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Adopting the New Integrated Analysis Data Reviewer's Guide (iADRG)

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ABSTRACT

For pharmaceutical and biotechnology companies, the culmination of collecting clinical trials data on their investigational products is providing the integrated data and analyses to regulatory agencies for approval. Integrated safety and efficacy data are submitted for regulatory review along with Analysis Data Reviewer's Guides. After sharing the draft and addressing public review comments, the PHUSE Optimizing the Use of Data Standards (ODS) Working Group is finalizing the integrated Analysis Data Reviewer's Guide (iADRG) template and supporting documents. These iADRG documents provide clarity and guidance to integrated data and analysis reporting.

This paper will discuss key points and examples in adopting and implementing the new iADRG template. The iADRG submission document describes the traceability, and transformation from individual study data to integrated analysis data. Key analysis considerations around data re-mapping, redefining analysis flags and data integration complexities are provided. Other points include harmonization of analysis data and documentation of differing regulatory agency requirements.

DISCLAIMER

All views expressed in this paper are those of the authors and are not necessarily those of PHUSE, CDISC or the author's companies: Ephicacy Consulting Services, ADC Therapeutics, Loxo@Lilly, and Alexion AstraZeneca Rare Disease. The approach to implementation of the new integrated analysis data reviewer's guide template presented in this paper should not be interpreted as a standard and/or information required by regulatory authorities.

INTRODUCTION

Within the pharmaceutical and biotechnology industry, the regulatory approval process can be lengthy and complex. Companies need to streamline their clinical trials and regulatory submission processes where they can. As a critical part of regulatory submissions, the integrated clinical data and analyses are provided for agency review and consideration. The submission data package includes data from numerous clinical trials and accompanying documentation, a Data Reviewer's Guide. As there is no standardization for pooled analysis data, different companies have different approaches to combine data and provide information and clarification about this data to regulatory agencies. The industry needs to have standardized documentation to support regulatory submission to multiple agencies.

The PHUSE Optimizing Data Standards (ODS) team has developed the integrated Analysis Data Reviewer's Guide (iADRG) template to provide clarity and consistency in documenting integrated analysis data. The Integrated Analysis Data Reviewers Guide template and associated documents provide structure, guidance to produce standardized content and additional context for integrated analysis datasets received as part of a regulatory submission. The Completion Guidelines and example documents guide the users through the implementation. Within the integrated Analysis Data Reviewer's Guide (iADRG), study protocols, source data, data standards, treatments, variable information and additional details are provided.

COMPLEXITIES OF ANALYSIS DATA INTEGRATION

The iADRG Completion Guidelines and examples provide many details and instructions on what information should be provided and how to document it using the integrated Analysis Data Reviewer's Guide (iADRG) template. While many of the iADRG sections are straightforward, other sections are more

challenging to apply. The difficulties in the iADRG implementation come from the more complex data integration issues, such as pooling strategies, data re-mapping or redefining analysis flags and other data integration complexities. We are sharing some suggestions and examples of different situations in implementing the iADRG for your consideration, however, it is the discretion of the sponsor for their own way to implement the template.

ANALYSIS POOLING STRATEGIES

Simple or complex submission analysis pooling strategies combine comparable data across studies to demonstrate product safety or efficacy. These strategies can be very straightforward, such as pooling all patients under 65 years of age and those 65 and over to compare adverse events or other safety profiles. Another example would be summarizing patient data by indication (disease) for patients dosed with 150 ug/kg or more to compare the safety (e.g., adverse events) or efficacy of a presumed therapeutic dose. There can also be more complicated situations when integrating data from multiple studies. Studies with different disease populations, different treatment periods and /or different dosage and treatment combinations, for example, make pooling comparable patient data for safety or efficacy more challenging.

For example, we may have 3 studies with different dose and treatment combinations. Study designs are double-blind for Studies 1 and 3, and cross-over for Study 2 as shown in Figure 1.

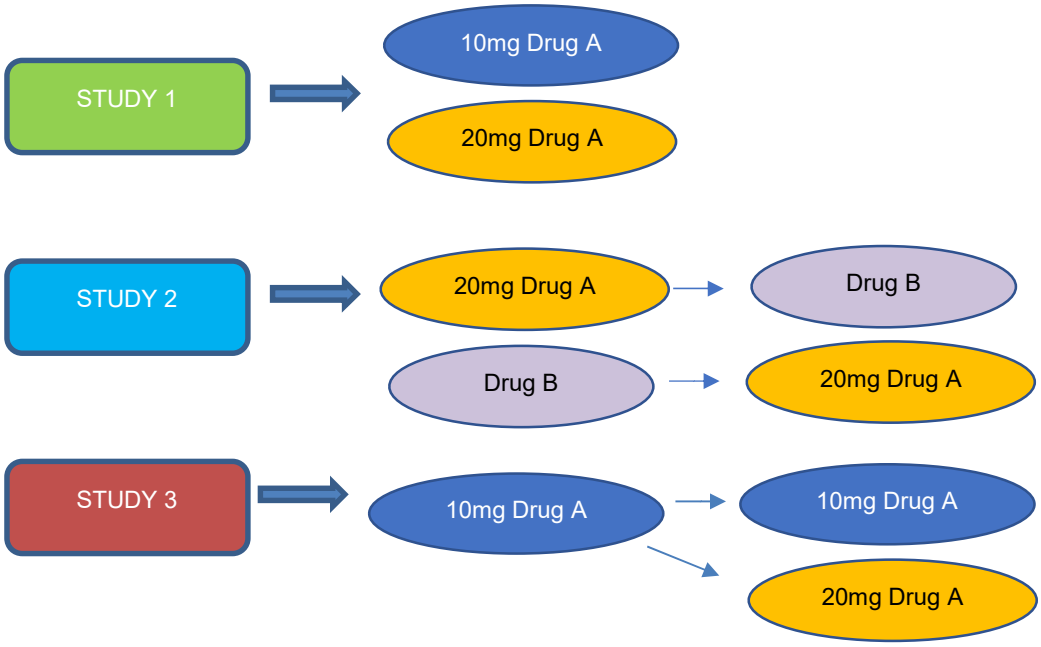

Figure 1. Study Treatment Designs for Studies 1, 2 and 3

Because at least one study has 2 treatment periods (two studies in this case), we need to document these using both TRT01P/TRT01A and TRT02P/TRT02A in iADRG section 2.2 Integrated Analysis Strategy and Design in Relation to ADaM Concepts to clarify the pooling and analysis strategies. One way to document this is shown below in Table 1.

Table 1. Treatment by Period by Study

Treatment ARM by Period	Study 01 (Double-Blind)	Study 02 (Double-Blind Cross-over)	Study 03 (Double-Blind Extension)
TRT01P	10mg or 20mg Drug A	20mg Drug A or Drug B	10mg Drug A
TRT02P		Drug B or 20mg Drug A	10mg or 20mg Drug A

To further clarify the planned study treatments by treatment period, we could present additional information in the iADRG Section 3.2 Treatment Variables. One way to document this would be to specify the STUDYID, ARM, TRT01P and TRT02P as noted in Table 2.

Table 2. Treatment Arms by Study

STUDYID	ARM	TRT01P	TRT02P
STUDY01	10mg Drug A	10mg Drug A	
STUDY01	20mg Drug A	20mg Drug A	
STUDY02	20mg Drug A – Drug B	20mg Drug A	Drug B
STUDY02	Drug B - 20mg Drug A	Drug B	20mg Drug A
STUDY03	10mg A -10mg A	10mg Drug A	10mg Drug A
STUDY03	10mg A - 20mg A	10mg Drug A	20mg Drug A

Together these two tables clearly define the treatment periods and possible treatment combinations for each study.

REMAPPING OR CREATION OF ANALYSIS VARIABLES

During the data integration of multiple studies, new variables may be created, or variables may be redefined to re-map existing data and ensure consistent use of definitions across studies. These new and/or redefined variables should also be documented in the iADRG section 2. 2 Integrated Analysis Strategy and Design in Relation to ADaM Concepts.

For example, treatment discontinuation reasons may need to be re-mapped to new categories if the studies being pooled capture different discontinuation reasons or use different terminology. If Study 1 treatment discontinuation reasons include “Death due to Adverse Event” and “Death due to Study Disease” while Studies 2 and 3 only include the category “Death”, based on the submission integrated analysis plan, you may want to re-map these two Study 1 death reasons to “Death”. This would provide a more useful grouping of deaths in the pooled treatment discontinuation reason summaries across the three studies.

Documentation of new population flags or redefined analysis flags is also important to provide clarity to the submission analyses. A new population flag may be created based on individual sensitivity analyses, identifying a subpopulation of particular interest. Often covariates such as baseline lab values (e.g., WBCBL) or disease stage (e.g. STAGEBL) lead to additional submission study analyses to take advantage of the larger pooled treated patient population.

While integrating study data, there may be inconsistent analysis flags. In this example data, Study 1 ANL01FL (worst test result) is the same as Study 2 ANL02FL and is not analyzed in Study 3. These analysis flags would be redefined for consistency or added if missing. This will ensure they represent the same definition and algorithms when you pool this data and perform summary analyses. These new or updated flag variables should be detailed in iADRG section 2.2 Integrated Analysis Strategy and Design in Relation to ADaM Concepts.

One way to document the redefined ANL01FL per patient for laboratory test ALT result or for new ANL02FL and ANL03FL variables might be as shown below in Table 3.

Table 3. Analysis Flag Definitions by Study and as Used in the Integrated Safety Summary (ISS)

Analysis Flag Definitions	Study 1	Study 2	Study 3	ISS Pooled Analyses
ANL01FL	Worst ALT test result across visits	Last on-treatment ALT test result	Cardiac function tests elevated from baseline	Worst test ALT result across visits
ANL02FL	N/A	Worst ALT test ALT result across visits	N/A	Severe elevation in all liver function tests (NEW)
ANL03FL	N/A	N/A	N/A	Severe changes in ECG results from baseline (NEW)

As seen in this table, Study 3 ANL01FL is flagging a completely different test result than for the other studies or as recomputed to use for the ISS. In these cases where the analysis flags are redefined, the analysis performed for this submission will not match the study safety analyses.

VISIT WINDOWING AND UNSCHEDULED VISITS

Many time analyses require the use of visit-windowing algorithms and/ or unscheduled visits; these details will be provided in the integrated ADRG within Section 3.4 Use of Visit Windowing, Unscheduled Visits, and Record Selection. You can describe the different methods for selecting or computing baseline measurements and whether to use unscheduled visits in this algorithm.

As an example, blood pressure data has been collected for each patient 2 times in the 30 days prior to the first study drug dose, and at Visits 1-3 with occasional extra visits between Visits 2 and 3. In Study 01, a patient's baseline blood pressure (BP) is defined as the measurements on the date and time closest to (on or before) the first study dose. For Study 02, a patient's baseline blood pressure is defined as the average blood pressure from the 2 pre-dose collection dates. If the integrated statistical analysis plan requires, the patient's baseline for the integrated data may be redefined across studies as, for example, the last measurement prior to the first study drug dose shown in Table 4.

Table 4. Sample Patient Blood Pressures by Visit by Study

Blood Pressure (BP)	Day -15 to -30 #1	Day -1 to -14 #2	Visit 1 (Post-Dose Day 1)	Visit 2	Unscheduled Visit 2.5	Visit 3	Study Baseline	Submission Baseline
Study 01 Patient 101 (A-101)	130/90	100/70	110/60	110/70	120/60	110/60	110/60 (Visit 1)	100/70 (Day -1 to -14)
Study 02 Patient 201 (B-201)	140/90	130/60	110/80	90/50	150/90	120/70	135/75 (average pre-dose visits)	130/60 (Day -1 to Day -14)

Because the submission baseline blood pressure will be different than that used for the Study 02 analyses, it is important to note this in iADRG section 3.4 for clarity to a regulatory reviewer.

For the Integrated Summary of Safety (ISS) analysis at Visit 2 per our imaginary integrated SAP, the by-visit analysis of this data requires the analysis flag (ANL01FL) to identify the **worst measurement** for Blood Pressure on or after Visit 2 up to Visit 3 including all unscheduled visits (Table 4). The algorithms used for ANL01FL for each study, Study 01 and Study 02, are defined in Table 5.

Table 5. ANL01FL Visit 2 Blood Pressure Record Selection for Study or ISS Analyses

Study	ANL01FL Visit 2 Analysis Definition	ANL01FL = 'Y'
Study 01	ADVS patient blood pressure assessments performed during the Visit 2 analysis visit window (+/- 5 days) including unscheduled visits. The results on the date **closest to analysis visit** 2 is flagged.	A-101: 110/70
Study 02	ADVS patient blood pressure assessments performed during the Visit 2 analysis visit window (+/- 5 days) including unscheduled visits. The results on the date **closest to analysis visit** 2 is flagged.	B-201: 90/50
ISS	In ADVS, patient's **worst measurement** for Blood Pressure on or after Visit 2 up to Visit 3 including all unscheduled visits	A-101: 120/60
ISS	In ADVS, patient's **worst measurement** for Blood Pressure on or after Visit 2 up to Visit 3 including all unscheduled visits	B-201: 150/90

The ISS submission analysis requires the ANL01FL to be recomputed based on the new definition selecting the worst measurement. This should also be documented to point out differences between the study analyses and the submission analyses of the same data.

SPLIT AND INTERMEDIATE DATASETS AND DATA DEPENDENCIES

Split and intermediate integrated analysis datasets are frequently used in regulatory submissions. Split and intermediate datasets and data dependencies are to be documented in Section 4 Integrated Analysis Data Creation and Processing Issues. The split and intermediate datasets will be included in the electronic submission package.

Split dataset creation should follow the Study Data Technical Conformance Guide[1] or other regulator's requirements; provide both split and non-split datasets in the submission data package and document them in the Reviewer's Guide section 4.1 for clarity. An example of documenting split datasets is shown in Table 6 below.

Table 6. Split Datasets Details

Source Dataset	Split Dataset	Split Value
ADLB	ADLB01	PARCAT1 = Chemistry
ADLB	ADLB02	PARCAT1 = Hematology

An intermediate dataset can be created for numerous reasons, such as merging or subsetting data, or computing patient-level results to be combined with other information in an analysis dataset. These should be described in section 4.3 Intermediate Datasets. You should also identify intermediate datasets in section 4.2 Data Dependencies to provide clear traceability from analysis data sources to the integrated ADaM datasets used for the submission analyses.

Several example tables and figures for split datasets, data dependencies and intermediate datasets are provided in the iADRG Completion Guideline and Example documents[4].

HARMONIZATION OF ANALYSIS DATA

One of the key aspects from a regulatory reviewer's standpoint is to understand the integration strategy, documenting the differences between individual study-level vs pooled data that may affect data integration across one or more datasets and help with accurate interpretation of the results. This includes

any special handling rules used for baseline definitions, study population, grouping core variables, variable/value-level metadata and the code list that are harmonized for integrated analyses.

A standard industry practice is the creation of core variables for subject summaries or sub-group analyses where analysis rules were modified in integrated analysis causing results to differ from individual studies, see Table 7 for an example. Sponsors can implement standardization of test codes, names, category variables, E.g. XXCAT, TESTCD across studies if standards were not aligned. Both harmonization strategies are widely used for submission analyses and should be clearly documented.

For example, you may have subject or protocol-specific considerations leading to subjects excluded from multiple integrated datasets. This should be documented along with the rationale for subject exclusion in section 3.3 of the iADRG template.

Table 7. Core Variables Grouping Analysis as Used by Study or Integrated Safety Summary (ISS)

ADaM variable	Study Analysis rules	ISS Analysis rule harmonization
ADSL.AGEGR1 (Age Group)	For STUDY01 and STUDY02, AGEGR1 was derived from AGE when subjects were categorized into 4 age groups as follows: 1. <55 years of age. 2. >=55 years, and is <65 years of age 3. >=65 years, and is <75 years of age 4. >= 75 years of age	For ISS submission, AGEGR1 variable computed by categorizing subjects into 3 age groups below- 1. <65 years of age. 2. >=65 years, and is <75 years of age 3. >=75 years of age Considering that STUDY01, STUDY02 and STUDY03 have age group derivations differing from the ISS analysis rule, the age information from the three studies was harmonized using ISS definition for AGEGR1. With this, data for Age group may not align with study CSR analyses.
	For STUDY03, AGEGR1 was derived from AGE when subjects were categorized into 5 age groups as follows: 1. <18 years of age. 2. >=18 years, and is <55 years of age 3. >=55 years, and is <65 years of age 4. >=65 years, and is <85 years of age 5. >= 85 years of age	
ADSL.RACEGR1 (Race Group)	For STUDY01 and STUDY02, RACEGR1 was derived from RACE by categorizing subjects into 3 Race groups- WHITE, BLACK and OTHER	For submission analysis, computed RACEGR1 by categorizing subjects into 3 Race groups- 'WHITE', 'BLACK' and 'ALL OTHERS'. Both STUDY01 and STUDY02 have the RACEGR1 derivation which differs from ISS analysis rule as Race group 'ALL OTHERS' includes subjects with 'Other', 'Others' or missing data for race. STUDY01 and STUDY02 harmonized using ISS definition and is presented in demographics summaries by Race for submission analyses.
	For STUDY03, RACEGR1 was derived from RACE by categorizing subjects into 3 Race groups- 'WHITE', 'BLACK' and 'ALL OTHERS'. In this, 'ALL OTHERS' includes subjects with missing data or 'Others' populated in the study CRF.	

A high-level summary about the updates made during the integration for controlled terminology, medical events dictionary (MedDRA), WHODD dictionary, CTCAE criteria, updates of values for variables at the study-level that are inherited into the integrated datasets should be provided in section 3.3. A rationale

and detailed description of these updates made to a specific integrated analysis dataset should be presented in section 5.2.X Integrated Analysis Datasets. In this case, an explanation if WHO-DD unification was not possible at integrated level should be provided as follows:

> *ADCM dataset contains data from three different source studies: STUDY01, STUDY02, and STUDY03. Previous and concomitant medications are coded with WHO-DICT. For studies STUDY02 and STUDY01 the WHO-DD version is: MAR2019, and for study STUDY03, the WHO-DD version is: MAR2014. No re-coding was performed because only limited descriptive analyses of prior and concomitant medications were performed.*

A common scenario pertains to date imputations or derivation methods performed differently for the ISS than for the individual studies, using special analysis rules used in multiple datasets during integration. In this case, the use of record level imputation, derivation or any other variable conventions used by a sponsor that cannot be easily established in define.xml, should be documented in section 3.5 Imputation/Derivation Methods. For example, document the description of algorithms followed to calculate timing variables used across integrated analysis datasets (e.g., ADY) for clarity, ensuring they are aligned with the definitions provided in define.xml.

Another example, DTYPE variable was used in both ADLB and ADVS datasets to compute derived records for a study-level CSR analysis. The DTYPE controlled terminology (CT) and derivation rules were modified during integration to align with the submission (ISS) analyses. In this case, you can provide a summary of controlled terminology updates used in both datasets in section 3.5, as in Table 8 below. For ADLB, DTYPE variable was re-mapped to align the controlled terminology and analysis rules used during integration. In ADVS, DTYPE was used to recompute the results to heart rate, temperature and blood pressure that have multiple measurements taken per visit. A detailed description of derivation methods and CT updates done in each integrated ADAM dataset should be documented in 5.2.x., as in Table 8.

Table 8. DTYPE Definitions by ADaM Dataset and as Used in the Integrated Safety Summary (ISS)

ADaM variable	ISS Derivation rule	Controlled Terminology
ADLB.DTYPE	No change in variable derivation, data mapped as is from STUDY01.ADLB.DTYPE	AVERAGE, LOCF, MAX, MIN, WORST
	Added derived records that has ‘MAXIMUM’ and ‘MINIMUM’ Lab result for each parameter on or after baseline visit including unscheduled visits where DTYPE assigned to ‘MAX, ‘MIN’ respectively when the Lab data is mapped from STUDY02.ADLB	
	Added derived records by computing patient’s worst measurement for each Lab parameter on or after baseline visit including unscheduled visits where DTYPE assigned to ‘WORST’; Else, DTYPE mapped from STUDY03.ADLB.ITYPE.	
ADVS.DTYPE	No change in variable derivation, data mapped as is from STUDY01.ADVS.DTYPE	AVERAGE, LOCF, WORST
	For blood pressure, heart rate, respiratory rate parameters, replaced 'MAXIMUM' by ‘WORST’ when derived records mapped from STUDY02.ADVS.DTYPE; For blood pressure, heart rate, respiratory rate parameters, added derived records by computing patient’s average measurement and assigned DTYPE to 'AVERAGE' if STUDY02.ADVS.DTYPE= ‘ ‘ and STUDY02.ADVS.DTYPE1 in ('DAYAVG','VISAVG');	
	For blood pressure, heart rate, respiratory rate parameters, added derived records by imputing missing patient’s	

ADaM variable	ISS Derivation rule	Controlled Terminology
	measurements using Last observation carried forward (LOCF) method. In this case, the last non-missing observation score for these parameters was taken for subsequent observation points when the assessments were made on or after the baseline visit. This includes unscheduled visits and the DTYPE assigned to 'LOCF'; Set DTYPE to 'WORST' when AVISITN=5555; Else, DTYPE mapped from STUDY03.ADVS.ITYPE	

One of the harmonization challenges we often encounter is if the sponsor has converted any non-standard source data during integration. For transformation of legacy data into integrated ADaM datasets, the Legacy Data Conversion Plan (LDCP) in the iADRG template appendix and created for this specific purpose, is executed. The conversion data flow, conversion data summary, including any issues encountered/resolved or outstanding issues should be documented in Section 8 (Appendix). However, the Appendix section is optional, and you can delete it entirely when no legacy source data was used for submission analyses.

Another example is STUDY01 where legacy tabulation data was used to create legacy analysis data, which was used for creating analysis results for the appendix of the CSR. For submission analyses, Legacy analysis data from STUDY01 needs to be converted to ADaM to facilitate ISS ADaM integration using the LDCP. The mapping specification from legacy data to ADaM is presented in Table 9. In this process, CDISC Controlled Terminology was applied where applicable and should go into the Appendix section.

Table 9. Mapping Specification from Legacy Data into ADaM Source Datasets Used in ISS Integration

Study ID	Legacy Dataset Names	Legacy Dataset Description	Mapped To ADaM Dataset
STUDY01	DEMOG, MEDHX, VITALS, CMED, DEATH	Demographics, Medical History, Vital Signs, Concomitant Medications, Death details	ADSL
	CMED, PRIORMED	Concomitant Medications, Prior Medications	ADCM
	DRUGADM, DOSECOMPL	Drug Administration, Dose Compliance	ADEX
	QUEST1, QUEST2, QUEST3	Questionnaire 1 (EORTC-QLQ-C30), Questionnaire 2 (FACT-Lym), Questionnaire 3 (EQ-5D-5L)	ADQS
	BLTTEST, TRESULT	Baseline Tumor Measurements, Tumor Measurement Results	ADTR
	TRESPONSE	Tumor Response	ADRS

A comparison between newly created key ADaM datasets and their corresponding legacy analysis data ensures traceability.

The conversion data flow, issues encountered, and their resolutions should be documented in the iADRG Appendix report, see the iADRG supporting documents[4] and Table 10 below.

Table 10. Summary of Issues Encountered and Resolved in executing Legacy Data Conversion Plan

Study ID	Legacy Analysis variable	Issue Description & Resolution	Mapped To ADaM variable
STUDY01	DEMOG.ENROLL	The original population flags for enrolled, randomized or safety subjects, were in numeric format. The numeric values were converted from 1 to Y and 0 to N.	ADSL.ENRLFL
	DEMOG.SAFETY		ADSL.SAFFL
	DEMOG.RANDMZD		ADSL.RANDFL
	NA	The ITT (intent-to-treat) population flag did not exist in the legacy analysis data. The flag was derived in the ADaM programs for the subjects who are randomized.	ADSL.ITT
	DEMOG.PS1START and PS1END DEMOG.PS2START and PS2END DEMOG.PS3START and PS3END	Originally phases were referred to as periods in the legacy analysis data but to be ADaM compliant the following changes were made: -- PS1START and PS1END mapped to Baseline Phase. This phase contains a screening period, Baseline visit that is needed for submission analyses. -- PS2START and PS2END mapped to Treatment Phase. This phase contains Up-titration (APERIOD = 1, AP01SDT, AP01EDT), Maintenance (APERIOD=2, AP02SDT, AP02EDT), and Down-titration (APERIOD= 3, AP03SDT, AP03EDT) periods. -- PS3START and PS3END mapped to Safety Follow-up Phase.	ADSL.APERIOD ADSL.AP01SDT ADSL.AP01EDT ADSL.AP02SDT ADSL.AP02EDT ADSL.AP03SDT ADSL.AP03EDT

CRITERION OF REGULATORY AGENCIES

A key drug submissions challenge is the compliance with differing regulatory requirements and multitude of standards that have evolved over time from various Health Authorities, including the US FDA, Japanese PMDA and Europe's EMA. Feedback from both pharma industry peers and agency reviewers was taken to develop a unified approach, creating a reviewer guide template that can accommodate the differences in agency requirements.

Although Pinnacle 21 data conformance checks are written specifically for individual studies, the iADRG template shows these conformance checks as an example of what might be implemented for integrated ADaM datasets. The Pinnacle 21 PMDA business and validation rules request both Rule ID and severity columns be presented in Conformance Summary section of the iADRG and shown in the iADRG template. The FDA has dropped severity from their conformance checks. For FDA submission, severity column is left blank for conformance summary. A reason should be provided if the integrated analysis has a column or validation rule that is not applicable and is regulatory requirement.

For example, if English is used in the dataset, the character set is specified in ASCII which is the case with FDA or EMA submissions. When using languages other than English, including Japanese, the character set E.g.: ASCII, Unicode (USC-2) and encoding scheme should be provided. For PMDA submissions, both character set and encoding scheme should be documented in section 1.3 Data Standards and Dictionary Inventory for Integrated Datasets of the iADRG template.

Be sure to consider the specific requirements for the regulatory agency to which you are applying. Both the FDA and PMDA have their own technical conformance guides. These or additional requirements may be applicable to your submission regulatory agency and division.

CONCLUSION

Implementing this new Data Reviewer's Guide template for integrated analysis data will standardize the format and important details to support regulators in their review process. With many different complex data models and issues arising in submissions, this paper provides some suggestions to help aid you in your submission reviewer's guide implementation. Providing a standardized integrated Analysis Data Reviewer's guide with your regulatory submission provides consistency and facilitates more efficient regulatory data review. Note that this paper only covers a few examples of complex situations with data integration providing suggestions or ideas on how they may be documented and does not delve at all into CDISC compliance which is another very important component when providing data to the FDA or other regulatory health authorities.

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RECOMMENDED READING

- Integrated Analysis Data Reviewer's Guide Completion Guidelines, Version 1.0[4]
- iADRG example 1[4]
- iADRG example 2_with_LDCP[4]

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