JOHNS HOPKINS
U N I V E R S I T Y

Center for Clinical Trials

Department of Biostatistics
Department of Epidemiology
Department of International Health

Department of Medicine
Department of Ophthalmology
Oncology Center

(7:17am Friday) 25 August 2000

Memorandum

To: Directors of Coordinating Centers in the Center for Clinical Trials (JT, SP, JH, BM, NM, AG) and Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Randomization override good practice policies and procedures (GPPP)

Definitions (*Clinical Trials Dictionary*)

protocol departure *n* - 1. A **departure** from specified **treatment**, **examination**, or **data collection** procedures in a **study**. 2. **treatment protocol violation** 3. **protocol change** (not recommended) syn: protocol deviation rt: **protocol infraction**, **protocol violation**

protocol exemption *n* - An authorized departure from an established protocol; an approved **protocol departure**.

protocol infraction *n* - 1. **protocol violation** 2. **protocol departure**, **protocol deviation**

protocol override *n* - A decision, after due consideration, to proceed with some act or procedure contrary to requirements of the protocol, eg, as with a **protocol exemption** or **randomization override**.

protocol violation *n* - 1. A **protocol departure** considered to be serious, eg, administration of the wrong **treatment** or **enrollment** of an ineligible person; especially when avoidable. 2. Any **protocol departure** whether or not considered to be serious.

randomization override *n* - A decision, after due consideration, to proceed with **randomization** in the presence of contraindications for randomization, eg, the decision to randomize a person who does not satisfy eligibility requirements for randomization.

If a rose is a rose by any other name, than a protocol violation is a protocol violation by any other name. We can call them protocol exceptions, protocol exemptions, protocol deviations, or use other bland sounding names for them but they remain protocol violations.

"Dispensations" granted for violations, no matter how convincing the rationale for dispensation may be, most likely will count for naught if the FDA audits for cause. To be convinced of that, one need merely sit through the review of the FIAU-FIAC tragedy (a series of trials that resulted in the death of several patients and liver transplants for several others). The people at the FDA

Room 5010 • 615 North Wolfe Street • Baltimore, Maryland 21205 • 410 955-8175 • Fax: 410 955-0932
E-mail: cctmail@jhsph.edu • Web site: http://www.jhsph.edu/Research/Centers/CCT

conducting the review regarded the protocol as a blueprint and defined violations as acts contrary to the written protocol, regardless of explanations tended. The people in the enforcement portion of the FDA have the same amount of sympathy for a noncompliant investigator as a policeman writing a ticket for running a red light.

Some insight into the "ticket" writing behavior of the FDA can be obtained by visiting the http://www.fda.gov. The website contains copies of warning letters issued by the FDA, as made available under the 1996 amended FOIA. A prominent feature of warning letters issued to clinical investigators relates to enrollment of ineligible persons. Sample language from the three most recent such letters posted, as issued from the Center for Biologics Evaluation and Research is as follows:

Letter to EJ Kopp; 21 June 2000 (CARE Center, Raleigh, North Carolina)
Two of 14 subjects did not meet protocol criteria regarding duration of _____.

Letter to HR Terebelo; 20 June 2000 (Providence Cancer Center, Southfield, Michigan)
Subject eligibility: Class III-IV congestive heart failure is an exclusion criteria, however, subject _____ was enrolled in the study on 12/14/95 with Class III-IV congestive heart failure (diagnosed 10/3/95). ... We view enrollment of ineligible subjects as a serious protocol deviation.

Letter to JM Isner; 28 April 2000 (St Elizabeth's Medical Center; Boston, Massachusetts)
Subject _____ was enrolled into study VEGF2-CAD-001 (cardiac arterial disease study); however, the subject met the protocol exclusion criteria.

Coordinating Centers, at best, have only limited means for preventing violations. In general, they are reduced to detecting and reporting violations after the fact. They do, however, have the means of preventing enrollment of persons not eligible for randomization by withholding release of assignments in the presence of disqualifying conditions.

The series of GPPP P&P statements below are proposed with the view that the CC should not override safeguards designed to prevent randomization of persons not eligible for randomization and that overrides for procedural violations (eg, in regard to missing baseline data or baseline data not collected within the permissible time window) should be granted only sparingly and then only after due consideration.

P&P 1: Consider a person to be ineligible for randomization if the person does not met all eligibility requirements specified in the study protocol, or if the person has at one or more excluding conditions.

P&P 2: Design the randomization system to prevent release of an assignment until essential baseline data have been recorded, all listed eligibility conditions have been satisfied, and the person is known to be free of excluding conditions.

P&P 3: Do not honor requests to randomize persons not meeting eligibility requirements specified in the study protocol, even if the departures are seemingly minor (eg, a laboratory value just slightly below the minimum for enrollment).

P&P 4: Limit overrides of randomization to cases involving interpretation of protocol and to minor infractions regarding collection of baseline data.

P&P 5: Set up procedures for requesting an override; detail in writing; distribute to study investigators via numbered memo.

P&P 6: Set up internal procedures for reviewing and approving individual requests for overrides; procedure to include review of the request by the CC director or deputy directors; detail procedures in a memo to CC personnel; copy to clinic directors and clinic coordinators.

P&P 7: Withhold release of assignment in the presence of an excluding condition; release only if the condition is resolved.

P&P 8: If the trial is designed to allow for waivers of eligibility requirements:

- The protocol submitted to IRBs should indicate that waivers are allowed
- Should indicate the conditions under which waivers will be considered and medical conditions that are subject to wavier
- Should outline the system for deciding whether a wavier is granted
- Requests for waivers should not be honored at the CC until the system for waivers has been reviewed and approved by responsible IRBs

P&P 9: If a system of waivers exists as outlined in P&P 8 and the CC grants a randomization wavier, that wavier should not be granted until or unless the following applies:

- The responsible study physician requests the waiver in writing; that request should detail the reasons for the request and reasons why the enrolling physician believes it is safe to enroll the person in question
- That the request for wavier is signed by the requesting physician and supported by a fellow clinician
- That the order to randomize in the CC is not given in absence of written justification or if there is concern that enrollment places the person at risk of harm because of the medical condition being overridden.
- If the request is granted, that the enrolling investigator notify his or her IRB of the override and the reasons for it, that such notice be provided within one working day of the override, and that the notification and acknowledgment of the notification be on file at the investigator's institution and at the CC.

P&P 10: Set up the randomization procedure to check for collection and recording of essential baseline data; withhold release of assignment if essential baseline data are missing.

P&P 11: Set up the randomization procedure to determine whether baseline data have been collected within allowable time windows; withhold assignment if windows are violated until or unless requirement is overridden as per P&P 6.

P&P 12: That the CC provide clinics, via numbered memos, with a written statement of its policy on randomization; statement should detail conditions under which the CC will refuse randomization, procedures for requesting and reviewing requests for overrides of randomization safeguards, and conditions under which randomizations will be refused for missing baseline data or baseline data outside allowable time windows.

P&P 13: That the CC provide to study investigators reports at periodic intervals designed to enumerate protocol violations, requests for overrides of randomization, the reasons for such requests, and the outcome of those requests; the reports should be by clinic and by type or class of violation or request.