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Striking a Balance: Adoption of Analysis Results Metadata in Early Stage Development Studies

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ABSTRACT

The analysis results metadata (ARM) contains substantial information on primary and key secondary results that can quickly orient the reviewer to understand reporting programs and input variables and dataset that contributed to the analysis.

The benefit of the ARM is apparent when it is included in a filing; however, the submission milestones (e.g. NDA or BLA filing to FDA) are not always foreseeable in early stage studies. It has been a discussion whether to assign resources early to implement the ARM as a tactical decision regardless of future outcomes.

The focus of this paper is to share Merck's approach to pilot delivery of an ARM for a subset of early stage development (ESD) studies. The paper will address the ARM for selected types of studies; proposal for selected tables, listings, and figures; and manage risks, if any changes occur in the strategy. The general principle of the approach can be extended to other types of studies.

INTRODUCTION

Regulatory reviewers expect data flow traceability from the collected data to the analysis datasets and the results displayed in tables listings and figures (TLFs). While the principles of SDTM and ADaM implementation promotes this linear data flow approach, it is the Analysis Results Metadata that helps to connect the most critical analysis (e.g. primary endpoint) back to the input datasets, programs and documentation to support results and to strengthen validity.

While several regulatory health authorities expressed the usefulness of the ARM in submissions, currently regulatory guidances have not specifically defined the extent of the implementation of the ARM. The following questions can be raised in this situation: Is it helpful to include the ARM for all submitted studies or is it more tactical to implement the ARM only for a subset of clinical studies? From a sponsor's perspective, how do the companies define the details in the ARM especially in early stage clinical studies when there is no certainty of a submission? Is there a benefit in adopting the ARM early in the clinical development?

The objective of this paper is to present a proposal which Merck plans to implement for creation of the ARM in ESD studies using information available from CDISC and regulatory guidance. Our proposal will not be applicable to some therapeutic areas with unique characteristics, such as early oncology or other exploratory studies not specifically intended for submission. This paper will examine regulations, discuss the benefits and risks of adopting the ARM in the early stage studies, and review a proposal to pilot the implementation of the ARM for a subset of ESD studies while aligning in accordance to available regulatory recommendations.

CDISC RESOURCE AND REGULATORY DOCUMENTS

Before drafting the proposal to create the ARM for most of early stage studies, a team of statistical programmers, statisticians, and quantitative scientists (pharmacometrics) had to first understand the purpose and value of the information presented in the analysis results metadata. To examine this, the team had to learn the intent of the ARM design when it was introduced by CDISC and then finally interpret FDA's and PMDA's position in regulatory documents to date.



CDISC ANALYSIS RESULTS METADATA SPECIFICATION

CDISC released the ARM Specifications (Version 1.0) for Define-XML (Version 2.0) in January 2015 as a standardized XML schema. The ARM was designed to be a machine-readable metadata that would be included in the ADaM analysis package. The primary purpose is to describe the relationship between the key results and the information describing the reason for performing the analysis, the dataset(s), programs and selection criteria(s). Although specifications for generating the ARM within the XML schema is documented in the specifications, sponsors can still provide an ARM as a supplemental PDF document.

The benefit to providing the ARM supplies end to end data traceability while giving the reviewers a means to trace results from the displays back to the programs, datasets, statistical analysis plans and supportive documents. The availability of the ARM in a submission can quickly orient a reviewer to the key (sometimes complex analysis) in a study, integrated pooled analysis, or submission. To enhance the reviewer's experience, the define.xml hyperlinking feature allows reviewers to navigate within the XML and to the external displays and references outside the ARM.

FDA EXPECTATIONS

According to the FDA Data Standards Catalog, FDA requires sponsors to submit Define-XML version 2.0 for all studies that started after December 16, 2016; however, the inclusion of the analysis results metadata is still considered optional. Although the FDA Guidance and Study Data Technical Conformance Guide stresses the need for study traceability to enable reviewers to relate the displays to the underlying data, neither FDA documents differentiate between what types of studies (Phase I-III) would be beneficial to include the ARM. Though, the ARM could be extremely beneficial to facilitate the review of the analysis of the primary and key secondary results.

PMDA EXPECTATIONS

For submissions to Japan, PMDA requests applicants to submit the ARM to facilitate reproducibility of the primary results and to provide navigation features that allow reviewers to access the analysis datasets and programs quickly. PMDA strongly recommends that sponsors create the ARM for all submissions after March 31, 2020. Furthermore, PMDA specifically indicated that clinical pharmacology studies include the ARM if it supports the main results of the clinical study using CDISC standard formats.

REST OF WORLD EXPECTATIONS

Aside from submissions planned to the US and Japan, regulatory agencies in other countries, including EMEA and China have not required the use of an ARM. Since most countries do not require datasets, these countries have not exercised the full potential of study data standards, including the analysis results metadata.

REGULATORY INTERACTIONS

While there is no regulatory documentation differentiating study data standard deliverables applied in early or late stage studies, industry sees that FDA views these two components as an integral part of a submission package. To further understand the review, sponsors have leveraged historical therapeutic area experience to understand the needs and to give reviewers a better review experience. Drawing feedback from submissions or prior interactions, sponsors can use this knowledge to author the ARM and direct reviewers to the main analysis.

Generally, sponsors can request a stage gate meeting to discuss issues or obtain feedback from health authorities. For early stage studies, the Pre-IND meeting is an opportunity for sponsors to receive direct FDA confirmation about the drug development plan. The focus is on specific regulatory and/or scientific issues that would otherwise result in a clinical hold. The granular and technical details such as the content of ARM cannot be the intended focus of the meeting.

An alternative to discuss technical details in early phase studies is Type C Technical Meeting which allows sponsors to seek clarification on the study data standards implementation that enables future review. In practice, sponsors do not exercise this option without consulting and consolidating all questions before submitting a request. And in some cases, studies may have already been initiated before the meeting is honored.

CONTRASTING BETWEEN LATE AND EARLY STAGE ARM IMPLEMENTATION

If we follow the principles of the ARM implementation as defined by CDISC and regulatory documents, which is to display tables and figures that support the primary, secondary or exploratory endpoints or contain complex analyses, one could say it is more inclined to the characteristic of the late stage development studies.



Safety endpoints such as events of special interest AEs, Tier 1 AEs, Tier 2 AEs are well-characterized, and they are part of secondary objectives/endpoints. It is straight-forward to identify table outputs for specific efficacy and safety endpoints in LSD studies. On the contrary, ESD studies do not have that level of granularities in safety as it is unknown and most of the studies start with healthy subjects. Hence presenting all safety (including labs) tables as a part of secondary endpoint in ARM seems redundant while the safety information is present or will be observed in LSD studies.

Moreover, there are several pharmacokinetic (PK) endpoints as the primary or key secondary endpoint in an early stage study that are the main interest for clinical pharmacology. Therefore, to avoid an over-crowded ARM, a limited number of safety and PK outputs should be selected pragmatically for ARM in ESD studies to satisfy the primary intent of ARM. Also, the content of ARM in ESD should be closely consistent with the content of ARM in LSD, but not necessarily an exact copy.

In the initial ARM implementation pilot, teams within Merck are striving to follow a process regardless of the study phase (early or late). There are several challenges, risks and benefits that were raised during the planning of the pilot.

CHALLENGES WITH ARM IMPLEMENTATION IN EARLY STAGE DEVELOPMENT STUDIES

During the early phase clinical development, several types of studies, including First in Human (FIH) studies for a candidate compound, are examined to see if the product has potential for addressing an unmet medical need with a differentiating commercial aspect in today's drug market. It is here that so many compounds fail to enter late stage (Phase II/III). Even compounds that advance to Phase II have a high rate of disappearing from a sponsor's portfolio. If there is a successful Phase II program, only a few products enter Phase III and even fewer compounds go to a regulatory submission.

Once a planned submission is identified, sponsors gather all the necessary components to build a submission. At this juncture, all the key ingredients to support a meaningful review are staged and assessed for completeness against regulatory requirements, including study data standards (case report forms, SDTM, ADaM and ARM) across the early and late stage program.

CHALLENGE #1: TIME LAPSE

There may be a prolonged time lapse (e.g. up to 10 years) between the FIH completion and the final submission. Several early stage studies such as FIH or Drug-Drug Interaction (DDI) studies may have long completed with the creation of the CSR while the Phase II or III studies are still ongoing. If sponsors need to entertain retrospectively applying the ARM or other elements (e.g. ADaM datasets, Define.xml) to support a complete submission package, it is a time-consuming task to apply updates to a current requirement for a single study, let alone 15+ studies in an early development program. This is a substantial risk and cost that involves contracts and staff that may no longer be active.

As the Merck team defined the ARM implementation pilot for early stage development, the team proactively considered modeling the ARM consistent with late stage studies. Collectively, the team recognized the substantial cost and associated resource issues affront to prepare study packages with ARM for studies in early phase while no submission decision made. However, with the volume of studies, the Merck team determined that the benefit to create the ARM in advance outweighed the cost of performing task to create ARM retrospectively.

A question can be asked: When is the right trigger point to start preparing the ADaM package including the ARM for early stage studies? Creating the ARM at the start of Phase II or End of Phase II meeting with regulatory agencies could be considered as a reasonable choice. The triggers should be discussed thoroughly within the sponsor to minimize retrospective tasks discussed in this paper.

CHALLENGE #2: FULLY OUTSOURCED STUDIES

In early stage development, there are several studies which could be conducted by CROs. These types of studies are referred to as fully outsourced studies. For these types of studies, the ARM and all other deliverables should be completed along with the CSR preparation. There is an initial expense for having a CRO to prepare the analysis deliverable, including ARM. However, the initial cost pays off if the compound is successfully submitted for a filing. One can argue that the work can be done once the compound shows its success in the late stage development. It is possible that the partnership may not exist in future or the sponsor may not be able to retrieve all the details from the distant past. It will be a time-consuming task to retrospectively perform the work and the associated cost can increase exponentially with operational difficulties. Hence, the overall cost and resource burden can be saved by using the discussed approach in the long-run.



CHALLENGE #3: SELECTING THE CONTENT IN ARM FOR ESD STUDIES

In most ESD studies, there is no single endpoint or well-defined endpoint (unlike LSD studies) that can be presented in ARM. There is a general objective which encompasses several endpoints including safety, PK, and in some cases, PD also, so it is not an easy task to follow verbatim the general principle of including primary and key secondary results. It seems redundant to include all safety and PK tables in ARM defeating its purpose. Hence a pragmatic approach in line with general principle to select the content of ARM in ESD studies is a challenging and thought-provoking task.

GENERAL APPROACH FOR CREATING ARM IN ESD STUDIES

As a general expectation, the ARM adoption is not intended to be implemented for all displays in the submission, but rather a subset of key analysis tables or reserved for complex analysis. The ARM should only identify outputs that aid reviewers to gain a fair understanding on the study results. The efficiency and usefulness of the ARM rely on a well-thought selection of outputs. A pragmatic approach was utilized to come up with the proposals for ARM in this paper. The proposal is based on the criteria outlined below.

1. The model-based pharmacokinetics (PK) and/or pharmacodynamics (PD) analyses related to primary and key secondary objectives/endpoints should be included in the ARM. Any tables corresponding to hypotheses testing (Bayesian or p-value/confidence interval based) should be included.
2. The descriptive summary (PK/PD/Safety labs) outputs seem less relevant to be included in the ARM. The listings and data dumps are excluded from the ARM.
3. To be consistent with LSD studies, baseline and disposition tables should be included.
4. For safety endpoints (AE), the number should be limited to one or two tables. For proof of concept type studies (with patients), the number of safety tables could be higher.
5. No tables for exploratory analysis (model-based or descriptive) need to be presented in the ARM.
6. No figures seem necessary for the ARM. It may be included if it is critical and directly linked to the primary endpoint (e.g. oncology studies).
7. No tables for vitals, ECG and other safety measures need to be present in the ARM.

Note that, all the protocol specified analysis are included in CSR. If there are any concern regarding the study results and conclusions, the reviewer should consult the CSR. The ARM is not a repository for all output-generation details, but rather a document to facilitate a quick and brief review.

The discovery/experimental medicine studies, pre-clinical studies, platform trials are beyond the scope of this document. However, those studies can follow the similar pragmatic approach based on general principle for the ARM documentation.

PROPOSALS FOR ARM

In this section, we will introduce a proposal for the ARM for the major types of ESD studies. Our proposal encompasses a majority of the ESD clinical studies, which are generally required and included in submission. The proposal for ARM documentation below may change based on any regulatory requirement or due to a unique feature of a study.

FIH SINGLE ASCENDING DOSE (SAD) OR MULTIPLE ASCENDING DOSE (MAD) STUDIES

First in human (FIH) SAD and MAD studies are conducted to understand the safety, pharmacokinetic (PK) and pharmacodynamic (PD) properties of a drug at least initially in the setting of normal healthy volunteers. If SAD & MAD studies are combined into one protocol, the list below could be repeated for each part of the study. A portion of results from these studies may ultimately go into the drug label or at minimum be referenced in the product label.

The list below describes which tables should be included in the ARM documentation.

- ❖ Baseline Table
- ❖ Disposition Table
- ❖ PK and/or PD endpoint as primary or key secondary (e.g., C24hr > xx; PD measurement > yy%;
- ❖ Safety Table (AE >0% SOC/PT table)



DDI, FOOD-EFFECT (FE), FORMULATION BIOCOMPATIBLE (FC)/ BIO-EQUIVALENCE (BE) STUDIES

The primary purpose of a Drug-Drug Interaction (DDI) study is to assess pharmacokinetics/ pharmacodynamics and safety after co-administration of two or more drugs and to explore perpetrator and victim potential (liver enzymes and transporters). It also helps to determine inclusion / exclusion criteria for patients. Similarly, Food-Effect (FE) studies investigate effects of food on PK of the drug of interest, thus providing a clear direction on how to take medicine (with or without food). The results are included in the product labeling. The formulation comparison studies assess the PK of different formulations of the drug of interest. A bio-equivalence study (BE) is conducted to establish equivalence of two formulations using a framework of either clinical or predefined similarity of selected PK endpoint (e.g., AUC and Cmax). The results from some of these types of studies go into the product label.

If there are more than one analytes or compounds of interest in the study, the list below should be followed for each analyte/compound separately (except baseline and disposition). The list below describes which tables should be included in ARM documentation.

- ❖ Baseline Table
- ❖ Disposition Table
- ❖ Primary Analysis Table (AUC and Cmax comparisons)
- ❖ Safety Table (AE >0% Incidence SOC/PT table)

ADME STUDIES

ADME studies are typically conducted on 6 healthy male subjects, and with a radioactively labeled drug. They are conducted for two purposes (1) to identify metabolites in plasma and excreta (urine and feces) in humans and (2) to establish mass balance. In general, non-model based descriptive results are provided in this type of study. The list below describes which tables should be included in ARM documentation.

- ❖ Baseline Table
- ❖ Disposition Table
- ❖ Safety Table (AE >0% Incidence SOC/PT table)

QT STUDIES

Thorough QT (TQT) is a safety study, performed by single high dose administration of the study drug to evaluate effects on cardiac repolarization. It is typically designed as single-dose administration of study drug, placebo, and positive control (moxifloxacin) in a randomized 3 or 4-period crossover design. Concentration QT study (PK-QT) is designed to investigate QTc exposure response and it may suffice to surrogate a TQT study. This type of study is required by regulatory agencies unless a waiver is granted. The list below describes which tables for a TQT should be included in the ARM documentation. The list for PK-QT studies is still under discussion.

- ❖ Baseline Table
- ❖ Disposition Table
- ❖ Primary Analysis Table (QTcF comparison table for primary and secondary hypotheses)
- ❖ Repeat above if QTcP is appropriate for correction
- ❖ Categorical analyses for QTcF (or QTcP if it is appropriate correction)
- ❖ Safety Table (AE >0% Incidence SOC/PT table)

PROOF OF CONCEPT ESD STUDIES

There are Proof of Concept/Biology (PoC/PoB) studies with patients performed in Early stage development. These studies usually have clearly defined PD or Efficacy based endpoints as primary and/or key secondary endpoints. If there is any event of special interest AE tables, it should be considered whether to include or not. The list below describes which tables should be included in the ARM documentation.

- ❖ Baseline Table
- ❖ Disposition Table
- ❖ Primary and Key Secondary PD Endpoints
- ❖ Safety Table (Overall AE Summary)
- ❖ Safety Table (AE >0% Incidence SOC/PT)
- ❖ Safety Table for Events of Special Interest, if necessary



FUTURE EFFORTS

It is worth exploring the creation of a standardized ARM template for specific types of early stage studies as a part of a future endeavor. Once the standardized templates are established after incorporating possible regulatory and industry feedbacks, the creation of the ARM will be a time-saving and cost-efficient task in a submission strategy.

There are studies which are not covered in this manuscript. For example, proposal for an ARM documentation for abuse-liability studies, PK-QTc studies, Special population studies (Renal or Hepatic) are the next challenging step. In addition, if required by regulatory agencies, the ARM for non-clinical and pre-clinical studies, as well as experimental medicine studies, could be challenging task.

CONCLUSION

Both FDA and PMDA stressed the need for end to end data traceability to enable reviewers to relate the results back to the underlying data. When the Analysis Results Metadata is included in a submission, it adds value to the review experience by giving health authorities quick access to the supporting data and references. Current technical guidance does not provide a clear and specific outline of an ARM for ESD studies.

The drafted proposal for the ARM to be implemented by Merck in several major types of ESD studies can be utilized as a standard template in conjunction with the creation of ADaM deliverables. The proposal could be used as a starting point for different types of ESD studies (e.g. Hepatic or Renal studies, Abuse liability studies) as well. The feedback from regulatory agencies can evolve the ARM proposal that is fit for purpose.

The implementation of the ARM in ESD studies can be streamlined and made more efficient when there is early input from the regulatory agencies. As a result of a proactive engagement, sponsors can save time and cost without having to retrospectively develop the ARM just prior to a known submission. Early interactions enable sponsors to receive feedback on the interested analyses, content and rationale. Advance discussions with regulatory gives clarity on whether the data and package will support regulatory review.

REFERENCES

CDISC Analysis Results Metadata Specifications (Version 1.0) for Define-XML (Version 2.0), <https://www.cdisc.org/standards/foundational/analysis-data-model-adam/analysis-results-metadata-arm-v10-define-xml-v20>

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