The importance of the Protocol as the gold standard for the clinical study is evident from the fact that a formal amendment process is required by the CFR when changes are to be made in a Protocol, once the actual clinical study has been started. Amendments to the Protocol find a basis in the CFR, as shown by the following excerpt (7):

> (b) *Changes in a protocol.* (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

a. Clinical Study Protocol Provides the Inclusion/Exclusion Criteria and Stratification

The Protocol sets forth inclusion criteria, exclusion criteria, and the stratification of the study subjects. These three concepts may overlap each other. Typically, the title of the clinical study identifies some, but certainly not all, of the inclusion criteria. The full list of the inclusion/exclusion criteria occurs in the synopsis, as well as in the body of the Protocol. It is possible to disclose the same criterion in the list of inclusion criteria, and also in the list of exclusion criteria. For example, the Protocol can have the *inclusion criterion*: "all subjects must be treatment naive," and also the *exclusion criterion*: "subjects must not have received prior treatment." Regarding the possibility of having the same criterion in both lists, it has been recommended that this sort of duplicity be avoided to prevent confusion during subsequent revisions or versions of the document (8).

Examples of titles are shown below, for a number of cancers and infectious diseases. The title of the following Clinical Study Protocol is one of the longest titles ever given to a Clinical Study Protocol. The title reveals an *exclusion criterion*, namely, that the patients must not have been treated for their multiple myeloma. The title also reveals an *inclusion criterion* that takes the form of an "or" statement, that is, they must be either 65 years of age or older, or they must not be candidates for stem cells. Consider the following title, which is from the cited clinical trial (9):

- *Title:* A Phase III, Randomized, Open-Label, 3-Arm Study to Determine the Efficacy and Safety of Lenalidomide (Revlimid®) Plus Low-Dose Dexamethsome When Given Until Progressive Disease or for 18 Four-Week Cycles Versus the Combination of Melphalan, Prednisone, and Thalidomide Given for 12 Six-Week Cycles in Patients with Previously Untreated Multiple Myeloma Who Are Either 65 Years of Age or Older or Not Candidates for Stem Cell Transplantation (10)

  According to the above title, one of the inclusion criteria is that the subjects must be women, and the women must have breast cancer. Another inclusion criterion is that the cancer must be at either stages 0, I, or II.

[7]21 CFR 312.30 (b) (version of April 1, 2010).

[8]Wood LF, Foote MA. Targeted regulatory writing techniques. Clinical documents for drugs and biologics. Basel/Switzerland: Birkhäuser Verlag; 2009. p. 56.

[9]Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N. Engl. J. Med. 2014;371:906–17.

[10]Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N. Engl. J. Med. 2014;371:906–17.