From: OC GCP Questions
To: [redacted]
Subject: RE: Statistical Analysis Plan Approval Question
Date: Thursday, February 06, 2014 10:52:00 AM

Good Morning,

I am not aware that the timing of signatures for the two documents are discussed in FDA regulations or guidance, however, I would refer you to a number of guidance document which discuss the need for a prespecificed statistical analysis plan. For example, the guidance document, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (May 2007), at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf . In this guidance (page 9), it provides that FDA and the applicant should agree prospectively on the statistical analysis plan for the study. Likewise, in the guidance document for the "Use of Bayesian Statistics in Medical Device Clinical Trials" (February 2010) (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm), FDA recommends close collaboration and agreement with FDA and your statistical and clinical experts. The guidance document, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" (December 2009), at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. On page 24, this guidance provides, "It is critical that the clinical trial protocol define the endpoint measures and the criteria for the statistical analysis and interpretation of results, including a specification of the conditions for a positive clinical trial conclusion, because determination of these criteria and conditions after data are unblinded will not be credible." On page 27, it provides, "Every protocol should describe the principal data analysis features in the statistical section with a detailed elaboration of the analysis in an SAP. We intend to determine the adequacy of clinical trial data to support claims in light of the prespecified method for endpoint analysis. We usually view unplanned or post hoc statistical analyses conducted after unblinding as exploratory and, therefore, unable to serve as the basis of a labeling claim of effectiveness"

In addition, the ICH E8 guideline, "General Considerations for Clinical Trials" (July 1997), states, "A description of the statistical methods to be employed, including timing of any planned interim analysis(es) should be included in the protocol (see ICH E3, ICH E6 and ICH E9). The results of a clinical trial should be analysed in accordance with the plan prospectively stated in the protocol and all deviations from the plan should be indicated in the study report" (section 3.2.4, pages 11-12). (See http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf).

In conclusion, for a particular clinical trial of a FDA-regulated product, the relevant FDA review division should be consulted early in the process regarding finalizing the statistical analysis plan.

I hope this information is helpful. Please contact us again at gcp.questions@fda.hhs.gov should you have additional questions.

Patrick J. McNeilly, Ph.D., C.I.P.
Office of Good Clinical Practice
Food and Drug Administration

From: [REDACTED]
Sent: Thursday, February 06, 2014 9:45 AM
To: OC GCP Questions
Subject: Statistical Analysis Plan Approval Question

To Whom It May Concern,

Can you please provide guidance on the timing of the signature approval of the Statistical Analysis Plan (SAP) in relation to the protocol signature approval.

Thank you!