Data Listings in Clinical Study Reports

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Contents

1: Overview: Purpose of this Document

The purpose of this white paper is to provide recommendations and justification for listings to include (and not include) in eCTD CSR Sections 14 and 16 and regulatory submissions, with example alternatives to static listings. Since the listings in CSR Section 14 are narrower in scope, the focus is mainly on general study data listings in Section 16.

2: Scope

The focus will be on Phase II to IV clinical trials and regulatory submissions. Phase I studies are out of scope because these studies often have a small number of subjects and sparse amounts of data. When data is limited, listings are often substituted for summaries because listings are sufficient to review and understand the data, and summary tables do not provide additional value.

Listings to facilitate site audits, Bioresearch Monitoring (BIMO) listings and listings prepared to support scientific publications are out of scope.

3: Acronyms and Definitions

Static listing – A listing that is created without any interactive features, to be viewed in its entirety on one or more pages. An example of a static listing would be an RTF or PDF file displaying data collected for a study. The file may be viewed, but no other interaction is possible.

Interactive listing – A listing that allows point-and-click technology and/or scroll bars to view the data. Examples of interactive listings range from spreadsheets containing downloads of study data for internal use to sophisticated data visualisation tools that allow a user to combine data from different sources, filter on specific conditions and drill down through multiple levels. Such listings may be defined in advance according to documented specifications or generated dynamically.

Acronyms

Term	Description
ADaM	Analysis Data Model
CRO	Clinical Research Organization, Contract Research Organization
CSR	Clinical Study Report
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
HMA	Heads of Medicine Agencies
ICH	International Council for Harmonisation
NMPA	National Medical Products Administration
PHUSE CSS	PHUSE Computational Science Symposium
PMDA	Pharmaceuticals and Medical Devices Agency
QC	Quality Control
SDTM	Study Data Tabulation Model
SOP	Standard Operating Procedure

4: Problem Statement

Sponsors often create voluminous static listings for Clinical Study Reports (CSRs) and submissions, and possibly for internal use to review safety information. This is likely due to the perception that they are required and/or lack of knowledge of various alternatives. ICH guidelines outlining recommended data displays were developed before widespread use of interactive data review tools and need to be updated to reflect current practice of including datasets in electronic submissions. Consequently, a lot of work is done to create these listings, and yet, in many companies, they are rarely used. Even when they are used, it is burdensome to locate the desired information by looking through static listings. Alternatives currently exist which can improve the user experience.

5: Background

Some sponsors have already deviated from the full list of CSR listings specified in the ICH Guidelines without negative repercussions. Crowdsourcing the decision of which listings have been included will help us to come to group consensus on a standard set.

The Safety Analytics Working Group, Listings for Clinical Study Reports project team, conducted an informal survey of representatives from various companies at the PHUSE CSS 2020 regarding which types of commonly produced listings were considered to be useful to both internal and external reviewers.

The results of the PHUSE CSS survey, in conjunction with our experience, indicate that the following short set of listings are commonly produced, even by companies that have stopped generating complete sets of static listings, as they are considered to be helpful when reviewing study data. While the survey didn't collect the rationale for choosing particular

listings, we speculate that some are created to facilitate the identification of participants requiring narratives and/or to provide sufficient individual detail when discussing/describing outcomes within the body of the CSR.

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

6: Recommendation

After reviewing the results of the survey on listings, we recommend that companies stop routinely producing complete data listings for CSRs and regulatory filings. Some sponsors have submitted CSRs and integrated documents without complete sets of static listings, and without repercussions. Regulatory guidance from the EMA requires only two participant data listings (protocol deviations and serious AEs), for inclusion in appendices of CSRs submitted in Marketing Authorization Applications; see Adopted guideline, 2004 [1]. The FDA, PMDA (Japan) and NMPA (China) all receive clinical study data in electronic format and have their own tools for reviewing data. 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 recognised data standardisation as a critical element for realising the full potential of big data and driving regulatory decisions. The Data Standardisation Strategy will serve as a roadmap to improve the way data on medicinal products is dealt with within the EU, and to support the development of globally applicable standards for the human and veterinary regulatory domains. Once its first version has been published, in 2022, the strategy will be reviewed regularly. It will evolve on data standardisation to support new ways of working in the regulatory processes over the coming years. While additional regulatory agencies may continue to request listings because they do not yet receive clinical data electronically (e.g. in CDISC SDTM format) or because of existing processes within their organisation, we expect the practice of requesting numerous listings to decrease as more agencies accept electronic datasets and adopt interactive data review tools. In the meantime, sponsors should explicitly consult with regulatory agencies about the need for listings before automatically producing them.

Some sponsors produce listings because they believe that they are required per ICH guidelines. While ICH guidelines do specify certain data displays, the spirit of the ICH guidelines are met through CSR summary analyses (including a few specific listings in Sections 14 and 16) along with the delivery of electronic clinical datasets that can be viewed and interrogated using interactive data review tools.

Moreover, static data listings do not provide an efficient method for reviewing clinical data. Interactive data review tools with search, sorting and visualisation capabilities provide more powerful and cost-effective means for reviewing and understanding clinical data. Considerable resources used to generate, QC and process listings could be better spent on more value-added activities. In place of static listings, we strongly recommend the adoption of SDTM/ADaM standards when creating study datasets; standardisation then facilitates the development and adoption of tools that can be used for reviewing the data.

In addition, there may be circumstances where a static listing might be more useful than a summary table/figure or an interactive data review tool, such as with a very small number of participants or a lack of expertise with interactive data review tools. Otherwise, with rare exceptions, there are better alternatives to static listings.

Some companies may produce listings for internal operational purposes, such as those displaying investigator information, randomisation and study medication lot numbers, which could be provided directly by internal operations groups as either supplemental files or static listings. Each company will need to evaluate its own situation. Companies are still obligated to provide this information, but may be able to do so more efficiently as something other than a static listing.

One case where listings may be preferred is when a CRO is contracted to write narratives for study participants meeting notable criteria. A listing of participants meeting such criteria might be warranted versus asking the CRO to rely on an interactive data review tool. However, we believe that, in general, interactive data review tools are better and more efficient than static data listings for internal operational processes. We recommend that companies enhance their processes and systems, and ensure their staff are appropriately trained in using interactive data review tools instead of relying on static listings so they can increase the efficiency and effectiveness of data review.

6.1: Discussion

Static data listings have historically been produced for Clinical Study Reports (CSRs) in order to provide participant-level information for data interpretation and to comply with ICH E3 guidance. With the advent of machine-readable, electronic datasets in standardised format, and the prevalence of interactive data visualisation/review tools allowing for data exploration at the aggregate or individual level, we challenge the dogmatic need for static listings. We assess the pros and cons of replacing static listings with electronic datasets for the purpose of CSRs.

Static listings are inefficient to review, especially when they are hundreds of pages long, and it can be a challenge to string separate pieces of data together when working with multiple listings. In addition, any listings required for further data exploration (e.g. subsetting, drilling down, individual profiling) would require additional statistical programming not readily produced by the user/reviewer.

Maintaining the integrity of source datasets, when using interactive displays within the review tool, is critically important. As with static listings, company policy needs to incorporate validation procedures, ensuring traceability and restriction of

access only to users who are authorised to see the data. Tools should not allow for modification of source data. Furthermore, there should be policy to restrict exporting of processed data or reports created by the tools to prevent improper use and accidental unblinding and to prevent the data from being stored in a location without proper access control.

Downstream impacts of eliminating one or more static listings will need to be carefully considered. For example, for internal QC and validation of any internal tools, companies will need to reference datasets instead of listings, and ensure that the datasets are accessible. In addition, references will need to include the data cut-off date. Sample text for internal QC references might state, "Of the N participants with adverse events of jaundice, xx participants did not have elevated liver function tests (datasets adae.sas7bdat and adlb.sas7bdat, 31 August 2012)." In-text tables could reference participant-level datasets in the same manner with a footnote.

Company policy will need to cover the QC process for any information generated from data review tools and incorporated into publications, decision-making or regulatory documents. If listings generated interactively from a data review tool are to be used as a reference when writing a clinical study report or other submission document, companies should consider how the tool should be validated according to FDA principles on software validation and requirements for computerised systems used in clinical investigations ("design of computerized systems, security safeguards, audit trails, date/time stamps, recommended Standard Operating Procedures (SOPs), controls for system changes, and training of personnel" (US Food & Drug Administration. May 2007. "Guidance for Industry: Computerized Systems Used in Clinical Investigations". Accessed Dec. 12, 2018. *http://academy.gmp-compliance.org/guidemgr/files/7359FNL.PDF*))

In summary, minimising dependence on static data listings will require a concerted and sustained multi-disciplinary effort. Cross-functional advocates for interactive data review tools in internal company departments will be needed, including from Medical Writing, Clinical and Safety.

6.2: Resources

1. EMA. (23 June 2004). Note for guidance on the inclusion of appendices to clinical study reports in marketing authorisation applications. Adopted guideline. *https://www.ema.europa.eu/en/inclusion-appendices-clinical-study-reports-marketing-authorisation-applications*)

2. E3 Structure and Content of Clinical Study Reports. (July 1996). *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e3-structure-and-content-clinical-study-reports* [Accessed 04 Apr 2021].

3. NMPA: *https://www.pharmews.xyz/2020/05/guideline-on-submission-of-clinical.html* (Draft version for public comment; final version has been published but not available in English.)

4. PMDA: *https://www.pmda.go.jp/files/000218990.pdf* (Japanese version; no English translation available.)

7: Disclaimer

The opinions expressed in this document are those of the authors and should not be construed to represent the opinions of PHUSE members, respective companies/organisations or regulators' views or policies. The content in this document should not be interpreted as a data standard and/or information required by regulatory authorities.

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9: Acknowledgements

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