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Integration Contemplation: Considerations for a successful ISS/ISE from Planning to Execution

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ABSTRACT

During the clinical development of an investigational drug, there are many potential reasons for ceasing advancement of the product. However, when the drug is successful, part of the submission process for approval by regulatory agencies, like the FDA, will require integrated summaries of safety and efficacy (ISS/ISE). Even if every study participating in the integration have achieved their goals to perfection, they are ultimately not designed for the purpose of integration, and the pooling will present challenges. Thus, for proactive, and perhaps optimistic, study planning based on the assumption for the drug to be successful, it would be prudent to plan ahead for an ISS/ISE submission.

Programmers tasked with integration of various studies often find that they are not immediately suitable for integration, which presents various technical challenges. In this paper, we will include multiple references to technical guidance documents that will enable solutions for anticipated problems programmers may encounter.

Programming managers may be further challenged with determining how to mitigate some of the programmers' technical issues, and minimize the time required to complete the work. We will also present different strategies to streamline the integration process by anticipating problems and preventing them when feasible.

INTRODUCTION

Clinical drug development is a long and arduous process comprised of many steps and multiple contributing parties, all hoping that they will eventually be able to collectively push the investigational product over the regulatory finish-line; successfully gaining approval and making the drug available to the patients who need it most. There is still much work to be done once a drug has gained post-marketing status and safety monitoring begins, but this is beyond the scope of this paper.

As with any long-term goal, the path to success is rife with opportunities for things to go awry – there could be issues enrolling the number of subjects needed based on the protocol resulting in an underpowered trial, flaws in the study design could result in not collecting the correct information needed to support certain claims, or perhaps everything could run perfectly until the product is ultimately deemed not clinically efficacious based on reporting results. However, despite these potential challenges, many people still dedicate themselves to these efforts, keeping a singular goal in mind – approval of a successful drug by regulatory agencies, and the opportunity to provide the drug to more patients who may benefit.

The FDA considers Integrated Studies of Safety and Efficacy (ISS/ISE) to be critical components of a marketing or licensing application. Therefore, ISS and ISE are required in applications submitted to the FDA in accordance with regulations for New Drug Application (NDA) submissions. Additionally, though not strictly required for Biologic License Agreements (BLAs), it is expected by the Center for Biologics Evaluation and Research (CBER) so is best considered for those situations as well.

As the clinical process can be quite difficult, not every investigational product will continue development to the point of requiring an ISS or ISE submission. However, to – perhaps optimistically – take initiative, it is prudent to plan as far ahead as is feasible for these submissions in all cases. With early consideration certain problems that can arise in these submissions could be more easily mitigated or avoided altogether.

Integrated submissions, by definition, require a pooling of all trials that were ever conducted in association with a particular compound. It is notable that even if each study participating in the integration has achieved its goals to perfection, because studies are not designed for the purpose of integration, the pooling will present challenges. In this paper, we propose two categories of solutions, compile and present technical resources that contain guidance for handling integration problems when the study planning did not evade the issues, but also propose certain considerations for study planning that aim to bypass specific issues. We intentionally excluded legacy data, or data with no CDISC applied, because they can be so vastly different that we did not feel we could make helpful recommendations for those specific cases.

INTEGRATION STRATEGIES (STRENGTHS AND CHALLENGES)

Reviewing the available literature, it is notable that determination of a pooling strategy is an important discussion. This is not a coincidence, determining a pooling strategy is integral to the task at hand. Although there exist myriad practical variations by which pooling could be achieved, they can be cleanly condensed into one of three general strategies.

Prior to detailing the strategies below, note certain prudent advice from Gao, 2023. The programming intention should be to perform sufficient pooling, or in other words “pooling adequate but not excessive data to fulfill all the required analysis.” Keeping this goal in mind, one should also consider another point from the paper that the question to start with should not necessarily be “how to pool” but rather “what should be pooled”. As an example, an ISS summary may not require laboratory toxicity grades that had originally been included in the studies CSR ADaM programming, rendering the presence of toxicity grades futile. Conversely, consider the situation where laboratory toxicity grades were not required for the creation of individual CSR ADaM datasets, but are indeed required for the integrated analysis. Either case may lead to a separate, and optimal, pooling strategy. Once the programmer understands what exactly is required, and how the specific candidate studies for integration are designed and programmed, the pooling strategy should become clear. Thus, any of the following may be the preferred method, provided analysis needs are being met without any superfluous data mapping.

POOLING STRATEGY 1

The first pooling strategy involves harmonizing the individual SDTM datasets and then pooling those datasets together to produce the integrated ADaM datasets, before ultimately creating any necessary reports:

Pooling Strategy 1: Individual CSR SDTM(s) used to directly create integrated ADaM

Figure 1

POOLING STRATEGY 2

Another option for beginning from SDTM involves pooling the data at SDTM level. Thus, an integrated and harmonized set of SDTM datasets will be used to create the integrated ADaM datasets.

Pooling Strategy 2: Individual CSR SDTM(s) used to create integrated SDTM, which in turn is used to create integrated ADaM

Figure 2

POOLING STRATEGY 3

Finally, there is also an option to begin with ADaM datasets. Utilizing this strategy, individual ADaM datasets can either be harmonized and then pooled together, or pooled together and then harmonized. In either case, CSR ADaMs are used to directly produce the integrated ADaM datasets:

Pooling Strategy 3: Individual CSR ADaM(s) used to directly create integrated ADaM

Figure 3

As alluded to earlier, there is no optimal pooling strategy that applies in general. However, depending on the particular characteristics of the specific integration being performed, there will be an optimal pooling strategy for each case. Below are a few examples.

MUSINGS ON POOLING

Donthi (2019) describes starting from SDTM as the easiest way to spot inconsistencies between the candidate studies for integration, and this advantage could be argued for either Pooling Strategy 1 or 2. This approach is not necessarily "easy", but it does offer all data available for the study to be assessed, and therefore leads to the most complete harmonization. Additionally, information may be required for the integrated analysis that was not needed for the individual studies' analyses, and therefore is not included in the CSR ADaM datasets. In this case starting instead from SDTM datasets provides the most straight-forward opportunity to map the required data. If the pooling strategy ultimately chosen does not begin from the individual study CSR datasets, the process to include the additional data required for analysis would become much more convoluted to include and document.

Patel and Tinazzi both share the sentiment that starting from SDTM provides the sponsor higher flexibility to attain standardized and harmonized data. Tinazzi cites an additional advantage that this approach allows alignment of algorithms, controlled terminology, and data domains, and Jenet appreciates that it reduces programming efforts at ADaM level. We agree that SDTM does offer these advantages, however it may increase the workload because it would require programmers to work with both SDTM and ADaM datasets. For this reason, we strongly suggest that an assessment is performed prior to the start of work, as soon as there is a stable ISS/ISE SAP, to determine if the individual study CSR ADaM datasets contain adequate content for the integration analysis, based on how much overlap exists between the analyses described in the respective SAPs.

Unsurprisingly, the reviewed paper conclusions do not necessarily agree in their findings about the pooling strategy beginning from SDTM – Guettner claims that a benefit to this approach is that only limited time and resources are needed, while Donthi disagrees with this opinion, claiming that this approach is more time-consuming. Tinazzi makes a point that does support Donthi's claim – this approach would require additional datasets, define-xml, and cSDRG be created for the integrated SDTM. An unspoken advantage to not creating an integrated SDTM is that each individual SDTM has already been submitted as-is, thus no additional documentation would be required. It is also of note that while Guettner and Patel both agree that this strategy produces pooled analysis datasets that are easily traceable back to the single study SDTM as all datasets are within the CDISC standard. With that said, Guettner himself does also mention that it can be difficult to achieve traceability back to any single study's results if different algorithms are used for different derivations. The variety of opinions regarding advantages and disadvantages here strengthen our resolve: despite there not being an optimal strategy for general use, based on the specifics at hand there will be an optimal strategy to choose for each specific integration case. This further solidifies the need to appropriately assess and then plan for any integrated summary.

Regarding the integration strategy beginning from the ADaM datasets (Pooling Strategy 3), multiple authors overlapped in their experienced disadvantages. Both Donthi and Agnithotri cited the issue of needing to wait until all individual ADaM datasets are finalized before being able to begin work on the integration, thus building in a bottleneck that could be avoided if programmers were instead starting from SDTM. Additionally, Agnithotri mentioned that it often requires extensive documentation to explain the transformation and standardization, which was also a point that Patel agreed with about this strategy. Patel and Agnithotri also shared the opinion that a substantial programming effort is generally required to achieve the standardization effort. Like the first two strategies, Pooling Strategy 3 did garner mixed reviews from the authors of the reviewed papers. Tinazzi appreciated the clear traceability of this strategy and the additional advantage of this approach that original dictionary versions have a clearly specified place to be stored in standard variables in OCCDS. This remark is notable as he cited this as a disadvantage for the approaches beginning from SDTM, as in those cases there is no standard location to store the original dictionary versions, so there would need to be consideration of where those variables should be stored if Pooling Strategy 1 or 2 were used instead. However, regarding a situation where SDTM and ADaM are still being developed, Guettner offers, "*In theory [this] strategy would be traceable from the integrated analysis datasets (ADaM) back to the single study SDTMs. But as the SDTMs were created parallel to the analysis datasets this is only possible after a reconciliation of the analysis datasets with the SDTMs*". We interpreted this to mean that traceability will be extremely difficult to achieve while the SDTMs are still being developed. While this is a disadvantage that would eventually resolve itself when SDTM is completed, certain items may be challenging to program and validate if traceability is unclear.

In addition to the mixed reviews, we must share some additional positive findings included in the literature. Using Pooling Strategy 3 does offer flexibility to handle inconsistencies between studies since, as Donthi points out, ADaM standards themselves are more flexible than SDTM, and this can help mitigate issues caused by different study designs. Guettner also lists multiple advantages to this approach. This strategy allows the opportunity to leverage derivations previously applied to the individual CSR ADaM datasets (if that information is required for analysis). It also mentions that in the case where ADaM datasets are adhering to the same standards, the only items that need to be added are variables and records for the integrated database. We would like to argue here that this caveat will not apply to all integrated studies – oftentimes the programmer tasked with leading an integration will be pooling studies that span a large amount of time and potentially have variances in the ADaM standards that are applied. This once again strengthens the argument that the decision of the pooling strategy will and should be heavily determined by the combination of the design of the candidate studies and the needs of the integrated analysis.

CONSIDERATIONS FOR HARMONIZATION

RATIONALE

Through consideration of the collected literature, a clear theme emerged among the pooling strategies – prior planning of an integration more effectively leads to success than picking a strategy without consideration and running into the noted pitfalls. This throughline also runs through the considerations for data harmonization. For example, let us discuss the harmonization of Controlled Terminology.

Any programmer who has experience with submissions should be aware of the FDA's Data Standard Catalogue (DSC). The official and most up-to-date version of the guidance can always be found on the official FDA website. It will contain information regarding what versions of various standards and controlled terminology are currently required, or otherwise acceptable for use, and will sometimes reflect the end dates of when support ends for any particular standard.

As of the publishing date of this paper, the current FDA DSC describes that for any studies that began on or after March 15th, 2019, it is a requirement to apply the current (as of the study start date) version of MedDRA dictionary terms to Adverse Events, with no end date listed for this requirement. Note that for studies beginning prior to that requirement date, the only requirement per the FDA DSC is that MedDRA version 8 or earlier must be applied. This provides another opportunity to plan for and consider the best approach – if the integrated analysis will consist of a majority of studies which were started before the

requirement date, this is a wonderful opportunity – the programming lead could make the decision to apply consistent dictionaries to each of the individual studies while they were ongoing – this is still adhering to all FDA requirements, and will make harmonization steps easier come the time of the integration.

Controlled Terminology (CT) versioning requirements can also be found in the DSC, and it is recommended to take a similar approach with those. Kirby makes a point for this in his paper from 2019 – to the extent practically possible, the same CT version should be used in as many studies as plausible. Consider that this may not look like adhering to the latest and greatest CT version for every new study, it could in fact be more effective to utilize a previous version that is still within regulatory guidelines. This example is proof that maintaining a clear understanding of the ever-evolving FDA guidance can provide an ability to be efficient and agile in the application of standards.

Controlled Terminology and Dictionaries are not the only items to consider for harmonization. When stacking datasets, it is only natural that certain steps need to be taken to make sure that variable values are not truncated, derivations are logically consistent, and any variables with the same names in different studies are scrutinized and determined to be the same or are otherwise handled appropriately. The converse scenario is just as problematic but can be harder to catch – programmers must look out for variables that have the same meaning and function but happen to have different names. In best practice, if this variable was required for the integrated analysis, it should be rederived using a singular name in the integrated datasets. From a programming team perspective, only so much can be done in these cases to technically apply these updates. Even from a management perspective, only so much can be done to prepare for an integration, as any individual studies do need to be adhering to CDISC standards for their own individual submissions. Consider the dataset size requirements described in the FDA's Study Data Technical Conformance Guide (SDTCG):

"The allotted length for each column containing character (text) data should be set to the maximum length of the variable used across all datasets in the study except for SUPPQUAL datasets. For SUPPQUAL datasets, the allotted length for each column containing character (text) data should be set to the maximum length of the variable used in the individual dataset."

The goal of this stipulation is to significantly reduce file size, which is reasonable, as the FDA will only accept xpt files. However, it could practically lead to individual candidate studies for integration containing common variables of many different lengths, which would ultimately lead to truncation if care were not taken. The resolution for this is programmatically simple – when combining any datasets for the purposes of pooling, set any variables in common to the maximum allowable length for SAS data transport files (200 characters) and retrim any variable lengths prior to outputting the resulting dataset.

Harmonizing programming logic and derivations can require more effort to resolve, however some pains could be averted with prior planning. Beware Donthi's warning, "Different variable content could result in severe programming errors as they present different meanings." In practice, this may look like an analysis flag being used differently in individual studies. If a programmer were to stack those without scrutinizing the logic, the flag would no longer be consistently assigned to all patients and will likely not provide the correct records for analysis of the integrated datasets. Donthi does share certain guidance to help alleviate this – at the time the paper was published the current version of CDISC ADaM Implementation Guide (IG) was 1.1, though this does remain true in the most recent version 1.3 as well – the variable "Analysis Flag zz" as specified in the IG can include additional descriptive text in the variable label, and its recommended to leverage this so that it is more visually apparent that there is a difference in logic upon the stacking of the datasets. Programming management potentially has an opportunity here to utilize this allowance from the IG as a requirement– implementing this as a company-standard could be a helpful planning step in making the lives of programmers easier.

Expanding on this, though it would take effort to plan, to use consistent CT, all ADaM variables could be predefined and consistent across all studies. This could be leveraged to resolve the inconsistencies in analysis flags discussed above. For example, while not required by the implementation guide, if common derivations are used for analysis flags, it is possible to develop a standard within your company of always using the same analysis flags for the same analysis reasons. In specific cases, this would still require the derivation of a new flag, when this has never been done before. However, it would ensure that for scenarios where integration is needed, the work of reviewing these common variables would already be

completed, as they are always implemented with standard definitions. This is another example of a planning step that could be implemented to ease the job of programmers when it is time to do the work.

GUIDANCE

Per the warnings above about truncation and variable harmonization, it's recommended to perform a PROC CONTENTS on any common variables. Checks on all variable attributes should be performed to ensure prevention of future programming errors and warnings. Agnihotri specifically calls for performing this in addition to other helpful guidance included in the reviewed paper – including the harmonization of STUDYID and USUBJID, reference start and end dates, as well as other technical details for re-evaluating and re-deriving key analysis variables.

In the case that Controlled Terminology does need to be updated to gain proper harmonization, Gao recommends a practical piece of advice to set up a codelist look up table in advance. Mapping codelist values that may have otherwise been time-consuming can still be planned ahead for by creating a utility macro to import a codelist file with a catalog of any formats that will need to be applied to the data. Agnihotri also adds that in cases where for some reason the CDISC CT could not be applied to all contributing studies, the details should be specified in the Reviewer's Guide.

Regarding Donthi's recommendation above [see section *Rationale*] to include a meaningful descriptor on common variable labels, this choice can be helpful, but care will still need to be taken with assigning the variables in the integrated data. The same paper notes that the programmer working on integration datasets should verify with the project statistician whether each iteration of ANLzzFL is even intended for inclusion in the integration – keep in mind that the needs of the individual studies will likely not match the needs of the integrated summary and there is possibility these would need to be revisited and reassigned with different logic.

Donthi additionally recommends updating each of the dictionaries to a single version as the first step to programming any integration. Agnihotri shares the sentiment, stating that in the case that the latest MedDRA version is applied to only one contributing study for an integration, all other studies should be upgraded to this version. Since new versions of coding dictionaries are released regularly, it is incredibly likely that there will be some differences in versions applied to candidate studies for integration. We agree with the authors and recommend avoiding downgrading dictionary versions because more studies have an older version; while the point of this paper is to urge you to find efficient and creative solutions for completing your integration, new versions of coding dictionaries tend to include additional terms which do not have an equivalent in the old version, so down-versioning is not generally a practical solution. With that said, mapping to a consistent dictionary version is sometimes not possible based on data collection at the time. For example, indication may not always be collected and may be necessary to apply the correct dictionary term, highlighting the need to scrutinize the decision per the common level of usability based on the collected data. Keeping this in mind, during study planning, it should be carefully considered what dictionary version to apply to any individual study, as it will have downstream effects come the time of integration. Agnithotri notes that like the guidance for CT above, details regarding dictionary versions should be specified in the Reviewer's guide.

INTEGRATED OUTPUT

The observant reader may have noticed that this paper has not covered information on integrated standards. The reason for this exclusion is because at the time of this publication, despite the extraordinary efforts of the ADaM development team, they have not yet been able to publish an integrated standard that is agreeable to the industry and regulatory agencies. With that said, there is ongoing development of templates for integrated cSDRGs and ADRGs by a dedicated PHUSE working group. Currently a draft icSDRG example is completed, and there is progress on the associated completion guideline. There are current plans to develop an iADRG template example and related completion guideline. It may be wise to continue to watch the progress of this group and utilize the guidance they produce as it is completed.

Even given the lack of integrated standards, the work can be completed leveraging existing CDISC standards at the study level. Naturally, this is limited because CDISC standards are designed to support one study at a time.

At the time of completion of programming activities – including at least determination of pooling strategy, development of specifications, creation of dataset and TLF programs, production of necessary datasets and the related reporting efforts – you must decide what to do with everything that has been prepared. Thankfully, you can follow the guidance explained in the Guidance for Industry FDA Document, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*. Within this document you will find explanations of how to read the general eTCD, and examples, so you understand how to package the integration. Based on this guidance you will be able to place your integrated summary in the appropriate Module – while it is specified that Module 5 (section 5.3.5.3, Reports of Analyses of Data from More than One Study) is the appropriate location for ISS and ISE and additionally has no space limitation, certain allowances can be made for placing items in Module 2. Like most other items considered in this paper, the ideal integrated file structure will likely depend on specifics about the submission, so the literature should be reviewed and the best decision for your integration should be made.

CONCLUSION

Integrated summaries serve as a vital tool in presenting comprehensive, cohesive, and scientifically rigorous information to regulatory bodies. The papers reviewed present several different strategies to create the integrated datasets; the tasks are quite similar, but no singular method stands out as a general solution. Rather, after careful consideration of the study design of the candidate studies for integration and review and understanding of the goals of the integrated analysis, there will be an optimal strategy in each case. While there is much that cannot be controlled, proper planning can ease certain steps and ultimately make the integration effort more efficient. We implore that you do not attempt to derive a "standardized" approach to integrated studies, as best practices in one case may not carry over to another. However, by maintaining an understanding of current standards and requirements versus recommendations, you can make the best decisions for your specific integration and tackle it more effectively.

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