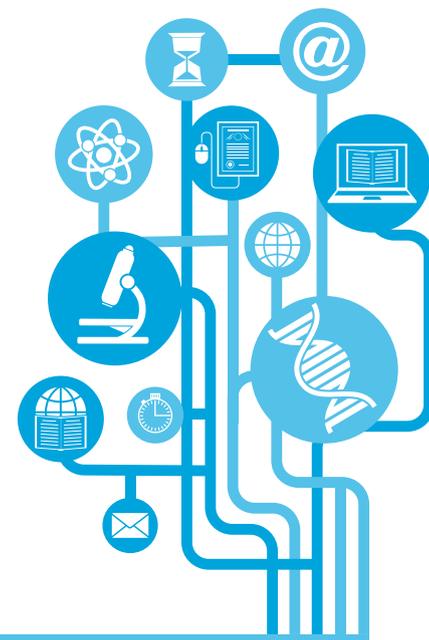


# CLINICAL TRIALS

## AVOIDING PROTOCOL DEVIATIONS IN CLINICAL RESEARCH

Deviations should be rare. The protocol helps to keep the study on track.

BY RYAN BOUCHARD



In a clinical trial, the protocol gives a detailed description of the entire study, including the operational aspects of how it should be conducted. The described study procedures within a given protocol have been developed to safeguard the health and safety of the study participants as well as to provide sufficient statistical power.<sup>1</sup> Deviations from the approved procedures could therefore harm the subjects in the study and/or compromise the analysis of the data collected.

### WHAT IS A PROTOCOL DEVIATION?

While not defined by the FDA protection of human subjects regulations (21 CFR 50), a protocol deviation is generally considered to be a departure from the study protocol, or other study-related documents, that has not been approved by an institutional review board (IRB).<sup>2</sup> In general, deviations fall into two categories (the terminology can vary slightly from one IRB to another): (1) those that have the potential to be significant, meaning they could potentially affect subjects' safety and/or the data's integrity, and (2) those that are insignificant, meaning they could not. Typically, insignificant deviations are unplanned minor or administrative instances of noncompliance on the part of the subject, investigator, or study staff. With regard to deviations that may have an impact on subjects' rights, safety, or welfare and/or the data's integrity, various IRBs may use different terms such as *significant deviations*, *violations*, and *serious noncompliance*.<sup>3</sup> Deviations of this kind typically include a more serious breach such as falsifying records or data, failing to obtain informed consent prior to any study procedures, and working under an expired professional license/certification.

Realistically, deviations should be rare; if they become more

frequent as the study progresses, the investigator and study sponsor should consider whether the protocol was written appropriately.<sup>3</sup> It is important to monitor protocol deviations carefully while the study is active and to make any necessary IRB-approved amendments to the protocol as swiftly as possible so as to avoid future deviations.

It is also important to note that, if a study subject is at risk of harm, protocol deviation may be required to ensure his or her safety.<sup>3</sup> Whether unplanned or planned in an effort to protect study subjects, any deviation from the protocol must be recorded and its severity assessed. Each IRB is likely to have its own reporting criteria, which the principal investigator should follow.

### TIPS ON AVOIDING COMMON DEVIATIONS

Protocol deviations can occur during any clinical trial at any time. Deviations may be caused by the investigator or study staff, or they may relate to the subjects, where they misunderstand what is expected of them during the trial. Still, there are many ways to help mitigate and avoid protocol deviations.

Start with a protocol that is clearly written and approved by an IRB.<sup>3</sup> Prior to writing the protocol, have a comprehensive understanding of the disease, population, and investigational device under study so that the protocol can be as detailed as possible. This will help to sort out any potential questions while the study is underway and facilitate smooth interactions between study staff and subjects. The protocol should clearly identify the study inclusion and exclusion criteria so that the proper study population is enrolled from the start.

One frequently observed deviation in device clinical trials is an "out-of-window" visit. When writing the protocol, the investigator and sponsor should carefully consider setting window visits.

(Continued on page 73)

(Continued from page 74)

Also, be aware of the time of year and the anticipated start and length of the study, because planned vacations or national holidays can throw a wrench in the study timelines.<sup>3</sup> If study subjects miss their visit window by several days (for reasons of illness, forgotten schedules, lack of transportation, etc.), it is considered a deviation. Subsequent deviations also occur if/when the study staff are scheduling the next visit and, in an effort to keep the between-visit spacing correct, schedule an additional out-of-window visit.<sup>3</sup> Having clear expectations written in the protocol and specifying the number of plus or minus calendar days, as opposed to workdays, can help keep study staff and subjects on track.<sup>3</sup> Ask the sponsor or the contract research organization if it will be providing you with a visit-tracker tool. It may be as basic as a Microsoft Excel file, as efficient as a web-based app, or a part of the electronic data capture system.

As the heads of the study, it is crucial that the principal investigator and study coordinator attend the investigator meeting and participate in discussions of the protocol, regulatory issues, enrollment criteria, and the conduct of study procedures. The information ascertained during this meeting is critical to avoiding deviations and should be relayed to the entire study staff. Also, ensure that the all members of the study staff working on the trial are trained and qualified. They should be well versed in good clinical practice guidelines, institutional (particularly IRB) policies, and study visit procedures.<sup>3</sup> Key members should assess whether the study team members have been properly trained on their roles within the study and on how to perform designated tasks. Additional training, or retraining, should be provided in real time, as needed.

Finally, study staff members can take several measures to help boost subjects' compliance. Reminder calls/e-mails to the subjects about appointment times are often beneficial, and study staff should make sure to document their efforts of due diligence. Also, educate the study subjects during the screening and enrollment process on the importance of keeping their study visit dates and maintaining their study visit schedule. Perhaps most important, study staff should be actively engaged in the trial and maintain an attitude of due diligence and a desire for compliance.

## CONCLUSION

A well-thought-out and complete protocol is the cornerstone of a well-executed clinical study. As a primary investigator, be sure to attend all sponsor-related meetings associated with the clinical study. If you have questions on the protocol or other study-related documents, ask them immediately to avoid potential issues later. Finally, take a look at the study visit schedule, and plan ahead to minimize deviations associated with the schedule. ■

1. Liverpool School of Tropical Medicine. Guidance on protocol deviations and violations. <http://www.lstmliverpool.ac.uk/research/clinical-trials>. Released January 11, 2010. Accessed April 16, 2015.

2. Bhatt A. Protocol deviation and violation. *Perspect Clin Res*. 2012;3(3):117.

3. University of Cincinnati. How to Avoid Protocol Deviations and Violations in Clinical Research Conduct. [http://researchcompliance.uc.edu/Libraries/Human\\_Subjects\\_Research\\_IRB\\_Documents/6\\_How\\_to\\_Avoid\\_Protocol\\_Deviations\\_and\\_Violations.sflb.ashx](http://researchcompliance.uc.edu/Libraries/Human_Subjects_Research_IRB_Documents/6_How_to_Avoid_Protocol_Deviations_and_Violations.sflb.ashx). Published May 2011. Accessed April 16, 2015.

### Section Editor Ryan Bouchard

- director of medical devices at Ora
- (978) 332-9574; rbouchard@oraclinical.com