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# Anticipating Common and Unforeseen Issues in Developing the ISS/ISE: What You Need to Know

## Highlights:

- Years of clinical development goes into the ISS and ISE, both required for all new drug applications in the U.S.
- Producing the integrated datasets is the most challenging and time-consuming task of the ISS/ISE process. Given this and the potential for other issues to arise, planning should start early in the project lifecycle.
- Other issues in data integration, resources and timelines, and unforeseen events can prevent timely delivery of integrated summaries.

## Introduction

A decade of clinical development can go into creating the ISS and ISE, 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 through comprehensive safety and efficacy data collected throughout development. Both are a requirement for all new drug applications (NDAs) in the U.S.

But even with proper planning, issues can occur. Timely delivery of these integrated summaries is not guaranteed.

While no one has a crystal ball to foresee all potential challenges that may arise, there are common pitfalls that drug developers can anticipate. This guide focuses on common challenges that must be assessed to increase likelihood of timely integration and drug approval.

## Planning for the Unexpected

Challenges in the ISS and ISE typically occur in three areas that must be managed to improve smooth integration: **data integration**, **timelines**, and **resources**.

## Data Integration

Producing the integrated datasets is the most challenging and time-consuming task of the ISS/ISE process. Because of this, it is advised that drug developers get started as early in the project as possible.

Errors in the integrated datasets are a common cause for refusal to file from the FDA. Additionally, when the data is integrated incorrectly, analysis results may be incorrect and may not represent the true features of the study drug. Efficacy may look better or worse than the reality.

Numerous types of data and multiple steps are typically required to get the data ready for integration. These include:

- Assessing lab data
- Up-coding to medical dictionaries such as MedDRA, WHODrug, CTCAE
- Performing CDISC (Clinical Data Interchange Standards Consortium) conversion
- Assessing derived variables to ensure consistency
- Performing consistency checks
- Making treatment group determinations

**Lab Data**

Lab data is often the most complicated information to assess across datasets. It can be time-consuming and difficult to combine and is most often done incorrectly.

Drug developers should consider the following steps in integrating lab data:

- Remap data (e.g., units, scales, normal ranges) at the STDM (Study Data Tabulation Model) level to standardize it
- Obtain medical assistance with remapping/review
- Document all changes identifying data exceptions in the specifications and in the data reviewer's guide for traceability

**Dictionary Up-Coding**

It is often necessary to modify medical coding across studies, as it is unlikely the version of the WHODrug and MedDRA dictionaries used will be the same. The coding team may need to up-code medications, adverse events (AEs) and CTCAE (Common Terminology Criteria for Adverse Events) for legacy studies and, potentially, even Phase III studies if there are multiple CROs running pivotal and long term studies.

When it comes to coding terminology, make the version determination to up-code terminology from legacy studies far enough in advance so as not to affect integration timelines. Freeze data during Phase III execution and use this predetermined dictionary version across all studies. To follow best practices:

- Allow enough time to complete this task in advance – assign a timeline for completion during normal team meetings and ask for status updates.
- Document changes to preferred terms and provide this to the FDA – note that medical review of changes in medical terms will be needed before integrated analyses are performed.

**CDISC Conversion**

These data standards to support acquisition, exchange, submission, and archiving of clinical research data and metadata are required by the FDA. CDISC conversion may not be required for all legacy studies. You should confirm your plans for conversion with the FDA in advance if you do not plan to convert all legacy studies.

A common challenge in CDISC conversion is that data is typically inconsistent in legacy datasets. It often needs to be remapped in order to be standardized. Drug developers will need to determine whether to start CDISC conversion at the SDTM or ADaM (Analysis Data Model) level for overall data structure, naming conventions, and variable requirements. This is an important consideration. If you start at ADaM and find out the data is not integrating or not converting, the programmers may have to re-start at STDM and recreate the ADaM dataset.

Regardless of how data is remapped, the processes for converting them should be documented. Data exceptions should be documented in the specifications and in the data reviewer's guide. The CDISC datasets need to include the original variables and newly derived endpoints, and these should also be documented.

The dataset should be submitted frequently to the validator during development. CDISC validator findings often uncover:

- Missing domains
- Duplicate records
- Data inconsistencies
- Controlled terminology messages
- Missing values
- Incorrect variable names, labels, types
- Incorrect values

Dry runs of tables, listings, figures (TLFs) should be run at the study level to confirm that the data in CDISC agrees with individual study results. This should be done before the integrated analysis is performed/produced. Areas where data is not in agreement with individual study results summarized in the individual clinical study reports (CSRs) need to be documented and explained as to why (such as applying new methods for handling missing data) in the reviewer's guide.

**Derived Variables and Data Handling**

Derived variables may include primary and secondary endpoints. Often, they are inconsistent between studies. Derived variables may not be included in all of the individual studies. The Statistical Analysis Plan (SAP) should be very specific regarding the endpoints to be included in the integration. Include descriptions of derived endpoints for the integration that identify whether any of these variables will be included and how they will be derived.

Missing data and its handling may not be consistent between studies. For example, you may have used last observation carried forward (LOCF) from a Phase II study and used multiple imputation in your Phase III study. You will need to document changes in results due to imputation differences between individual study data and pooled data, and make sure this is consistent across studies.

Another area where data may not be consistent is with regard to visits scheduled between studies. You may need to remap the data to appropriate visit schedules so that your studies are consistent regarding when data was reported. If the datasets are inconsistent and are not revised to move the data to a consistent visit schedule, the data summaries and analysis will likely not be correct. Remapping your data as to when the study was recorded is imperative to correctly report on the data.

Drug developers should also participate with CROs in discussions on combining treatment groups and appropriate groupings. For example, do you have multiple placebo groups? And should they be combined into one group? Or should they be kept separate?

You can have a similar situation with active treatment groups. Did some patients receive one-time-per-day dosing and others receive two-times-per-day dosing, where the dosage amount of medicine at the end of the day was the same for each subject? You may pool those subjects into one treatment group or keep them separate. These are some of the things you will need to assess with your data integration team.

**Data Reviews/Consistency Checks**

Data needs to be reviewed at the individual study level and consistency checks run between studies before integrating the data. Proc Freq should be written, run and reviewed often. These checks/reviews will identify inconsistent data between studies.

Drug developers should review results to identify inconsistent categories such as:

- Visit windows – you will need to determine if you want these to be made consistent. Note that your decision may affect the data in the integration. For instance, if visit windows are widened, this may include more data in the integration, and if they are narrowed, this may include less.
- Categorical variables – such as with AE relationship that may differ between studies. Sometimes this information is captured on a five point scale from "unrelated" to "related" and sometimes it is only reported as "not related" or "related." In this instance, the data needs to be remapped before it can be summarized.
- Inconsistent visit schedules – also need to be assessed.

Proc Freq should be used to review all endpoints for analysis. While the variable names in the dataset may look the same, they may actually include different data (or, variable names may not be consistent across studies and may need to be changed). Review and confirm before integrating to determine if data needs to be remapped and/or variable names need to be changed.

Run Proc Freq checks early and often until you are confident that the data is consistent and can be integrated for study analysis. Look at data for extent of exposure. Data may have different dosing regimens (units, frequency, etc.). You will also need to

assess dosing compliance calculations and determine whether these were computed consistently across studies.

In summary, when it comes to data integration:

- The decision will need to be made to integrate at the STDM or at ADaM level
- The version of the implementation guide needs to be determined early and used consistently across studies
- Annotations should be included and consistent
- Terminology should be up-coded, and
- Data checks using Proc Freq and Pinnacle 21 should be done often

## Timeline Issues

Another common issue with integration is timelines:

- The timeline for Phase III studies may change, affecting your timeline for integration. Enrollment may be slower than expected, delaying the Phase III study timeline, or may be faster than expected, moving up timelines for integration. Will your team be ready to adapt to these changes? And to move quickly if the timelines speed up?
- It may be that you originally decide to integrate at the ADaM level only to find out that data issues are prohibiting integration and the dataset integration needs to start at STDM, with ADaM datasets being created after STDM. If this happens, it will be unfortunate, as it will likely result in a significant time delay in restarting at the SDTM level. It is also likely to result in timeline revisions for producing the TLF and medical writing. The best thing to do in this case is to have conversations with your team on how to update timelines. It may require commitment and additional hours to get back on track.
- Integrated data output (mainly tables and figures) that are poorly designed can make writing the ISS and ISE difficult for medical writers, causing delay in delivery time for review, which will impact submission timelines. Though you may feel rushed, it is important to allow time to complete the integration process. Errors will often result if not enough time is allowed.

## Resource Issues

Resource issues can result when enrollment, or another aspect of the trial, occurs faster than planned and there are not enough resources to accommodate integration work earlier than expected. Conversely, and more often, if Phase III studies take longer than expected, this may delay the integration process, and integration teams that are already committed to another project may be constrained on their ability to help during this later timeframe.

In some instances, a CRO may be able to offer resources for a certain period of time. Make sure deadlines are communicated in team meetings and regularly adjusted to enable integration teams to accommodate moving timelines.

Other common causes of resource issues include:

- Phase III study results are not as expected at the efficacy or safety level. This may require suspension of integration activities until the Pre-NDA meeting or you may decide to proceed with the integration. If you do proceed, you may want to run post hoc analyses on the pivotal study(ies) to help explain the study results prior to integration. If the integration team is the same team working on your pivotal studies, integration work may be halted while post-hoc analyses are designed and produced. Regardless of which path you take, the change in timing and requirements may impact team availability.
- Unexpected changes in the integration team. This is often inevitable and can include resignations, medical leaves, new hires and so on.
- Internal resource issues at the drug developer(s). Often these types of issues can cause a delay in timely response to questions.
- Magnitude/significant number of data issues. This may delay timelines and require a larger study team.

## Reacting to the Unforeseen

Unforeseeable issues in integration may require drug developers to make some of the most difficult decisions they will ever need to make. Common issues and how to address them include the following.

- **Original timelines have proven to be too aggressive** – give careful consideration before declining requests to expand timelines. If the integration is hurried, it is likely there will be issues that may further delay timelines and integration. Issues are likely to be missed, analysis may be hurried, and data may not be consistent across studies. This may require additional time to redo work. Errors may be caught by a writer or, worse, not until the data is being reviewed by the FDA. If you have concerns about progress, address these during team meetings or call a special meeting. Ask for more frequent progress reports.
- **Dataset integration was performed at the incorrect level** – if you later determine your integration should have started at STDM versus ADaM, do not despair. Request additional resources for your team. Request more work from them and a committed timeline. Request progress reports more often—weekly or biweekly.
- **Unexpected results of Phase III (pivotal) studies/where results were inconsistent** – try not to panic. This is decision time. Request work on the integration be halted and schedule a meeting to discuss study results and to determine a plan of action. This will often require additional meetings. A well thought out action plan could mean the difference between getting approval versus getting integration done on time only to have the approval denied. Include the statistician responsible for integration in meetings about potential post hoc analyses. Do not give up if Phase III results are less than expected without careful consideration and analysis of data on what to do.
- **Rescue** – at what point do you consider a rescue? If things are not going well with your CRO during integration, in general, it is not advised to switch half-way through

the process. If you do decide to bring in a rescue team, it may be easier for the new CRO partner to start over at the beginning–versus going through all the data to assess each study for errors. Either way, switching CROs will likely delay the integration timeline and submission to the regulatory agency. It is not an easy decision to make.

- **Refusal to file** – if you receive a refusal to file letter from the FDA, the reason(s) for the refusal will be identified, and your next step should be to meet with the FDA. In the meeting, you will receive further clarification and can come to an agreement with the agency on critical components. Again, you should include your statistician in this meeting.

## Conclusion

Creating the integrated summaries often requires summarizing years of important work. The integration needs to be thoughtful, well-planned, and progress and potential pitfalls should be well-communicated throughout the process.

As drug developers, you are encouraged to develop an integration plan and to ensure oversight of the plan.

- Start early
- Include your statistician at end of Phase II and pre-NDA meetings
- Use an experienced data integration team and medical writers
- Require thorough data integration reviews with frequent consistency checks using Pinnacle 21 validator and Proc Freq statements
- Make sure the reviewers guide includes exceptions and explanations
- Schedule regular team meetings where progress reports are required and action items are assigned

At Synteract, we draw on three decades of experience in bringing clinical trials to life. Contact us today for more on how we can help with your integrated summaries and any and all critical aspects of your clinical trials, right from the beginning.