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Clinical Study Report Review: Statistician's Approach

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ABSTRACT

A clinical study report (CSR) is one of many types of regulatory documents that comprise a marketing application for a drug, biologic, or device. A study statistician is a co-author of CSR which is a descriptive account of a single clinical trial accompanied by tables, listings, and figures (TLFs) displaying all study data and results. The study statistician works closely with the medical writer to ensure clarity and accuracy in conveying statistical findings and interpreting results, and addresses any statistical questions. This paper will discuss study statistician's responsibilities in preparing and reviewing CSR. The checklist for study statistician will make clinical study report review relatively easy.

INTRODUCTION

A clinical study report (CSR) is one of many types of regulatory documents that comprise a marketing application for a drug, biologic, or device. It reports the results obtained from a research study conducted in test subjects during the phases of clinical development. A CSR is a descriptive account of a single clinical trial accompanied by tables, listings, and figures (TLFs) displaying all study data and results with all required appendices compliant with International Conference on Harmonization (ICH) E3 (Structure and Content of Clinical Study Reports) guidelines.

A CSR is a scientific document addressing results of study objectives such as efficacy and safety, and not a sales or marketing tool. Pharmaceutical Company's goal is to sell a drug, biologic, or device; they want to showcase a product and the problem it solves. To weave a product marketing application together, sponsors use key messages which are important study findings that are repeated throughout the marketing application. Medical writing, Regulatory, Clinical, Statistical, and Marketing Experts collaborate to craft key messages. Medical writer is responsible for writing the CSR, while rest all are co-authors.

Study statistician works closely with medical writer to ensure clarity and accuracy in conveying statistical findings and interpreting results, and addresses any statistical questions. To become an efficient reviewer, a statistician needs to educate oneself about clinical trials and the study; how trials are planned, conducted and reported; and about, regulatory requirements. Each clinical trial is a unique scientific experiment. There are hundreds of study design variations and many complex statistical techniques. But in every trial, there are at most two fundamental questions:

- Is the treatment efficacious?
- Is the treatment safe?

If the statistician understands the trial with respect to these two primary questions, research the condition being treated, and study the results closely, the CSR will almost write itself.

ACTIVITIES TO BE DONE PRIOR TO THE PREPARATION OF CLINICAL STUDY REPORT

Before preparing and reviewing the CSR, a study statistician is accountable to execute few activities with the help of medical writer prior and after the database lock.

PRIOR TO DATABASE LOCK

During the review of Statistical Analysis Plan (SAP) and TLF shell, study statistician provides the medical writer the draft SAP accompanying TLF shells and other necessary documents such as final protocol incorporating all amendments and protocol amendment summaries, final CRF, the SAP template used to create the SAP, and investigator's brochure. Medical writer review takes place in parallel with the stats quality check (QC) review along with other functional QC review. Medical writer reviews the SAP and TLF shells for content, reliability, and format. Medical writer review is essential as the clinical study results are drafted using the TLFs based on the SAP and output shell document. It is cumbersome to revise the final TLFs, if medical writer provides the comments on TLFs after the database lock. In order to avoid this, it is always advisable to have medical review of SAP and TLF shells prior to database lock.

Once the SAP is finalized, medical writer drafts CSR shell which is a non-data-dependent draft of the CSR that comprises all sections as determined by the applicable template but without the inclusion of actual results or appendix details. Medical writer circulates the CSR shell for co-authors' review. The internal review assists the study team to resolve conflicting comments prior to the preparation of the draft CSR.

AFTER DATABASE LOCK

Once the database is locked and final TLFs are run, study statistician is responsible for providing the following to medical writer before any writing of CSR begins

- Final SAP including any amendments
- Randomization scheme (if applicable)
- Interim analysis findings (if applicable)
- Approved TLFs in a specific format including a Table of Content (TOC)
- Ad-hoc request: any additional analyses not included in the TLFs (if applicable)

After the database lock, the project team reviews the final TLFs to be familiar with the findings, creates a list of key messages and questions (if any), and discusses them internally. During the CSR development, study statistician works closely with medical writer to ensure clarity and accuracy in conveying statistical findings and interpreting results, and addresses any statistical questions. Study statistician attends the CSR key message meeting to review study results and discuss clinical and statistical insights in a conventional format to assure understanding of CSR content based on actual data.

The CSR review process can be done more efficiently if the internal review activities are done by the statistics and medical writing group prior to and after database lock in a timely manner.

STUDY DOCUMENTS THAT A STATISTICIAN READS BEFORE REVIEWING A CLINICAL STUDY REPORT

Before reviewing a CSR, a statistician should read these study material, in roughly this order:

- **Study Protocol:** The protocol is a detailed plan for conducting the study. It describes all study procedures and defines how all study end points are presented and analyzed. The protocol is approved by regulators prior to initiating the study. The statistician needs to understand this document in detail. When reading a protocol, they need to focus throughout on the objectives and end points. The statistician needs to understand the rationale for choosing the experimental hypotheses and how each study procedure contributes to answering them.
- **Disease Process:** By knowing the pathophysiology of the condition being treated, one can anticipate the adverse events and outcomes that trial subjects are likely to experience. When using online materials to research a disorder, make sure sources are scholarly.
- **Investigator Brochure (IB):** The IB is written for clinical site investigators who will administer the study product to patients and follow them clinically during the trial. The IB summarizes previous studies of the product conducted in animals and humans. It may include recent unpublished results. The IBs are updated frequently to incorporate significant new study findings. Skim the IB to learn the history of the product and the safety concerns identified in previous studies.
- **Competing Products or Other Treatments for the Same Disease:** Peruse Drugs@FDA or www.rxlist.com to learn about currently marketed products.
- **Case Report forms (CRFs):** The CRFs are electronic or paper forms used by clinical study sites to record information about each subject. They show the exact questions presented to investigators, they sometimes give a bit more detail than the protocol by showing the exact questions and the possible answers.

- **Statistical Analysis Plan (SAP):** The SAP is a plan for analyzing study results which is approved by study team prior to study conclusion. Read the SAP, this helps statistician double check whether they are discussing all important analyses in the CSR.
- **Randomization and Blinding Schemes:** Randomization methods in study protocols are often sketchy. However, all details about how subjects were randomized to treatment groups should be included in the CSR. The actual randomization codes are placed in an appendix to the CSR.
- **The Tables, Listings, and Figures (TLFs):** Statistician must understand how the TLFs correspond to the study's objectives and end points. Some TLFs require extensive discussion with project team.

STATISTICIAN'S REVIEW OF CLINICAL STUDY REPORT

While reviewing the CSR, a study statistician focuses on the statistical methods and results sections, to ensure that the reported statistical findings are accurate and consistent with SAP and TLFs. It is also checked that the data used in CSR text and in-text tables and all statements regarding statistical findings are accurate and consistent with TLFs. Statistician also ensures that the interpretation of results is appropriate and limitations are noted. In broader sense, the review can be classified as Content and Format review.

CONTENT REVIEW INCLUDES:

Consistency with Protocol

- Key components of the CSR shell template like the sections of CSR, descriptive text, appropriate level headings, etc. are included, as applicable.
- Study objectives, efficacy parameters, and safety parameters are consistent with the protocol.
- If there are changes from the protocol, the justifications are described.
- Versions of statistical software, World Health Organization Drug Dictionary (WHO DD), and Medical Dictionary for Regulatory Activities (MedDRA) are stated and referenced.

Focus on the Statistical Methods

- The statistical methods proposed to evaluate each parameter are clearly described and consistent with SAP.
- Study periods, visits, procedures, variables, drugs, and populations are consistently named and cased.
- Study time points for all measurements are consistently reported in CSR and in line with SAP text and TLF specifications.

Regulatory Guidelines

- Ensure the regulatory guideline ICH E3 (Structure and Content of Clinical Study Reports) is followed.
- The numbering, titling are consistent with ICH requirements for reporting.

Checking for Accuracy of the Data Used in CSR Text and In-Text Tables

- Primary, secondary, and exploratory analyses results are appropriately described and referenced and interpreted statistically as well as clinically.

Ensuring that the Interpretation of Results is Appropriate and Limitations are Noted

- The study conclusions are appropriately described.
- Study limitations, if any, are described.

FORMAT REVIEW INCLUDES:

Clear and Correct Writing

- Writing is clear and uses complete sentences and correct grammar.
- The document uses consistent past tense.
- Spelling is correct and consistently American or British, as applicable.

Consistency

- Standard American Medical Association (AMA) punctuation rules are followed.
- Designators for study days and visits are consistently capped (e.g., Day 1, Visit 6).
- Headers/footers are consistent and reflect version of CSR, date, sponsor, study.

Accuracy

- The TOC is correct, and the lists of TLFs in the appendix correctly reflect the titles of the TLF shells.
- Items in the abbreviation list appear in the text, and abbreviations in the text appear in the list.
- Internal cross-references within the document are accurate.
- Appropriate units of measurement as specified in the protocol.

The below checklist includes the content and format review checks.

REVIEW CHECKLIST

Review Item	Results
✓**Checkmark** = Item checked and 100% assured. **NA** = Not applicable. **P** = Problem that needs to be fixed.	
Content Review	
Key components of the CSR shell template like the sections of CSR, descriptive text, appropriate level headings, etc. are included, as applicable.	
Study objectives, efficacy parameters, and safety parameters are consistent with the protocol.	
If there are changes from the protocol, the justifications are described.	
Versions of statistical software, World Health Organization Drug Dictionary (WHO DD), and Medical Dictionary for Regulatory Activities (MedDRA) are stated and referenced.	
The statistical methods proposed to evaluate each parameter are clearly described and consistent with SAP.	
Study periods, visits, procedures, variables, drugs, and populations are consistently named and cased.	
Study time points for all measurements are consistently reported in CSR and in line with SAP text and TLF specifications.	
Ensure the regulatory guideline ICH E3 (Structure and Content of Clinical Study Reports) is followed.	
The numbering, titling are consistent with ICH requirements for reporting.	
Primary, secondary, and exploratory analyses results are appropriately described and referenced and interpreted statistically as well as clinically.	
The study conclusions are appropriately described.	
Study limitations, if any, are described	
Format Review	
Writing is clear and uses complete sentences and correct grammar.	
The document uses consistent past tense.	
Spelling is correct and consistently American or British, as applicable.	
Standard American Medical Association (AMA) punctuation rules are followed.	
Designators for study days and visits are consistently capped (e.g., Day 1, Visit 6).	
Headers/footers are consistent and reflect version of CSR, date, sponsor, study.	
The TOC is correct, and the lists of TLFs in the appendix correctly reflect the titles of the TLF shells.	
Items in the abbreviation list appear in the text, and abbreviations in the text appear in the list.	
Internal cross-references within the document are accurate.	
Appropriate units of measurement as specified in the protocol	

CONCLUSION

I have tried to touch base on statistician's approach on CSR review that can be a starting point for understanding the CSR review process. A statistician can be an efficient reviewer purely on the basis of his/her expertise in statistics with some knowledge of clinical domain. However, it is beneficial to have basic understanding of the process to complete the review more efficiently.

CONTACT INFORMATION

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