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ISS Challenges and Solutions for a Compound with Multiple Submissions in Parallel

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ABSTRACT

Integrated Summary of Safety (ISS) is required for new and supplemental drug or biologic applications. For an oncology compound with multiple indications and tens of ongoing trials, challenges seeking sound strategies and execution of integrating trials are numerous. In this paper, we share some challenges and successful executed solutions.

There are two parts in the paper. In part I, we share the challenges and solutions of establishing a centralized ISS team. To address the needs of the multiple submissions and filings of this compound, we first established a dedicated ISS team. The specialization enables the same team to work on multiple ISS packages, with successive or concurrent timelines in turnarounds of several weeks.

In part II, we share some essential established programming techniques. The ISS programs we use can accommodate multiple versions of SDTM source datasets and meet the needs of today's CDISC standards filing requirements. The presented techniques include 1) Stacking datasets in each SDTM version and then integrating all studies. The validated stacking programs are re-used; making the stacking of dozens of trials just a routine re-run that can be accomplished within one hour magically. 2) Alignment of the ISS implementation for consistency with the submission CSR and integration needs are discussed. The discussion includes details on integrating at the SDTM or ADaM level, baseline derivation, and general principal of essential variables derivations such as TR01SDT, TR01EDT, and TRT01A. It is satisfying seeing the team deliver again and again while working towards simplified, streamlined solutions.

INTRODUCTION

Integrated Summary of Safety (ISS) is required for new and supplemental drug applications [1]. For a compound with multiple indications, tens of trials on going for submission, the challenges of implementing sound systematic strategy for ISS reporting to a statistical and programming team are big; yet the fun may be abundant as we identify challenges and seek solutions.

This paper consists of two parts. In part I, we introduce the strategy of challenges and solutions our organization uses for our ISS reporting. The strategy includes establishing a centralized ISS team which aligns the reporting by providing the ISS mockup TLF (tables, listings and figures) templates for all the indications across the board. In part II, we share some ISS programming implementation techniques. Some thinking and discussions for challenges in terms of consistency, harmonization, integration, and standardization on ISS reporting are exampled. It is satisfying as we are finding better solutions and feasible path forward along the way.

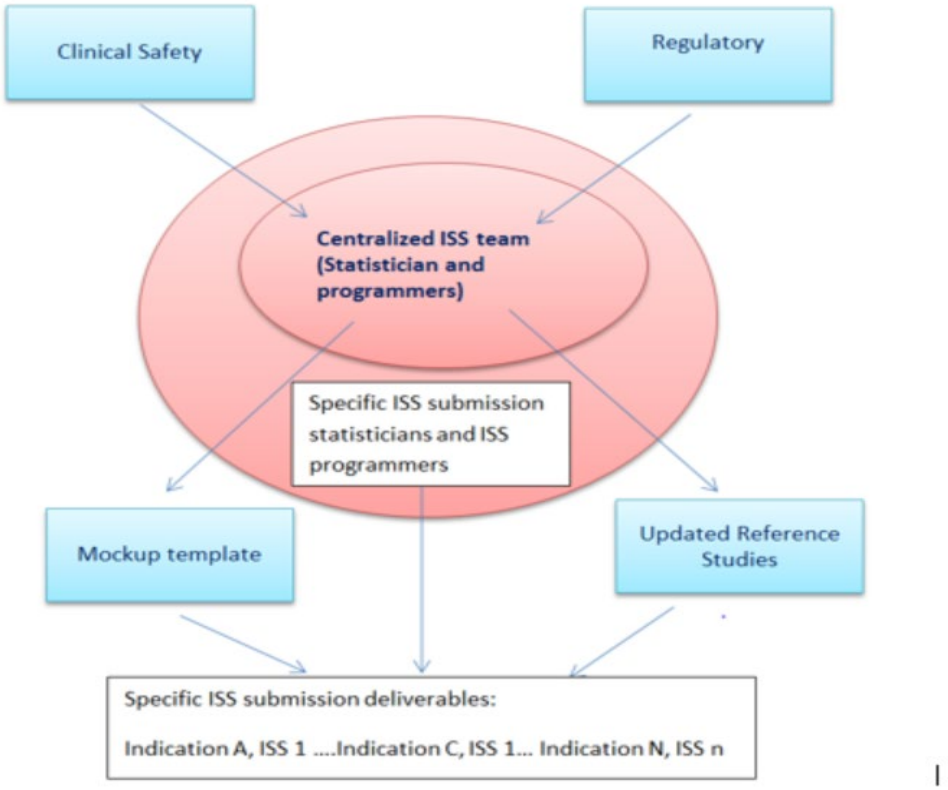
PART I. ESTABLISHING CENTRALIZED ISS TEAM: CHALLENGES AND SOLUTIONS

Challenges: In our case, for the same compound or the combination involving the compound, at certain time, there is always multiple-submission preparation in parallel across different indication teams. It becomes evident that the aligned reporting strategy needed to address the regulatory needs for integrated safety reporting across indications. Efficiency may be gained to have a specialized team working across the board in addition to ensure the consistency of deliverables.

Solutions: A centralized ISS team consists of statisticians and statistical programmers established (Figure 1). The main project management role may be shared by the statistician and statistical programmers. The statisticians include centralized ISS team core statisticians, and ISS statisticians for each specific submission who are implementing the decisions and strategies from centralized ISS team. One core lead statistician may work on sourcing and resourcing specific statisticians across the

organization. The lead statistician along with the programmer(s) with project management role reaches out to safety clinicians and regulatory for the aligned, consistent reporting strategies across the company. Some ongoing alignments include what studies may need to be included in the ISS reporting, while newly submitted studies may be added in as the reference safety studies. Based on the aligned strategy, the centralized ISS team authorizes the reporting mockup template. The individual ISS across indications just needs to adopt the template by updating indication pivotal trial or other indication studies to presenting analyses. The group of specialized programmers really facilitated the speedy quick turnaround.

Figure 1: Centralized ISS team for a Compound with Multiple ISS Submissions in Parallel



PART II. ADOPTING BEST FEASIBLE PROGRAMMING TECHNIQUES AND PATH FORWARD: CHALLENGES AND SOLUTIONS

Challenges 1: Stacking up variables of different lengths or types of SDTM domains:

Solutions 1: For stacking up SDTM data with variables of different lengths, there are two ways in general. One is using maximum lengths for every variable and then found out their real length through programming. This method would not have worked well for us because almost all the character variables may have like length of 200 or 255 for some studies, which means the size of datasets would be increased so much that the running time become formidable, especially for the huge lab data we have for dozens of studies. Despite timeline pressure, we choose to start automating the process in one of ISS by programming to find maximum real values for all variables; set length for each variable and then stack up all the datasets. We also included programming to resolve integration of a few earlier studies which had variables with different data types. The essential programming flow is illustrated as in Figure 2. This

approach has been used tens of submissions for over two years now. It is real satisfying when we see that our huge lab SDTM data, along with other safety domains such as AE, CM, DM, DD, EX, QS can be stacked up at any time by a computer within one hour by just single click.

Figure 2: A programming flow for stacking up SDTM domains with practical efficiency.

```
%macro integration (liblist = &libs, dmnlist = &dmns);
  %* Step 1: Initialization;
  %local i j k m n p v w;
  %let i = 1;
  %let dmn = %scan(&dmnlist, &i);
  %put dmn = &dmn;
  %do %while(%length(&dmn));
    data &dmn;  if 0; run;
    %* Step 2: Prepare data for loop to count length;
    %let j = 1;
    %let lib = %scan(&liblist, &j);
    %do %while(%length(&lib));
      ......
  %* Step 3: Get actual maximum lengths for all character variables;
   proc contents data = in&lib&dmn noprint out = &dmn.&j.
        (keep = memname varnum name label type  rename = (type = type&j label = label&j));
   run;    ......
  %* Step 4: Get processed labels for character variables; ......
  %* Step 05: Prepare length statements for output datasets; ......
  %* Step 06: Generate output datasets; .......
%let i = %eval(&i + 1);
%let dmn = %scan(&dmnlist, &i);

%end; *end of different domains loop;

%mend integration;

%integration(liblist = lpivtl lstdy1 lstdy2 lstdy3 lstudy4 lstdy5 lstdy6 lstdy7 lsdty8 lstdy9,

             dmnlist = lb ae ce cf cm dm ds ex ph mh relrec se sv);
```

Challenge 2: The meaning of consistency with CSR and integration needs

It is always a challenge to what degree for what ISS should be consistent with what has been done in CSR, and to what degree, harmonization, normalization and derivation needs to be done for the integration analysis purpose.

Solutions: In general, the guiding principal is that the presentations in ISS should be consistent with CSR. However, it may not be always the case; several examples are listed as below:

Example 1: the stratification factor Eastern Cooperative Oncology Group (ECOG) Performance Status used in the randomization maybe used for efficacy analysis baseline. While, for safety analysis, the closest value to the treatment date may be chosen.

Example 2: ADSL.TRT01A in the protocol normally takes values same as DM.ACTARM, while in the integrated analysis, we will see different names for the same treatment. It just makes sense to integrate

them to a value chosen.

Example 3: Evaluate definitions for some essential variables from time to time. For example, for the definition of TRTSDT, TR01SDT and TR01EDT, the ISS would follow what is in a CSR. While these definitions tend to long to guard against potential live data base data-issues, instead of simple first dose date for TR01SDT, the team may use, EPOCH, AVISIT, and so on to try to cover all the situations. For ISS, however, the database has already been locked. In our case, it turned out instead of one-page long definition of TRTSDT/TR01SDT from every study, and long various coding used in the CSR, we eventually could just use first dose information in EX domain to code all locked trials. Similarly, TR01EDT and APERIOD such variables may be examined and get their definition integrated as well.

In addition, for an ISS with dozens of studies, some logics in the initial CSR may no longer been used or contradictory to the current think, then the current ISS may adopt the current thinking.

Challenge 3: Integrating at SDTM level or at ADaM level?

The answer is probably depending. For those earlier studies or some external studies, we do not have ADaM datasets readily available, or analysis variables are simply not derived, we may be better off to use SDTM datasets. As more and more studies are analyzed based upon ADaM datasets, we may be better off choosing to normalize, harmonize ADaM datasets for integration analysis. For integrating on ADaM level, some variables, such as age group and race group are easier to standardize, others like region except EU/Ex_EU and US/Ex_EU, the definition of East Asia and so on may need to be aligned. The treatment variable values often need to be normalized due to the number of studies conducted at different times. Finally, ISS team needs to be informed if safety-ADaM datasets are updated after initial delivery.

CONCLUSION

For a compound with multiple submissions in parallel, the ISS reporting can be challenge, while there are also opportunities gaining efficiency among the submissions. In this paper, we shared the challenges we encountered, as well as successfully executed solutions. We presented the advantage of the establishing centralized ISS team and some best efficient programming techniques and path forward.

REFERENCES

[1] FDA. “Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.” Published April 2009. Available at https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf.

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