IV. DISTINCTION BETWEEN STOPPING TREATMENT AND WITHDRAWING FROM THE STUDY

FDA's Guidance for Industry E6 (20) mentions the option of withdrawing from a study.

Fleming (21) provides a fine point regarding dropping out from a study and withdrawal of consent. There are only two valid reasons a subjects can leave a clinical trial, first, withdrawal of consent and second, achieving of all required efficacy and safety end points. According to Fleming (22), it is an unfortunate common practice for Clinical Study Protocols to provide a list of reasons that the subject will be "off study," such as inability to tolerate the intervention, toxicity, physician choice, or need for other therapies. These may be valid reasons for nonadherence (for being off study treatment), but not for being dropped from the study.

Thus, the Clinical Study Protocol should separately list the two reasons a patient could go "off study" and the many reasons the patient could discontinue the treatment, with an indication that efforts should be made to ensure patients who stop the study treatment be consistently followed for outcomes unless they have withdrawn consent.

V. ETHICAL DOCTRINES

Ethical doctrines relevant to consent forms include the Belmont Report (1979), the Declaration of Helsinki (1964), and the Nuremberg Code (1947). The Belmont Report arose from an Act of the US Government, namely, the National Research Act of 1974. This Act created the *National Commission for Protection of Human Subjects of Biomedical and Behavioral Research*, which issued the *Belmont Report*. These ethical doctrines arose, in part, as reactions to notoriously unethical experiments on human subjects. As reviewed by Rice (23), these notorious studies include experiments by Nazis on prisoners, the Willowbrook Hepatitis Studies, and the Tuskegee Syphilis Study.

While the *Belmont Report* was not codified as any law or rule of the US Government, it did serve as a basis for parts of the CFR that concern consent forms used for clinical trials (24). These parts are Title 21 CFR Sections 50 and 56, and Title 45 CFR Section 46. The combination of 21 CFR 50 and 45 CFR 46 is called *The Common Rule* (25,26,27).

[20]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. E6 good clinical practice: consolidated guidance; April 1996.

[21]Fleming TR. Addressing missing data in clinical trials. Ann. Intern. Med. 2011;154:113–7.

[22]Fleming TR. Addressing missing data in clinical trials. Ann. Intern. Med. 2011;154:113–7.

[23]Rice TW. The historical, ethical, and legal background of human-subjects research. Respir. Care 2008;53:1325–9.

[24]Zimmerman JF. The Belmont Report: an ethical framework for protecting research subjects. The Monitor; Summer 1997.

[25]Mehlman MJ, Berg JW. Human subjects protections in biomedical enhancement research: assessing risk and benefit and obtaining informed consent. J. Law Med. Ethics 2008;36:546.

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[27]Luce JM. Informed consent for clinical research involving patients with chest disease in the United States. Chest 2009;135:1061–8.