Planning for ISS/ISE Integration:
4 Critical Steps to Get Started

With the goal of the ISS (Integrated Summary of Safety) to display overall safety of the drug, and ISE (Integrated Summary of Efficacy) to show efficacy, both are required for all new drug applications (NDAs) in the U.S.

But even with proper planning, timely delivery of these integrated summaries is not guaranteed.

How can drug developers plan for integration to try to ensure as smooth and timely an integration as possible? Following are a few items to consider as drug developers begin the planning process.

☐ **1. Early planning is key!** Planning for ISS and ISE integration and FDA interaction should typically occur after Phase II.

- **The integration process should include:**

  - An integration plan
  - Statistical analysis plan (SAP)/mock tables, listings, and files (TLFs)
  - Upcoding of medical terminology for adverse events (AEs) and Common Terminology Criteria for Adverse Events (CTCAE) mapped to the Medical Dictionary for Regulatory Activities (MeDRA) and medications mapped to the WHO Drug dictionary
  - Clinical Data Interchange Standards Consortium (CDISC) Foundational Standards for supporting research processes from end to end applied to all studies from legacy through pivotal to long term safety (LTS) studies
  - Medical writing with development of the ISS, ISE, summary of clinical efficacy (SCE), and summary of clinical safety (SCS)

- **Important steps to ensure success in the planning stage, include:**

  - Discuss integration with the Regulatory Agency, including analysis and reporting requirements, early on or at the end of the Phase II meeting, and follow up with a second discussion at the pre-NDA meeting. It is important to conduct this communication, as the FDA may identify certain endpoints they want included in integration that you may not be planning for, such as data from patient reported outcomes (PROs). These are becoming more standard in assessment and the FDA is increasingly requiring them.
  - Include the integration statistician(s) at these meetings.
  - Allow sufficient time/budget for ISS/ISE processes. The work required for integration is substantial. Integration will also likely require a sizable budget.
  - Create an Integration Plan. The integration team should understand conclusions you want to draw in the summaries following the integration of the data, so that outputs in tables and figures coincide with outcomes you want to make.
  - Create CDISC Standards and develop an internal standard for SDTM (or ADaM) implementation.
  - Identify the version of the Implementation Guides (IG) to use in coding and require CRO adherence to your/sponsor standards and IG.

☐ **2. Identify legacy studies in your integration plan.**

- Provide the required study documents to your integration team as necessary (e.g., protocols, annotated case report forms (CRFs), statistical analysis plans (SAPs), datasets, etc.)

- Assess whether or not legacy datasets will require CDISC conversion. This is a requirement for studies starting after December 17, 2016.

  - You may not intend to combine efficacy data from some or all of your studies.

  - But you will need to convert legacy studies if enrollment occurred after that date, regardless of integration.

  - You may also need to convert to CDISC for some of the studies. Confirm with the FDA, and have a plan upfront if you do not, otherwise, intend to convert legacy studies.

- You will need to up-code medical terminology to MedDRA and WHODrug and determine study groupings.

☐ **3. Develop Statistical Analysis Plans Early.** After your Phase III SAPs are finalized and considered stable, now is a good time to begin work on the SAP for integration.

- You may choose to do one SAP for both the ISS and ISE or you can have individual SAPs for each.

- Include detail of studies to be pooled in your SAP along with the data that will be summarized in each integration SAP. In the analysis plan, the populations and treatment groups should be identified along with methods for handling missing data and the statistical methodology that is going to be applied.

- The plan should also include mock TLFs.

- Hold regular team meetings to confirm work is being done/progress is being made. You can also use these meetings to assess any emerging concerns from the integration team that may impact timelines.

☐ **4. Know the Requirements.** An ISS and ISE are required for FDA submissions. The FDA doesn't require integration for biologics license application (BLAs), but they do recommend it.

- Additionally, the Summary of Clinical Efficacy and Summary of Clinical Safety Requirements can differ between integrations.

  - You have multiple options for the location of your ISS and ISE in the eCTD. Module 2 sections 2.7.3 and 2.7.4 are for your summary of clinical efficacy (SCE) and summary of clinical safety (SCS). The purpose of both sections is to discuss the study design and general efficacy. These can be derived from ISS and ISE sections but are not usually straight copy from them.

  - Please note, module summaries are restricted to 400 pages in Module 2.

- The ISS and ISE should include effects and risks in your subpopulations. The FDA does require a summary of data for the subgroups age, race, sex and ethnicity. Also consider the region of your clinical site and other subgroups as well.

  - Explore effects and risks in subpopulations.

  - The Appropriate Location in the eCTD is in Module 5.3.5.3.

  - Module 5 documents have no space/page count restrictions.

  - Your ISS and ISE may be placed in Module 2 if certain applications apply, such as when your application is comprised of only one or a few studies and it falls under the 400-page limit.

- Data listings are not typically required for your integration, but you should include them for certain types of data changes. For example, if you have missing data and it's being handled differently between studies, you should include a listing for newly imputed data. If you have newly derived data, you will want to list those endpoints out in a data listing. Up-coded medical terminology should be included in a data listing, with the original terms and the up-coded terms.

- Use an experienced medical writing team. While not required, it's a good idea to have them develop a medical writing plan.
  - An experienced medical writer is a worthwhile investment. He/she is familiar with the process and will often anticipate questions from regulatory authorities. This way, the questions can be answered before they are even asked.

Getting ready to start, or already working on, your integration plan?

To learn more about planning for an ISS and an ISE, please read: Anticipating Common and Unforeseen Issues in Developing the ISS/ISE: What You Need to Know.

Or Contact us today to find out how we can facilitate your next submission.

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