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Just Say No to Data Listings!

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ABSTRACT

Sponsor companies often create voluminous static listings for Clinical Study Reports (CSRs) and regulatory submissions, and possibly for internal use to review participant-level data. This is likely due to the perception that they are required and/or lack of knowledge of various alternatives. However, there are other ways of viewing clinical study data that can provide an improved user experience, and are made possible by standard data structures such as the Study Data Tabulation Model (SDTM). The purpose of this paper is to explore some alternatives to providing a complete set of static listings and make a case for sponsors to begin considering these alternatives. We will discuss the recommendations from the PHUSE white paper, “Data Listings in Clinical Study Reports.”

INTRODUCTION

The PHUSE Safety Analytics Working Group recently published a white paper, “Data Listings in Clinical Study Reports” [1]. The paper grew out of discussions at the 2020 PHUSE Computational Science Symposium (CSS) and went through public review before finalization. It focuses on participant data listings to include or not include in the Electronic Common Technical Document (eCTD) CSR Sections 14 and 16 and regulatory submissions. The purpose of this paper is to raise awareness of the recommendations of the white paper and discuss their potential impact on current practice.

The following definitions will be used:

- Static listing – A listing that is created without any interactive features, to be viewed in its entirety on one or more pages.
Example: RTF or PDF file displaying data collected for a study
- Interactive listing – A listing that allows point-and-click technology and/or the use of scroll bars and filters to view data
Examples: Spreadsheets containing downloads of study data or data visualization tools that allow a user to combine data from different sources, filter on specific conditions, and sort and drill down through multiple levels

BACKGROUND

The 1995 ICH E3 Harmonized Guideline, “Structure and Content of Clinical Study Reports” [2] “describes the format and content of a clinical study report that will be acceptable to all regulatory authorities of the ICH regions. It consists of a core report suitable for all submissions and appendices that need to be available but will not be submitted in all cases.” It outlines the recommended data displays to include in CSR Sections 14 and 16. ICH E3 was published before widespread use of interactive data review tools, both internally within sponsor companies and by regulatory agencies, and before submission of electronic study data to regulatory agencies took effect.

Many companies interpret the ICH E3 guideline as a requirement that all collected data be displayed in a listing and that all appendices included in the guideline are mandatory. Sponsors spend countless statistical programming hours to prepare nicely formatted, “publication-ready” data listings that are rarely used.

A CASE AGAINST STATIC DATA LISTINGS

Static listings can be burdensome to work with when locating specific participant information in a sea of data. They are especially inefficient to review when hundreds of pages long. In addition, the reviewer is faced with the challenge of stringing separate pieces of data together when working with multiple listings in static documents. Furthermore, any listings required for further data exploration (e.g., subsetting, drilling down, and individual profiling) need additional statistical programming and are not readily produced by the user or reviewer.

Some sponsors have already deviated from the full set of CSR listings specified in ICH guidelines without negative repercussions. An informal survey of participants at the 2020 PHUSE CSS Safety Analytics workshop identified a much smaller set of commonly produced listings considered helpful for reviewing study data (Table 1). These listings can be prepared as needed; for example, to inform CSR narratives or to enable a detailed discussion of individual outcomes.

Deaths	Adverse Events Related to Study Treatment
Serious Adverse Events	Demographics/Baseline Characteristics
Adverse Events Leading to Study Treatment Discontinuation	Markedly Abnormal Clinical Laboratory Values
Study Withdrawals	Randomization
Protocol Deviations	Study Medication Lot Numbers by Subject
Adverse Events of Special Interest	Primary Efficacy Parameters

Table 1. Commonly Produced Listings from Informal 2020 PHUSE CSS Survey (Source: PHUSE WP-061; [1])

Are we over-interpreting the ICH guidelines for clinical study reports? Are static listings the best means to review individual participant data? Should we continue to produce static data listings when more efficient and effective alternatives exist?

RECOMMENDATIONS FROM THE WHITE PAPER

The Phuse CSS WP-061 white paper recommends the following:

- Stop routinely producing complete data listings for CSRs and regulatory filings
- Consult with applicable regulatory agencies about the need for listings before automatically producing them
- Follow SDTM/ADaM standards when creating study datasets for both internal and external use
- Adopt interactive data review tools for internal use and ensure that staff are appropriately trained

Do not assume that the health authorities require static listings. The 2004 Adopted EMA Guideline [3] clarified the ICH E3 requirements described in Section 16, requiring systematic inclusion of only two data listings, namely protocol deviations and serious AEs. All other appendices “may be made available on request of the competent authorities.” Moreover, with participant-level study data submitted in standardized electronic format, health authority reviewers can readily examine the data using their own data review tools. FDA, PMDA (Japan) and NMPA (China) all receive clinical study data in electronic format and have their own tools for reviewing data, while EMA is investigating data review tools. “The EMA is currently developing a Data Standardisation Strategy for the European Medicines Regulatory Network (EMRN) and its stakeholders following the recommendations of the HMA-EMA Joint Big Data Task Force and the workplan of the HMA-EMA Joint Big Data Steering Group, which recognized data standardisation as a critical element for realising the full potential of big data and driving regulatory decisions” [1].

We should not automatically produce static listings without prior consultation with the agencies. Oftentimes we find it expedient to prepare listings and include them in submissions in order to minimize questions or information requests. However, the time and resources spent on creating the listings could be better spent in determining what listings would add value, consulting with the agencies early in the process.

If static data listings are typically used for internal data review (e.g., medical or safety monitoring), consider using interactive review tools instead. Some sponsors have already been successfully using interactive tools such as spreadsheets, JReview® and Spotfire®, as a means for medical monitoring. While interactive review tools themselves require programming, the up-front investment will result in a more efficient and more effective review process.

DISCUSSION

The above recommendations come with additional considerations.

DATA INTEGRITY

The use of interactive displays and review tools requires extra steps to ensure that we do not compromise the integrity of the data. Particular attention should be given to validation procedures, data traceability and access restriction. Measures should be put in place to prevent modification of source data while reviewing data interactively. The ability to download or export reports from interactive tools should be well-controlled to avoid improper use and storage of the data and to prevent accidental unblinding.

IMPACT ON INTERNAL PROCESSES

The use of interactive displays will affect internal processes within sponsor companies. Changes may include the following actions:

- Instead of referencing static listings for QC purposes or to support in-text CSR tables, reference participant-level datasets, ensuring that they are identifiable, findable and accessible, adding data cutoff dates as applicable.
- For CSR narratives, pull directly from the study datasets, with or without the use of interactive displays. Consider automating (or semi-automating) the generation of the narrative content.
- For operational listings that have been historically included in CSRs, such as investigator information and study lot numbers, consider preparing them directly from the source data maintained by Clinical Operations, as supplemental files if needed.

VERIFICATION AND VALIDATION

The need to validate data does not go away whether we use interactive data review tools or static listings. In addition, the interactive data review tool, itself, will need to be validated. Company policy and/or operating procedures should include a well-articulated process for the verification and validation of results and conclusions generated from interactive data review tools. We could review or explore data interactively and as a by-product generate a listing that could serve as reference in CSRs or regulatory documents. Validation of the interactive tool used to create the listing would be in line with systems requirements for clinical investigation purposes and software validation principles (see, for example, “R: Regulatory Compliance and Validation Issues--A Guidance Document for the Use of R in Regulated Clinical Trial Environments” [4]).

CONCLUSION

Some sponsors have successfully reduced the number of static listings generated for both internal purposes and regulatory submissions to a small number (<10). Submission of study data in standard format, plus wider adoption of interactive data review tools, enables reduction, if not elimination, of complete sets of routine study “data dump” listings.

We recommend that sponsor companies stop routinely producing static participant-level data listings in regulatory submissions and instead consult with health authorities early in the process to agree on which listings are essential. Minimizing dependence on static data listings will require a concerted and sustained multi-disciplinary effort. Sponsor companies will need cross-functional advocates for interactive data review tools in internal company departments, including but not limited to Medical Writing, Clinical, Safety, and Statistics.

REFERENCES

1. PHUSE Safety Analytics Working Group. "Data Listings in Clinical Study Reports." PHUSE WP-061, Version 1.0. 23 November 2021. Available at <https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Safety+Analytics/WP061.pdf>
2. ICH Harmonised Tripartite Guideline. "Structure and Content of Clinical Study Reports E3, Step 4 Version. 30 November 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf
3. EMA Committee for Medicinal Products for Human Use. "Note for guidance on the inclusion of appendices to clinical study reports in marketing authorisation applications." EMA Adopted guideline 23 June 2004. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-inclusion-appendices-clinical-study-reports-marketing-authorisation-applications_en.pdf
4. "R: Regulatory Compliance and Validation Issues--A Guidance Document for the Use of R in Regulated Clinical Trial Environments." The R Foundation for Statistical Computing. 18 October 2021. Available at <https://www.r-project.org/doc/R-FDA.pdf>

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