

“[b]ased on documentation available at the time, study monitors ... should have recognized that drug kits ... should not have been administered to subjects.”

d. Close-Out Letter

The issues regarding the CRO, as described above, had a happy ending. The above Warning Letter, which complained about study drug to two subjects at exactly the same time, and about the out-of-range temperature, was followed by a favorable Close-Out Letter. As stated by FDA (194), “[a] close-out letter will not be issued based on representations that some action will or has been taken. The corrective actions must actually have been made and verified by FDA. Usually, the standard for verifying that corrections have been implemented will be a follow-up inspection. If the Warning Letter contains violations that by their nature are not correctable, then no close-out letter will issue.” On occasion, the FDA’s website provides, along with its Warning Letter, a second letter that is a Close-Out Letter. The Close-Out Letter discloses if or how the problem was eventually resolved.

Regarding the deficiencies of the CRO described above, the Close-Out Letter stated that (195), “[t]he Food and Drug Administration has completed an evaluation of your firm’s corrective actions in response to our Warning Letter ... [b]ased on our evaluation, it appears that you have addressed the violations contained in this Warning Letter.” The Close-Out Letter was dated about 5 years after the initial Warning Letter.

¹⁹⁴U.S. Food and Drug Administration. About Warning and Close-Out Letters. December 8, 2011. Accessed from the FDA website on July 30, 2015.

¹⁹⁵Warning Letter No. 10-HFD-45-11-04 (November 27, 2009) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

¹⁹⁶Bellary S, et al. Basics of case report form designing in clinical research. *Perspect. Clin. Res.* 2014;5:159–66.

¹⁹⁷Warning Letter No. 14-HFD-45-12-01 (April 30, 2014) from Dr Sean Y. Kassim, PhD, Office of Compliance, CDER, U.S. Food and Drug Administration.

XIX. CASE REPORT FORMS

a. Case Report Form was Generic and was not Relevant to the Clinical Trial

Case report forms are drafted to be aligned with details of the clinical trial. Bellary et al. (196) state that the “CRF should be designed for optimal collection of data in accordance with the study protocol compliance, regulatory requirements and shall enable the researcher test the hypothesis or answer the trial related questions. A well-designed CRF should represent the essential contents of the study protocol and in an ideal situation, CRF is designed once the study protocol is finalized.”

Real-world guidance on the content and filling-out of case report forms comes from Warning Letters that are issued by the FDA against personnel involved in regulated clinical trials. A failure of a case report form to be aligned with goals of a clinical trial resulted in a Warning Letter complaining that (197):

We do not find it acceptable for you to assign these responsibilities to study coordinators without first considering the **specifics and requirements of each study** that you undertake and determining the extent, if any, to which the study coordinator is qualified to be the primary author of all source documents and **Case Report Forms**. . . [w]ith respect to the sample **Case Report Form** that you provided, we are unable to determine the purpose of this sample Case Report Form and when you plan to use it. We are concerned that you may introduce error into future studies by using Case Report Forms that are **not study-specific**.