

WRITING YOUR FIRST CLINICAL STUDY REPORT

Are you an experienced manuscript writer eager to learn about writing regulatory documents for the pharmaceutical and biotechnology industries? This article will teach you to write a clinical study report (CSR) by building on your manuscript writing experience.

The Who and What of a Clinical Study Report

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 CSR is a descriptive account of a single clinical trial accompanied by tables, listings, and figures (TLFs) displaying all study data and results. The CSR's structure is similar to that of a peer reviewed manuscript, so writing a CSR is a good entry point into regulatory writing for an experienced scientific writer.

A successful writer understands the reader. Your audience is the FDA or another regulatory agency. Study the [Guideline for Industry: Structure and Content of Clinical Study Reports](#). This document, called "E3" by regulatory writers, stipulates the content of a CSR and has been adopted by most regulatory agencies worldwide.

Clinical Trials

To write an excellent CSR, educate yourself about clinical trials. Unless you are already familiar with how trials are planned, conducted and reported, read some books about clinical trials, regulatory requirements, and product approval:

[Fundamentals of Clinical Trials](#) by Friedman, Furberg, and DeMets

[Targeted Regulatory Writing Techniques](#) edited by Wood and Foote

[Fundamentals of US Regulatory Affairs](#) edited by Regulatory Affairs Professionals Society

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:

1. Is the treatment efficacious?
2. Is the treatment safe?

Purpose of a Clinical Study Report

A CSR is a scientific document addressing efficacy and safety, not a sales or marketing tool. But the sponsoring company's goal is to sell a drug, biologic, or device. Sponsors want to showcase a product and the problem it solves, and they want regulators to focus on the forest, not the trees. To weave a product marketing application together, sponsors use key messages.

Key messages are important study findings that are repeated throughout the marketing application. In the CSR, key messages are found in the synopsis at the beginning and are reiterated in the body of the document as topic sentences, in summaries of sections or subsections, and in the conclusions. Sponsors hone key messages thoughtfully, selecting words and ideas to convey desired nuances. Although study findings determine key messages, messages may be informed by other factors such as results of prior studies and characteristics of competing products. Regulatory, clinical, statistical, and marketing experts collaborate to craft key messages.

Content of a Clinical Study Report

The content of a CSR is similar to that of a peer reviewed manuscript. Examine the table of contents of [Guideline for Industry: Structure and Content of Clinical Study Reports](#). The CSR includes summary sections, appendices, and many details, but the meat of the document is comprised of sections already familiar to you: introduction and background, experimental methods, description of study subjects, efficacy results, safety results, and conclusions.

The CSR should expedite the reviewer's job. Even though all study data are in the tables and appendices at the end of the CSR, liberal use of in-text tables and figures allows the reader to find important study results without having to bounce back and forth between the text and appendices. Most TLFs are too large to include in the body of the CSR. I either design my own simple in-text tables using the TLFs or ask the statistical programming group to create them.

Study Documents I Read Before Writing a Clinical Study Report

Prepare to write by educating yourself about the study, as you would for any scientific manuscript. If you understand the trial well, research the condition being treated, and study the results closely, the CSR will almost write itself.

Don't be frightened by the list of documents below. You need not read them all closely; many can be skimmed. With some experience, you will be able to read everything in a day or so. Keep in mind that some of these documents can change slightly during the course of the study, so remember to track versions and dates of implementation.

Before writing a CSR, I read these study related materials, in roughly this order:

- **The 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 writer needs to understand this document in detail.* When reading a protocol, I focus throughout on the objectives and end points. I try to understand the rationale for choosing the experimental hypotheses and how each study procedure contributes to answering them.
- **The disease process:** By knowing the pathophysiology of the condition being treated, I can anticipate the adverse events and outcomes that trial subjects are likely to experience. I consult

recent textbooks, review papers, references in the study protocol and investigator brochure, and Web sites such as <http://emedicine.medscape.com>. When using online materials to research a disorder, make sure sources are scholarly.

- **The 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. 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. If your product lacks the side effects or deficiencies of a competing treatment, demonstrate that in the CSR.
- **The case report forms (CRFs):** CRFs are electronic or paper forms used by clinical study sites to record information about each subject. Each screen or 8 by 11 inch paper form is called a CRF page, and the collected pages for a particular patient are called a CRF book. In a lengthy or complex trial, each CRF book is hundreds of pages long. Because CRFs 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. Skim these and map each page to the corresponding study procedure in the protocol.
- **Manuals of operations or other instructional materials:** I quickly skim all written instructions or training information given to clinical sites, radiology reviewers, clinical event committee members, or study subjects. These documents and webinars occasionally offer a little more detail than the protocol, allowing me to describe study methods accurately.
- **The statistical analysis plan (SAP):** The SAP is a plan for analyzing study results. It is written by statisticians and approved by regulators prior to study conclusion. Read the SAP, but don't be concerned about comprehending statistical minutia. Instead, map the calculations and analyses in the SAP to the end points in the protocol. I create a section heading in the CSR for each study end point in the SAP. This helps me double check whether I am discussing all important analyses in the CSR.
- **The 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, so I often check with the statistical group to fill in blanks. The actual randomization codes are placed in an appendix to the CSR.
- **The tables, listings, and figures (TLFs):** These are created by the study statistical group to present the data. *The writer must understand how these correspond to the study's objectives and end points.* Some TLFs require extensive discussion. Others can be summarized in a sentence, and some can be omitted entirely if they are duplicative (eg, results in a table that are

also in a figure). Often the numerical order of the TLFs is not the order in which I will discuss them in the CSR. I rearrange them to correspond to the CSR sections: disposition, demographics, efficacy, and safety.

- **Data monitoring committee (DMC) minutes and recommendations:** During some trials, a committee of independent clinical and statistical experts reviews study data on one or more planned occasions while the study is ongoing. After each data review meeting, DMCs issue recommendations to the sponsor that are also reported to institutional review boards. Their recommendations sometimes impact the study. For example, DMCs can recommend protocol amendments, additional study procedures to assess safety or efficacy, or early termination of a study for reasons of safety or efficacy. Minutes and recommendations from DMC proceedings help me in two ways:
 1. DMC minutes sometimes explain reasons for unusual or unplanned changes in a study. For example, if a trial is stopped early based on a DMC recommendation, the DMC minutes document why. I also check the SAP, the protocol and the DMC charter to find the monitoring plan and communication procedures required for stopping the study. In the CSR, I document these details and state whether they were properly followed.
 2. DMC minutes offer insight into how independent subject matter experts interpret the study data and what findings and issues they consider important, occasionally providing a fresh perspective.

Introductory Sections

The introductory section of a CSR is simpler than that of many manuscripts. Chemical, physical, and clinical knowledge about the study product is found elsewhere in the marketing application and need not be repeated. Literature review is abbreviated or absent. Briefly identify the study population and objectives. Summarize the protocol or the protocol synopsis.

Methods

The protocol and SAP already describe methods, so I paste the methods from those documents into the CSR and put them in past tense, simplifying to exclude unnecessary details.

Randomization and blinding are crucial elements of the study plan. Explain the randomization plan in full. Demonstrate that treatment assignments were truly random and subjects were given their assigned treatments, or discuss departures from the intended plan.

Willful or inadvertent unblinding can jeopardize study integrity. When investigators or subjects know or suspect treatment assignments, they may behave or report findings differently and thereby influence study results. Some studies feature partial blinding. For example, if a study treatment alters clinical laboratory parameters or imaging results, seeing such findings can unblind investigators, who might overtly or unintentionally relay that knowledge to subjects or other trial personnel. To prevent this,

some groups of people may be blinded (eg, investigators and subjects) and others unblinded (eg, clinical laboratory personnel). State who is blinded and how blinding is maintained. Discuss breaches of protocol that threaten blinding.

Study Subjects

Describe the study population and disposition of subjects in detail. I use a table or figure to illustrate entry and exit of subjects from the study. Bias can be introduced by improper screening procedures or inclusion of ineligible subjects. Subjects may withdraw from the study, cross over to another treatment arm, or discontinue study treatment because of adverse events. Report the frequency of and reasons for such events by treatment arm.

In addition to comparing treatment groups to one another or to a reference group, look for other relevant comparisons dictated by the study design. For example, in Phase II trials, subjects are sometimes dosed in consecutive increasing dose cohorts. This allows a safety assessment after each dose level so investigators may determine the advisability of using a higher dose for the next cohort. Since cohorts are not treated at different times and clinical site procedures can change subtly from one cohort to the next, cohort differences can introduce bias. Therefore, even if formal statistical comparisons among cohorts are not planned, summarize subject characteristics by cohort. Whenever treatment groups are pooled or historical controls are used, report the baseline characteristics of the individual groups.

Assess subject compliance with study treatment procedures. If all randomized subjects completed all procedures and took all doses, mention that fact. Subject noncompliance is most important when it differs among treatment groups or results in discontinuation of study treatments or study withdrawal.

Study Populations

At least two populations are usually defined in the protocol and SAP. The intention to treat population (ITT) is comprised of all randomized subjects, whether or not they actually received study treatment. The safety population includes subjects who received one or more study treatments. In a perfect world, these two populations contain the same subjects. Other populations might be used for certain subgroup analyses. For example, some analyses may be conducted only in subjects who possess a certain baseline characteristic or who demonstrate a minimum level of compliance with study treatments.

The ITT is included in analyses of demographic and baseline findings and efficacy results. In ITT population analyses by treatment arm, subjects are included in the treatment arm to which they were randomized. The safety population is included in analyses of adverse events, vital signs, clinical laboratory findings, and other safety data. In safety population analyses, subjects are included in the treatment arm corresponding to the treatment they actually received.

These are the usual definitions of the ITT and safety populations, but many variations are possible. Clearly state which study population is described in text sections and in-text tables and figures within the CSR.

Efficacy

Statistical members of the study team often assist with writing the efficacy section. First discuss the primary study results and then describe other results in decreasing order of importance.

Safety

Safety results usually include clinical laboratory values, adverse events, vital signs, medical history, and examination findings, and sometimes other types of data. Clinical members of the study team often assist with writing the safety sections. The level of detail reported in the CSR varies with the study indication, study population, condition being treated, expected risks of the study product, and therapeutic alternatives, but I always discuss adverse events that are serious or precipitate study discontinuation or drug withdrawal.

Sponsors want to present their products in the best possible light, and the safety section is the best place to do so. There is little latitude in the efficacy section because we specify measurement and statistical analytical methods prior to the trial. But the safety section is squishier: safety objectives and end points tend to be less precise and more open to interpretation. The safety section therefore presents an opportunity for “spin.”

It is never correct to mislead or fail to report important information, but placing undesirable study results into context is acceptable. Carefully study the adverse events, then dig through other data to see whether explanatory factors are present for subjects experiencing concerning adverse events. I use the medical history and physical examination, including those performed at baseline, eligibility violations, compliance data, concomitant medications, vital signs, clinical laboratory values, other influential adverse events (eg, vomiting or diarrhea possibly causing incomplete absorption of a dose), and any other relevant data I find. Present all data that support a relationship between an adverse event and a factor other than the study product.

Conclusions

Summarize important safety and efficacy findings. Study conclusions should mention the study’s objectives, state whether those were achieved, and reiterate the key messages.

Practical Tips

You don’t have to follow the E3 table of contents slavishly, but maintain its structure and chronology.

You might find data or programming errors in finalized TLFs. Let the study team know politely but immediately.

Final grammatical error checking is essential, and ideally should be performed by someone other than the primary writer. Verify every fact in the text and in-text tables and figures.

Understand how a CSR fits into the larger product approval process. A marketing application includes multiple CSRs and other summary documents. Look at FDA's Web site for an overview of other types of regulatory documents:

[Guidance for Industry: Good Clinical Practice: Consolidated Guidance](#)

[Electronic Common Technical Document](#)

[Providing Regulatory Submissions in Electronic Format](#)

[Comprehensive Table of Contents Heading and Hierarchy](#)

Challenge yourself to write a CSR that reads like a gossip magazine. A well written study report minimizes internal review time and signals competence to regulators. Emphasize clarity. Create informatively titled sections, short paragraphs, and simple tables and figures.

Final Advice

All team efforts involve compromises. CSRs are co-authored, so your influence may be limited and time constraints may preclude the polished product you envision. Express your opinions and recommendations, but don't expect to always prevail. Stylistic disagreements about content and composition are rarely critical, so unless you believe an inclusion or omission is scientifically dishonest, remain flexible.