From: OC GCP Questions
To: [redacted]
Subject: RE: Waivers, Protocol Deviations
Date: Tuesday, June 10, 2014 1:43:00 PM

Dear [redacted],

Since you are asking about waivers and protocol deviations together, I will assume the waivers are to requirements in the protocol and are granted by the study sponsor. There is very little discussion of protocol deviations in FDA guidance documents and none with regard to waivers that I am aware of.

With regard to protocol deviations, the GCP document ICH E6, which is considered official FDA guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf), states, under section 4 on the investigator, that deviations from the protocol must be reviewed and approved by the sponsor and reviewing IRB before enactment, except when necessary to ensure the rights, safety, or welfare of study subjects (see section 4.5). Any deviations that occur without such prior approval must be reported to the IRB, the sponsor, and, where applicable, regulatory agencies. Additionally, in the compliance program guidance manual (CPGM) which provides instructions to FDA investigators for conduct of an inspection of a clinical investigator (CI) (http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133773.pdf), Part III (Inspectional) discusses protocol deviations with regard to inspecting compliance with the protocol in section D and includes a discussion of what FDA considers a protocol deviation.

Deviations from the protocol lessen the poolability of study data across sites and therefore the power of the given study. Therefore, sponsors attempt to write study protocols such that deviations will be as infrequent as possible. In assessing the data submitted to support marketing, FDA therefore needs to have complete data on all protocol deviations that occurred during the study to ensure the sponsor performed a proper analysis of study results.

While I am not aware of any discussion in a guidance document, FDA has addressed protocol waivers in Untitled and Warning Letters following FDA inspections, particularly to sponsors who have been found to give numerous protocol waivers. Since the effect is the same on the poolability of the data as protocol deviations, sponsors should discourage requests for protocol waivers. If many requests are received for a given study, the sponsor needs to reassess the protocol to determine if an amendment is necessary with regard to any requirement CIs find difficult to meet. A meeting with CIs may be necessary to determine if such requirements are too restrictive given the nature of the intended study population or present a major departure from standard medical practice that the CIs do not see as warranted for accruing the desired study endpoints.

Hope this information is useful. If you need further information and/or have additional questions, please feel free to contact us once again at the official GCP mailbox, gcp.questions@fda.hhs.gov. You may also find it useful to access the set of redacted GCP e-mails found at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm since we find that many questions and concerns are repeated over time.
Sincerely yours,
Jean Toth-Allen, Ph.D.
Office of Good Clinical Practice
Office of the Commissioner, US FDA
This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: [redacted]
Sent: Tuesday, June 10, 2014 11:33 AM
To: OC GCP Questions
Subject: Waivers, Protocol Deviations

HI,

Would you be able to direct me to where I can find FDA guidance on Waivers and Protocol Deviations? I recently started working at a small startup company and SOPs are being developed regarding Waivers and Protocol Deviations. In general, I am aware that waivers are not an ideal way to proceed however for an early phase oncology trial they were granted.

Thank you for your help!

Kind regards,
[redacted]