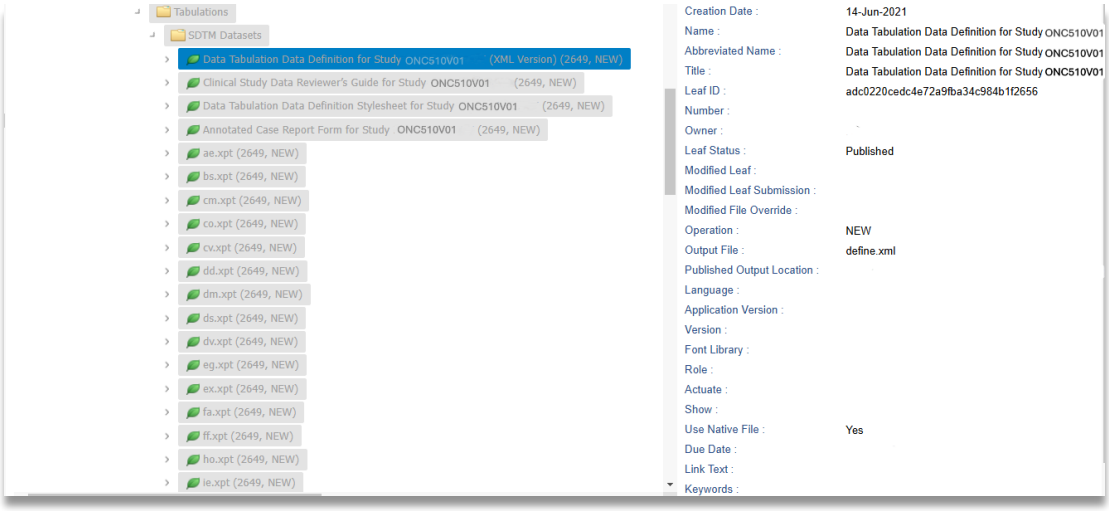


**Fig. 7.** RTOR-2 eCTD Submission SDTM Package: Lists all leaf elements as "NEW."

**RTOR PACKAGE-3- eCTD PUBLISHING**

In our RTOR submissions, Sequence#2567 corresponds to the RTOR-1 package, Sequence#2649 relates to the RTOR-2 package, while Sequence#2706 pertains to the RTOR-3 package. The RTOR-3 package intends to replace the define.xml with an updated version using the "REPLACE" operator. Additionally, it includes new leaf elements: adcm.xpt, addili.xpt, adeg.xpt, admh.xpt, adrg, and analysis reviewer metadata. We would like to emphasize the replacement of define.xml in each subsequent submission. Sequence#2649 introduced the define.xml file as a replacement for the original file submitted in Sequence#2567. Likewise, Sequence#2706 replaced the define.xml file again from Sequence#2649 (Table 3). The leaf element includes a "modified leaf" attribute that denotes the title of the replaced leaf "Analysis Data Definition for Study (XML VERSION)" from the prior sequence, while the "modified leaf submission" attribute gives the prior Sequence#2649 (Fig. 8).

| 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 3.** The define.xml file was introduced in Sequence#2649 as a replacement for the original file submitted in Sequence#2567. Similarly, the define.xml file in Sequence#2706 is another replacement for the define.xml file submitted in Sequence#2649.

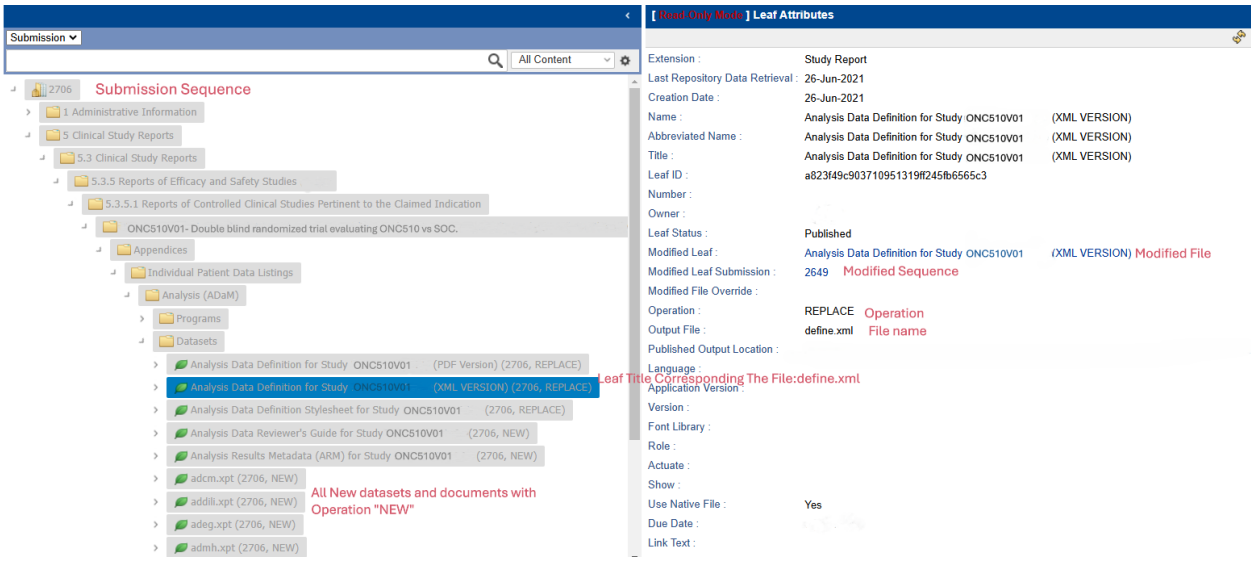


**Fig.8.** The RTOR-3 package replaces the define.xml (Operation="REPLACE") and adds new datasets/documents: adcm.xpt, addili.xpt, adeg.xpt,admh.xpt, adrg, and analysis results metadata (Operation="NEW"). The leaf element includes a "modified leaf" attribute with the title of the replaced leaf from prior sequence: "Analysis Data Definition for Study (XML VERSION)", while the "modified leaf submission" gives the prior Sequence#2649.

## REGULAR PACKAGES REQUIRING UPDATES

For regular submissions that require updates, it is important to apply the appropriate lifecycle operators—New, Replace, Append, and Delete—carefully during the submission process. As previously discussed, use the "NEW" operator when introducing entirely new files for the first time, such as a clinical study report or a set of supporting analysis datasets. In contrast, the "REPLACE" operator should be used to update or modify existing documents. While the "APPEND" operator can be utilized to add supplementary information to existing documents, it should be avoided for study data that require updates; instead, the "REPLACE" operator must be used.

The "DELETE" operator is applied when a submitted document is no longer relevant and should be removed from review. We encourage applicants to discuss with the relevant regulatory authority prior to updating the attributes to confirm the appropriateness and correct approaches for such changes, particularly while using "DELETE" operator.

To illustration this process, consider two submissions: Sequence#0000 represents the initial submission of the file "nausea-sr15.pdf". Subsequently, Sequence# 0001 serves as an amendment where the applicant requests the deletion of the file "nausea-sr15.pdf" from Sequence#0000, asking the reviewer to disregard its contents due to an incorrect initial submission (Table 4.).

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

**Table 4.** No new file has been submitted in this case. Instead, 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.

## THE eCTD VIEWING TOOL CAPABILITIES

The eCTD viewing tool utilized by regulatory agencies provides two views to facilitate the regulatory review process: the current view and the cumulative view. The current view allows reviewers to access the most up-to-date files associated with an application. In contrast, the cumulative view displays the entire application, highlighting all historical sequence numbers and lifecycle operators. This view details the content that has been newly added, replaced, appended, or deleted helping reviewers to trace changes over time.

## COLLOBOARTION

Effective collaboration between statistical programming and regulatory publishing is important for submission management. When authoring documents, it is important to consider lifecycle management details upfront and to implement a submission tracker—whether it is a simple Excel file or a more sophisticated tool. Such a tracker should outline all content within each submission, including submission dates, document components, and lifecycle operators.

To ensure that published documents align with the submission plan, collaborative reviews are conducted through the Pre-Assembly Review (PAR) and the Assembly Review (AR) processes. The PAR occurs prior to the AR and serves to verify the content within each eCTD module, including the accuracy of each element, its attributes, and the hyperlinks within documents. Following this, the Assembly Review (AR) verifies the accurate inclusion of documents, the appropriate use of sequences and life cycle operators, as well as the correctness of hyperlinks. This review is the final opportunity to ensure a complete and organized presentation of all submission content before it is submitted to regulatory authorities.

## CONCLUSION

In conclusion, the effective management of regulatory submissions using eCTD sequences and lifecycle operators is important. This paper offers a streamlined submission process for a RTOR and provided practical examples with snapshots that demonstrate the utilization of sequences and lifecycle operators. Furthermore, we provided approaches for handling regular submissions that require updates to previous submissions. We emphasize the importance of collaboration between statistical programming and regulatory publishing teams in setting the plan for the submission and producing an accurate published dossier through Pre-Assembly Reviews (PAR) and Assembly Reviews (AR). Finally, we believe that the examples and the methodologies presented in this paper will serve as a valuable point of reference when addressing and overcoming complex submission challenges.

## REFERENCES


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2. Real-Time Oncology Review (Real-Time Oncology Review | FDA)
3. eCTD Technical Conformance Guide (eCTD Tech Guide v1.8 Final.pdf)



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