precise requirements regarding who needs to do what and when) can result in the trial not reflecting 'real world' clinical practice, as well as causing too many protocol deviations." Moreover, "[t]oo many complex assessments can tire subjects and site personnel, resulting in missed or inaccurate evaluations as well as subjects discontinuing from the study."

A variety of protocol deviations are described in the Warning Letters cited below. These deviations include:

- Failure to report deviations to the FDA;
- Failure to comply with the protocol's inclusion/exclusion criteria;
- Failures in randomization;
- Failure to comply with dosing schedule;
- Failure to comply with instructions to carry out laboratory procedures;
- Failure to comply with dose modification requirements;
- Failure to report illnesses during the study;
- Failure to report concomitant treatments on the case report form.

d. Failure to Report Deviations to FDA

Referring to the "investigational plan," the letter referred to various protocol deviations. The letter complained that (125):

> An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan, and all applicable regulations for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under clinical investigation.
>
> Our investigation reveals that you failed to fulfill your responsibilities as a clinical investigator under 21 CFR 812.100 and 21 CFR 812.110(b) in that **you failed** to maintain an adequate internal quality control program and **to immediately document and report all protocol deviations**, as required by the protocol. More specifically, on several occasions, your staff falsified study subject consent forms, which falsifications you have admitted the existence of in a letter dated January 20, 2004.
>
> Examples of some of the falsifications are as follows: The consent forms for subjects . . . were apparently filled out by a clinic staff member who signed as both the study subject and as the staff member administering the consent, as you explained in your letter . . . [t]he consent forms for study subject [redacted] and [redacted] were apparently filled out by a staff member who signed as a study subject using false names, as you explained in your letter . . . [o]ne study subject was apparently enrolled three times under the same name but under different study subject numbers (. . . on 6/10/03, . . . on 8/28/03, and . . . on 11/04/03); as you explained in your letter.

e. Failure to Comply With the Protocol's Inclusion/Exclusion Criteria

The letter complained that (126), "the protocol and the HIV-1 Sample Collection Case Report Form Instructions require that enrolled subjects be 18 years of age or older. However, on at least three occasions detailed in the table below, you enrolled subjects . . . in the study despite the fact that **they were under the age of 18** at the time of study enrollment, all this in violation of 21 CFR 812.100."

In another Warning Letter concerning failure to comply with inclusion/exclusion criteria, FDA complained that (127), "[t]he study protocol excluded subjects with severe

[125]Warning Letter No.CBER-07-001 (October 12, 2006) from Mary A. Malarkey, Office of Compliance and Biologics Quality, CBER, U.S. Food and Drug Administration.

[126]Warning Letter No.CBER-07-001 (October 12, 2006) from Mary A. Malarkey, Office of Compliance and Biologics Quality, CBER, U.S. Food and Drug Administration.

[127]Warning Letter to Allegheny General Hospital (no Warning Letter No.) (May 23, 2007) from Timothy A. Ulatowski, Office of Compliance, Center for Devices and Radiological Health, U.S. Food and Drug Administration.