



By Federal Express

Food and Drug Administration  
Center for Devices and  
Radiological Health  
2098 Gaither Road  
Rockville, MD 20850

## WARNING LETTER

AUG 30 2000

Mr. Leslie D. Hirsh  
President and Chief Executive Officer  
The Cooper Health System  
1 Cooper Plaza  
Camden, New Jersey 08103

Dear Mr. Hirsh:

During the period of February 22 - March 1, 2000, Ms. Judith A. Jones, an investigator from the Food and Drug Administration's (FDA) New Jersey District Office inspected the Cooper Health System Institutional Review Committee, the Institutional Review Board (IRB). The purpose of the inspection was to determine whether the IRB's activities and procedures for the protection of human subjects complied with Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. These regulations and observations apply to clinical studies of all products regulated by the FDA.

Our review of the information from this inspection revealed that the IRB failed to adhere to pertinent federal regulations as contained in 21 CFR Parts 50 and 56. The findings were listed on the Form FDA-483, "Inspectional Observations," which was presented to and discussed with you at the conclusion of the inspection. Dr. Carolyn Beckes, Vice President of Medical Affairs and Chief Compliance Officer, and Dr. Louis Zeiger, Institutional Review Committee Chairman, were also present during this discussion. The following violations are not intended to be an all-inclusive list of the IRB deficiencies.

1. **Failure to have adequate written procedures for conducting initial or continuing review of research as required by 21 CFR 56.108 (a) and 21 CFR 56.115(a)(6).**

The regulations require IRBs to adopt and follow written procedures for conducting their review of research. Neither the IRB's nor the parent institution's written procedures were adequate.

For example, these procedures do not describe how the IRB determines significant risk (SR) and nonsignificant risk (NSR) for medical device investigations as described in 21 CFR 812.66. In addition, there are no procedures or directives for review of a medical device available under a Humanitarian Device Exemption as described in 21 CFR

814.124 and Section 520(m) of the Federal Food, Drug, and Cosmetic Act. Also, neither the IRB's nor the Cooper Health System institution's written procedures specifically describe which projects require continuing review more often than annually and which projects need verification from other sources.

The written procedures do not cover all required functions and operations of the IRB. These procedures do not describe, in detail, the responsibilities of other institutional committees or other persons such as the Institution Bio-safety Committee, or "ad hoc" committees. The role of primary reviewers in the review of proposed research and the continuing review of studies is not described. In addition, procedures do not fully describe what constitutes a "conflict of interest" by IRB members.

**2. Failure to follow written procedures as required by 21 CFR 56.108, 21 CFR 56.109, and 21 CFR 50.25.**

According to the IRB's procedures, clinical drug and medical device studies under an investigational new drug (IND) or investigational device exemption (IDE) do not qualify as research for expedited review. However, there were instances where the IRB Chairperson used expedited review for significant protocol amendments to research approved under an IDE or IND. For example, the IRB Chairperson used expedited review for protocol amendments to studies [REDACTED]

The IRB failed to follow its written procedures to ensure prompt reporting by the clinical investigators who are involved in research and for ensuring that changes in approved research are not initiated without the IRB's review and approval. In two of four studies reviewed by the FDA, the IRB failed to review protocol amendments and revisions for studies [REDACTED]. In addition, the IRB failed to ensure the prompt reporting of all serious adverse events including any deaths in study [REDACTED]

The IRB failed to include all informed consent elements as required in their written procedures for studies [REDACTED]. The IRB failed to follow its written procedures to notify FDA when they suspended IRB approval of study [REDACTED]

**3. Failure to maintain adequate records of IRB activities and operations as required by 21 CFR 56.115.**

The IRB failed to maintain adequate records of IRB activities, including the review of research. The IRB's practice of filing protocols, periodic reports, and other IRB correspondence is inadequate. The record-keeping system does not allow the IRB to

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readily determine the status of a study or to locate all documentation associated with a specific protocol.

Documentation of the IRB membership and its roster was inadequate in that it did not identify those who were knowledgeable in regulations, institutional commitments, applicable law, and standards. The records do not identify the relationship of each member to another member and to the institution. The records did not identify primary reviewers.

The violations listed above may not be an all-inclusive list of the deficiencies in your IRB operations. As an IRB, it is your responsibility to ensure that investigations you approve are conducted in accordance with applicable FDA regulations. FDA observed similar activities and practices by the IRB during a 1996 inspection. At that time, the IRB responded and promised to comply with FDA requirements and implement new policy and procedures. Despite the assurances provided in the IRB's response, violations similar to those noted above persisted.

Please advise this office, in writing, **within fifteen (15) working days of receipt of this letter** of the specific steps that you have taken to correct these violations and other violations known to you, and to prevent the recurrence of similar violations in current or future studies. Failure to respond can result in further regulatory action without additional notice. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Your corrective actions may be reviewed and verified during a future inspection.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I, (HFZ-311), 2098 Gaither Road, Rockville, Maryland 20850, Attn: Kevin Hopson, Consumer Safety Officer. If you have any questions or require additional time to respond, you may contact Mr. Hopson at (301) 594-4720, extension 128.

We have sent a copy of this letter to our New Jersey District Office, 10 Waterview Boulevard, Third Floor, Parsippany, New Jersey 07054. We request that you send a copy of your response to that office.

Sincerely,

  
for Steven M. Niedelman  
Acting Director  
Office of Compliance  
Center for Devices and Radiological Health

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cc: Louis Zeiger, M.D.  
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