

Good Clinical Practice Q&A: Focus on Protocols

What is the difference between a protocol revision and a protocol amendment?

Protocol revisions are not formally defined in FDA regulations or guidance documents. Generally speaking, a protocol revision refers to a minor change to the protocol – one that has absolutely no impact on risks, clinical decision-making, procedures, or a subject's decision to enroll in a study. Such minor changes might include the correction of spelling mistakes, page renumbering, or changing the name of the corporate medical director. In general, these are administrative housekeeping changes that do not require much, if anything, in the way of an IRB or FDA review. In some cases, such a revised document is called an "administrative amendment."

Protocol amendments, on the other hand, are more significant in nature, and result from sponsor and investigator concerns about deficiencies in the protocol. Such changes would include the removal or addition of an enrollment inclusion/exclusion criterion, the addition of a lab test due to safety concerns, and changes to the definition of what constitutes an adverse event (e.g., certain percentage decreases in platelet counts).

Obviously, distinctions between the significance of certain changes - and whether they are considered revisions or amendments – are not always clear. Is a protocol change that increases the targeted number of enrollees from 500 to 550 a major change, for example? Some would argue that an increase in exposure to risks associated with unapproved drugs is always major, while others might consider the 10 percent increase in patient exposure to be benign and trivial given the universe of other, more significant, changes one might make to a protocol.

All protocol revisions and amendments must be submitted to an IRB, however. Some IRBs merely acknowledge their receipt, while others actively review and approve these changes.¹

Are there any regulations or guidelines on whether patients can enter more than one trial?

No provisions in either the FDA regulations or the ICH GCP guideline prohibit a subject's enrollment in more than one study at the same time.

Many protocols stipulate, however, that individuals cannot be enrolled in a clinical study if they were enrolled in another investigational study within the previous 30 days. The reason for this provision is that sponsors want some level of assurance that the study drug has completely washed out of an individual's systems before he or she is enrolled in a new study. The concern focuses on both the subject's safety (i.e., to avoid a possible drug-drug interaction), and the sponsor's desire to avoid any skewing of the efficacy data based on unknown effects of the previously administered drug and its impact on the efficacy of the current investigational product. Generally, an enrollment prohibition carries over to the entire study time period (e.g., while actively enrolled in a study, a patient should not be enrolled in a second drug study).

In a recent press report on Phase 1 clinical studies (Evans, Smith and Willen, "Big Pharma's Shameful Secret," Bloomberg Markets, December 2005), so-called "professional" clinical trial subjects spoke openly about how they worked around study site controls designed to limit a subject's participation to one study at a time (e.g., lying to site personnel, using fake

documents/identities, enrolling in simultaneous studies rapidly) and about how common such practices were. Some Phase I units spoke about their efforts, including fingerprinting study subjects, designed to limit such practices but conceded that tracking study participation was impossible without a central clearinghouse.²

References

1. "Good Clinical Practice: A Question & Answer Reference Guide", Barnett International, 2005, pg. 145
2. Ibid, pg. 150

Source

"Good Clinical Practice: A Question & Answer Reference Guide 2005," is available for \$39.95 at <http://www.barnettinternational.com/>