Paper SI10

Automating the Analysis Data Reviewer's Guide (ADRG) in Early Stage Development Studies

Pranab K. Mitra, Ph.D., Merck & Co., Inc., Rahway, NJ, USA
Janet Low, M.S., Merck & Co., Inc., North Wales, PA, USA

ABSTRACT

The analysis data reviewer's guide (ADRG) contains concise information on protocol, analysis datasets, related conventions, and analysis programs that can quickly orient the reviewer to understand necessary details for reviewing analyses included in the submission package. It is a very useful part of the regulatory submission package. Automated documentations (standard text) of ADRG can be implemented in early stage development (ESD) studies during the preparation of submission deliverables. Since most of the studies in ESD are primarily based on standard safety and pharmacokinetics, standard text to narrate most of the details in ADRG can be devised.

The focus of this paper is to share a sketch of this approach with numerous benefits in ADRG (based on PHUSE template) documentation for ESD studies. It will substantially reduce time, cost, editorial errors and resource-burden during the submission activities. It can be used as a reference for outsourcing partners preparing submission packages.

INTRODUCTION

Regulatory reviewers expect data flow traceability from the collected data to the analysis datasets and the results displayed in tables, listings, and figures. While the principles of SDTM and ADaM implementation promotes this linear data flow approach, it is the Analysis Data Reviewer's Guide (ADRG) that helps to connect the most important information on analysis datasets, their locations, the list of submitted programs and related information. In short, it is brief documentation that helps reviewer to get quickly orient with the analysis datasets and its related information.

The benefit of providing ADRG is that it supplies necessary information for understanding analysis datasets while giving the reviewers a means to trace details of analysis back to the programs, datasets, and supportive documents. To enhance the reviewer's experience, ADRG includes hyperlinking feature that allows the reviewers to navigate within the document. It may be linked with external displays and references outside the ADRG as an optional navigation feature. Note that, the acceptable format of an ADRG is PDF to date.

The objective of this paper is to propose a framework for creating automated or standard text for the ADRG using the PhUSE template for typical clinical pharmacology studies such as single/multiple ascending dose studies, drug-drug interaction studies, bioequivalence studies, formulation studies, food effect studies etc. conducted in early stage development (ESD). Discovery/experimental medicine studies, pre-clinical studies are beyond the scope of this paper.

REGULATORY EXPECTATIONS

Although the ADRG is not a mandatory component in the analysis package for submission, both FDA and PMDA have recognized and recommended the ADRG in their respective Study Data Technical Conformance Guide as an important supportive document. When sponsors follow the PhUSE ADRG template, it provides reviewers relevant context and a single point of orientation to the analysis datasets.

Aside from the US FDA, PMDA, and currently China's National Medical Products Administration (formerly CFDA), the regulatory agencies in other countries, including EMEA have not required or recommended the inclusion of the ADRG in the submission package. And since most of these regulatory agencies other than those in the aforementioned do not require standardized data, they also have not exercised the full potential of study data standards, including the ADRG.

CONTRASTING BETWEEN LATE AND EARLY STAGE ADRG IMPLEMENTATION

If we follow the principles of ADRG implementation as defined by CDISC and regulatory guidance, which is to provide important details that support the analysis datasets, one could say it is beneficial in late stage development studies (LSD). It has been implemented in LSD studies to facilitate the review of complex analysis datasets; however, regulatory agencies do not differentiate between the requirements of the components in ESD and LSD studies for a submission. Hence, ADRG implementation is cascaded to ESD studies and regarded as an important document.

Unlike LSD studies, ESD studies have more commonalities in type and nature, and are mostly standardized across the pharmaceutical industry, except for a few special studies. The analysis datasets and endpoints are quite standard and typically common in ESD studies, and hence, ADRG can be written using certain generic text for standard analyses and endpoints. A typical ESD study will have ADSL, ADAE, ADEG, ADEX, ADLB, ADVS and most importantly, ADPC and ADPP, which have standard data structure based on ADaM principle (CDISC ADaM Implementation Guide). Therefore, with a limited number of standard datasets and standard endpoints, several sections in ADRG using the PhUSE template can be written in a generic way with a possibility of some edits during finalization. Of note, the number of ESD studies in support of a submission can add up to approximately 15 to 20, depending on the nature and therapeutic area of the compound.

BENEFITS AND RISKS

Once a planned submission is determined, sponsors gather all the necessary components to build a submission package. 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 other documentation such as cSDRG, ADRG, data definition [define]) across the early and late stage studies.

TIME AND COST EFFICIENCY

There are several types of clinical pharmacology studies such as single/multiple ascending dose, drug-drug interaction, bioequivalence studies, formulation studies, food effect studies etc. conducted in early stage clinical development. Since there are typically so many ESD studies included in a submission, having standard generic text populated in several sections in the ADRG document can save time, costs and more importantly lessen the editorial burden and potential for typographical errors. Resources will be better spent on dataset creation and preparation of ADRG documents within relatively shorter time. Time will also be saved on internal reviews, as standard generic text will not require a detailed review.

FULLY OUTSOURCED STUDIES

In ESD, some studies (referred as “fully outsourced”) may be conducted by contract research organizations (CROs). For these types of studies, ADRG and all other deliverables should be completed for submissions. If there is a templated version of ADRG for standard ESD studies, the CRO can use that while preparing ADRG. It will reduce the sponsor’s time and effort to review these documents. Moreover, it will help to standardize documentation for most of the part in ADRG across the CROs. It will enhance the efficiency in review process with a substantial reduction in time and associated costs.

RISKS

There is an associated risk of making errors due to “copy and paste” without understanding the text’s appropriateness. This is common in any templated documentations. Authors should be aware of this risk while using the generic text from the template for the ADRG of interest. However, with the volume of ESD studies, the benefit of creating generic text for ADRG outweighs the possible risks. A careful adaptation of the generic text should minimize the risk.

GENERAL APPROACH FOR CREATING ADRG IN ESD STUDIES

As a general expectation, the ADRG should be available for all studies included in the submission package. Its efficiency and usefulness rely on a well- thought and concise representation of details of the protocol, analysis datasets and its related information necessary for context. The PhUSE template introduced in 2015 is available for ADRG and has been well-accepted by regulatory agencies and pharmaceutical industries. Our proposal is based on that template and aligned with the well accepted PhUSE template. A practical, cost and time efficient approach was utilized to come up with the proposal below.

1. PhUSE template of ADRG should be used to provide documentation format to the regulatory agencies in a consistent and usable format (e.g. PDF format with navigation/hyperlinking).

2. Generally, ESD studies have a handful number of ADxx datasets, such as ADSL, ADAE, ADEG, ADEX, ADLB, ADVS and most importantly ADPC and ADPP. Hence, documenting details for fewer kinds of endpoints is needed.

3. The relevant and occasionally subtle details of analysis datasets should be presented in a clear, concise and unambiguous manner. Note that, protocol includes all design details and data definition (define) includes all analysis details. ADRG is not a repository for all protocol and analysis details including deviations; it is indeed a document to facilitate a quick and concise understanding of the analysis datasets under review.

DETAILED PROPOSAL FOR ADRG

We will introduce a proposal for generic text for the sections in the ADRG (based on PhUSE template) for the major types of ESD studies generally required and included in submissions: single/multiple ascending dose, drug-drug interaction, bioequivalence studies, formulation studies, food effect studies. In general, ESD studies have ADSL, ADAE, ADEG, ADEX, ADLB, ADVS, ADPC and ADPP. There may be instances of some other additional ADxx datasets which are not discussed here. The proposal may evolve based on any regulatory requirement or due to a unique feature of a study.

Section 1 - Introduction:

The introduction can have some generic text as appropriate. For example, Sections 1.2, 1.3 etc. can be made standard with a possibility of a few edits.

Section 2 - Protocol Description:

This section is protocol specific and cannot be made generic.

Section 3 - Analysis Considerations Related to Multiple Analysis Datasets:

Section 3.2 can be made generic by adding standard core variables and their descriptions. Authors can add additional variables as per analysis requirements. Section 3.4, 3.5 and 3.6 can contain generic text which could be standardized for most ESD studies. Other subsections in Section 3 can have some generic text, however additional details will be needed.

Section 4 - Analysis Data Creation and Processing Issues:

Sections 4.1. 4.2, 4.3 and 4.4 can be made generic with some amount of flexibility, mainly in Section 4.2 where data dependencies are described. Data dependencies in the majority of ESD studies are standard and straight forward.

Section 5 - Analysis Dataset Descriptions:

Section 5.1 can be generic with some flexibility. Section 5.2 can be standardized, and a generic tabular representation can be created with a possibility of minimal edits. Section 5.2.x where analysis datasets (ADxx) are described can be made generic and standard text (based on the sponsor's set up) can be used. Since the datasets are in CDISC ADaM structure, the generic representation of the details in text and table can be devised without much difficulty.

Section 6 - Data Conformance Summary:

Section 6.1 can be made generic. However, section 6.2 will contain Pinnacle 21 individualized study issues.

Section 7 - Submission of Programs:

Section 7.1 can be made generic provided the standard programs are set up by the sponsor or CRO. Section 7.2 could be made generic, although it would require standard programming set up with standard nomenclature and standard macros.

Appendix:

This optional section can be included in ADRG as needed.

POSSIBLE EXTENSION OF THE APPROACH

There are Proof of Concept/Biology (PoC/PoB) studies with patients which are conducted in ESD in some pharmaceutical companies. These studies usually have clearly defined Pharmacodynamics (PD) and/or Efficacy based endpoints as primary and/or key secondary endpoints. Since efficacy and/or PD could be very different from one study to another study, generic text for the template is not advisable. However, generic text can be written for certain standard safety datasets, such as ADAE, ADLB etc. In the ADRG, a similar principle can be followed as described previously.

FUTURE EFFORTS

It is worth exploring the possibility of creating standard text for ADRG document based on PhUSE ADRG template for specific types of early stage studies, such as ADxx for Thorough-QT studies/ Concentration-QT studies, special population studies (Renal or Hepatic) as a part of a future endeavors. In addition, similar principle could be applied for certain standard datasets such as ADAE, ADLB etc. in LSD studies.

CONCLUSION

The reviewers get substantial benefit from additional, human-readable, documentation of analysis methods, datasets, and programs that cannot be fully explained within the ADaM metadata, hence ADRG serves as a useful bridging document. Using the PhUSE template will ensure the consistency and acceptable format for this regulatory document. Introducing a generic text to ADRG sections for typical ESD studies will enhance the efficiency, minimize the editorial burden and typographical errors, and most importantly, reduce sponsor's internal review cycles. Once the standardized versions are established after incorporating possible review feedbacks, the creation of the ADRG in ESD studies will be a time-saving and cost-efficient task in a submission strategy.

The proposal can be implemented for most of the ESD studies and can be extended to other types of studies in ESD as appropriate. The benefit lies within the careful execution of the discussed approach during submission workflow.

REFERENCES

FDA Study Data Technical Conformance Guide,
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624623.pdf

PhUSE Template for ADRG,
https://www.phusewiki.org/wiki/index.php?title=Analysis_Data_Re viewer%27s_Guide

ACKNOWLEDGMENTS

Sincere thanks to Deborah L. Panebianco and Jing Su for their supportive reviews and valuable inputs which helped to improve the presentation in this paper. Authors would like to thank Patrick J. Larson for his review.

Deleted: ¶

CONTACT INFORMATION

Pranab K. Mitra, Ph.D.
90 E Scott Ave
Rahway, NJ 07065
Merck & Co., Inc.
(w) 732-594-3607
pranab.mitra@merck.com

Janet C. Low, M.S.

Merck & Co., Inc.
351 N. Summneytown Pike
North Wales, PA 19454
(w) 267-305-8215
janet_low@merck.com