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Food and Drug Administration
Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville MD 20852-1448

Warning Letter

MAR - 9 2000

L. Terry Chappell, M. D., Secretary
Great Lakes College of Clinical Medicine IRB
122 Thurman Street
Post Office Box 248
Bluffton, Ohio 45817

Dear Dr. Chappell:

From November 16 to December 1, 1999, Mr. Hugh McClure III, an investigator with the Food and Drug Administration (FDA), inspected the Great Lakes College of Clinical Medicine (GLCCM) Institutional Review Board (IRB). The purpose of this inspection was to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

A copy of the list of Inspection Observations (FDA Form 483) left with you at the end of the inspection is enclosed, and is referenced below. Our inspection noted the following deficiencies:

- 1. Failure to prepare detailed written procedures for conducting the review of research, including periodic review.**
[21 CFR 56.108(a), 56.115(a)(6)]

A. There are no detailed instructions as to how the IRB is to operate.

The document titled, "Basic Policy for Protection of Human Research Subjects for The Great Lakes College of Clinical Medicine" does not constitute detailed written procedures. Simply restating or rewording the federal regulations does not meet the requirement for written procedures.

The regulations require that the IRB shall adopt and follow written procedures for conducting its review of research. The procedures should describe the IRB organization, how many voting members make up the IRB, how IRB members are selected, explicitly outline how applications are processed, who will receive pre-meeting materials to review, how the review is to be conducted, how decisions are made, what criteria are used,

to determine the basis of approval of research proposals, the frequency of continuing review, how continuing review is conducted, how controverted issues are decided, and describe how records must be maintained to fulfill federal requirements. The written procedures should explicitly define how the IRB will consider research proposed by IRB members, and how the IRB will avoid conflict of interest in its reviews.

B. The procedures for conducting periodic review are not adequate.

Written procedures should describe in detail the following aspects of IRB continuing review operations: how and when renewal notices are sent to clinical investigators, how administrative staff processes interim reports, how periodic reports are discussed, the voting method the IRB will use for continuing reviews, and IRB follow-up activities in the event of a lack of response or an incomplete response. The procedures should specify how the IRB will document its actions for ensuring that progress reports are submitted and reviewed at the specified time intervals.

The content of progress reports should be described in detail so that clinical investigators will provide the IRB with interpretable periodic reports. For example, Dr. Royal submitted approximately 50 pages of individual subject information with no summary of adverse events, risks, or benefits for IRB consideration in a periodic report. These data are not readily interpretable by the IRB, and therefore do not provide a periodic report which is meaningful for the IRB's determination as to whether the study should continue, be modified, or terminated.

C. Written procedures should describe how the IRB will determine when an investigation involves an investigational product subject to FDA regulation. The IRB's "Project/Protocol Information form for submission of research protocol for review" does not request information to determine whether the research involves a product regulated by FDA, and the IND or IDE number associated with the investigational drug, biologic, or device. The IRB also does not confirm whether the clinical investigator appropriately concluded whether an IND or IDE is required. The IRB should have a mechanism in place to contact FDA to discuss proposed research if the IRB is unsure whether an IND or IDE is required. The IRB should not rely solely on a clinical investigator's interpretation of FDA requirements. See item 5A, below.

D. Written procedures should describe how the IRB will determine when an investigation involves a significant risk device.

- E. The IRB should develop procedures for incorporating revisions to proposed research and for notifying the full IRB of those revisions. Written procedures should describe how the IRB will assure that studies “approved” pending modifications are not initiated before the IRB accepts the modified documents.
- F. Written procedures should describe the extent to which the IRB will review web site advertisements for studies approved by the IRB. information on web sites is considered advertising.
- G. The written procedures should explain the role of the IRB Chair. The minutes of the meetings conducted on September 20, 1997, noted that the IRB Secretary, Dr. Chappell, chaired the meeting even though Dr. Carter was in attendance. In addition, Dr. Chappell conducted the expedited review of at least one study; see item 10, below. Please comment in your reply.
- H. There are no written procedures to describe how adverse reaction reports are reviewed, by an “expedited” process or by the full IRB.

There are no written procedures for ensuring prompt reporting to the appropriate institution officials and FDA of the following:

- i. Any unanticipated problems involving risks to human subjects or others.
- ii. Any instance of serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB.
- iii. Any suspension or termination of IRB approval.

The IRB procedures should define whether the IRB will review proposed research to be conducted only in foreign countries, and whether there should be additional procedures when the proposed research is only conducted out of the United States. The IRB approved the study titled “Induced Malaria as Therapy for HIV Infection” conducted in China. The IRB did not review the Chinese translation of the protocol or consent form, and has no information about how subjects and malaria parasite donors are recruited and screened. See item 2, 6, and 11, below.

- K. The written procedures should describe how the IRB will review proposed research and proposed consent forms for information regarding the charging of study subjects for investigational products under FDA jurisdiction. The information should also be provided to clinical investigators. FDA prohibits charging for investigational drugs and biologics unless specifically approved with the limitations described in 21 CFR § 312.7. The limitations for charging for investigational devices are set forth in 21 CFR § 812.7.
- L. The IRB should consider requiring investigators to include the IRB approval date on consent forms to assure that the current consent form is used when the original consent form has been amended. This is not required by regulation, but it is considered to be a good practice.

2. Failure to consider community attitudes and cultural backgrounds. [21 CFR § 56.107(a)]

The IRB reviewed and approved the study titled “Induced Malaria as Therapy for HIV Infection” conducted only in China. There is no documentation as to how the IRB considered the local community attitudes or cultural attitudes towards two of the significant aspects of the research: the direct injection of blood from one person into another person, and that the subject will be administered live malaria parasites. Please explain how the IRB determined that this research was acceptable for Chinese citizens. Would the IRB’s approach have been different if the research was conducted in the United States?

3. Failure to include at least one IRB member who is not otherwise affiliated with the institution. [21 CFR § 56.107(d)]

The regulation states that an IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. The “GLCCM IRB Membership List 1999” identifies that the following individuals are “non-members”: Effie Buckley, R.N.; James Carter M.D.; George Kindness, Ph.D.; Barbara Faber, J.D.; and Frances Greenway.

We deem these individuals to be affiliated with GLCCM for the following reasons: Dr. Carter is the IRB Chair, and his curriculum vitae states that he was elected to Life membership in the Great Lakes Association of Clinical Medicine. Ms. Barbara Faber is the spouse of William Faber, D.O., a scientific member of the IRB. Ms. Buckley is employed by F. Timothy Gilford, M.D., who is a scientific member of the IRB. Ms. Greenway is employed by Theodore Rozema, M. D., who is a scientific member of the IRB. As employees of IRB members who are also members of the Great Lakes Association of Clinical Medicine,

Ms. Buckley and Ms. Greenway have connectors to the IRB which could influence their consideration of proposed research. Although they may not serve in the role of nonaffiliated member, they may continue to serve as IRB members.

Mr. Bob L. Smith is also identified as a nonaffiliated member. Mr. Smith's employer is a laboratory contracted to perform laboratory analyses for at least one study approved by GLCCM. The employer's web site also provides information about upcoming GLCCM conferences. This employer/employee relationship constitutes an affiliation to GLCCM. Mr. Smith may continue to serve as an IRB member, but he cannot be considered to be nonaffiliated with the institution. Also see item 4B, below.

Given that, by charter, the IRB will review only protocols proposed by GLCCM members, please explain in detail how you will recruit, train, and include members who have no affiliation with GLCCM.

4. Failure to insure that research is reviewed free from conflict of interest. [21 CFR § 56.107(e)]

IRB members did not always exclude themselves from deliberation and voting on their own research projects, and on projects for which they have a financial interest. The following are examples:

A. IRB member Dr. George Kindness participated in deliberations, made the motion to approve, and/or voted on the following studies in which he was personally involved:

i. "Stimulated Autologous Immune Serum and Autologous Tumor Vaccine in the Treatment of Refractory Solid Tumors (GAT)." Dr. Kindness conducted the preliminary review, made the motion to approve, and voted on the study. Dr. Kindness' business is the laboratory integrally involved in the study. The IRB concluded that additional laboratory tests were to be used to monitor the results.

ii. "Multi-Centered Project #M019 – Investigational Proposal for the Study of AM-2." Dr. Kindness' business was involved in the study.

iii. Dr. Kindness chaired and voted on modifications to the project titled, "Multi-Centered Clinical Registry on EDTA Chelation Therapy and Cardiovascular Disease" even though his business would perform all study-related laboratory tests.

B. IRB member Mr. Bob Smith made the motion to approve the study submitted by Dr. Kotsanis titled, "Use of Secretin to Remediate Autism, ADD, ADHD, and PDD" during the meeting held on November 20, 1998. Mr. Smith is employed by the Great Smokies Laboratories, which is identified in the protocol as the laboratory to perform protocol-required tests.

5. Failure to exercise authority to require modification in (to secure approval) or disapprove all research activities covered by these regulations. [21 CFR § 56.109(a)]

- A. The IRB does not assure that studies subject to FDA regulation are conducted under an investigational new drug application (IND) or investigational new device exemption (IDE). Research that is subject to FDA oversight must be performed under an effective IND or IDE, unless the IRB determines that a device study poses a non-significant risk (NSR). In this case, the sponsor and clinical investigator do not need an IDE; however, the study must comply with the abbreviated IDE requirements [21 CFR 812.2(b)]. In instances when an IND or IDE is necessary, the IRB should not approve research in the absence of an IND/IDE. The IRB appears to lack personnel who are knowledgeable about FDA requirements, and who can distinguish when proposed research must be performed under an IND or IDE. See item 1C, above.
- B. The meeting minutes of March 13, 1999, document that an IND was required for a study proposed by Dr. Hauser. The IRB approved the study even though an IND was not submitted. An IRB cannot supercede the authority of FDA to oversee the conduct of clinical studies involving investigational products.
- C. Current IRB practices are inadequate to assure that studies "approved" pending modifications are not initiated before the IRB accepts the modified documents. Review of meeting minutes shows that the IRB often recommends approval of a proposed clinical investigation pending certain revisions to be made by the investigator, but there is no procedure in place to confirm that required modifications have been completed. Also see item 8. below.
- D. The IRB reviewed the protocol submitted by Dr. Page, titled "Gene Activated Therapy (GAT) for the Treatment of Cancer" during the meeting held September 20, 1997. The IRB meeting minutes list six (6) "suggestions" regarding the study design and conduct, including the following: define the duration of the study and follow-up period, include lab tests to monitor the patients, define the centrifugation process, revise the consent form, consider adding an independent monitor, and provide

additional background information. These so-called “suggestions” are actually important questions or modifications that should have been addressed in the design of the clinical study prior to, or as a condition of its approval. The IRB notified Dr. Page that the study was approved in a letter dated October 9, 1997. However, the six “suggestions” listed above were not included in the letter to Dr. Page.

- E. The IRB does not review the proposed research to assess whether the study involves charging subjects for investigational products under FDA jurisdiction. See item 1K, above.

6. Failure to require that information given to subjects as part of informed consent is in accordance with the provisions of 21 CFR § 50.25. [21 CFR § 56.109(b)]

The IRB approved consent forms that do not meet federal regulations. The consent forms submitted by Dr. Page and Dr. Heimlich and approved by the IRB are representative examples:

- A. The consent form submitted with the original protocol titled “Gene Activated Therapy (GAT) for the Treatment of Cancer” was approved by the IRB on September 20, 1997. The consent form approved by the IRB is deficient for the following reasons (not a complete list):
 1. The consent form is written in the form of a protocol and does not directly address the perspective of a potential study subject.
 2. The consent form is written using technical language and medical jargon not readily understandable by a lay person.
 3. Item 13 (first item 13 on page 2) implies that the safety of this investigational product has been established. The purpose of this study is to determine whether the investigational product is safe and effective.
 4. The consent form does not contain the following required elements:
 - i. An explanation of the procedures to be followed and the expected duration of the subject’s participation. The procedures described in item 5 are vague as to the number of blood donations, the number, site, and timing of serum injections, who will perform the injections, the requirements of participants to travel, and other procedures.

- ii. The identity of whom to contact in the event of research-related injury to the subject.
 - iii. An explanation of whom to contact for answers to questions about research subjects' rights.
 - iv. A detailed explanation of the risks of participating in the research. The reference to risks is vague, confusing, and incomplete.
5. The paragraphs are not sequentially numbered, which could be confusing to potential study subjects. Some items are repeated.
- B. The study described in item 6A, above, was subsequently renamed "Stimulated Autologous Immune Serum and Autologous Tumor Vaccine in the Treatment of Refractory Solid Tumors (GAT)." The consent form provided by Dr. Page in the periodic report dated February 29, 1999 [sic] is deficient for the following reasons (not a complete list):
- 1. The consent states "I understand ... that I may have a copy of this document. " 21 CFR § 50.27(a) requires that a copy shall be given to the person signing the form.
 - 2. The consent form does not contain the following required elements:
 - i. An explanation of the procedures to be followed expected duration of the subject's participation.
 - ii. A description of any benefits to the subject or to others which may reasonably be expected from the research. The benefits of the research should be discussed separately from the alternate procedures which are described in the seventh paragraph.
 - iii. The consent form states, "Compensation for injuries as a result of participating in this study is not available except as may be required by law" (emphasis added). It is not reasonable that prospective subjects would understand what is required by law. This phrase requires clarification.
 - iv. The identity of whom to contact in the event of research-related injury to the subject.
 - v. An explanation of whom to contact for answers to questions about research subjects' rights.

C. The English version of the consent form for the study titled, "Induced Malaria as Therapy for HIV Infection" is deficient for the following reasons (this is not a complete list):

1. The consent form does not adequately describe the procedures to be followed. The consent form states, "Natural infusion of malaria parasites will be administered on day 1." The actual procedure involves injection of blood from a malaria-infected person into the study subjects. There is no description of the steps taken to screen malaria parasite donors for pathogens.
2. The duration of the study is described as "unlimited." The long-term risks of the study and the frequency of follow up are not defined.
3. The risks of receiving blood from another person are not described. The possibility of receiving blood-borne pathogens is not discussed.
4. There is no description of the consequences of a subject's decision to withdraw from the research, such as during the stage of malaria infection.
5. There is no description of the lifelong risks associated with malarial infection, other than ruptured spleen and death.
6. The consent form lacks the identity of whom to contact in the event of research-related injury to the subject.
7. The consent form lacks an explanation of whom to contact for answers to questions about research subjects' rights.
8. Use of the wording "You understand.." is inappropriate. The subjects may certify that they understand the statements in the consent form and are satisfied with the explanation provided by consent process, but many will not comprehend the underlying scientific and medical significance of all the statements, nor are they in a position to judge whether the information provided is complete. Subjects should not be required to certify such understanding or completeness of disclosure.
9. The name of the clinical investigator is indicated only by "XXXXXX." The IRB should know the identity of the person conducting the study.

10. The consent form contains exculpatory language in which the prospective subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

7. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, and include members with primary concerns in scientific and nonscientific areas. [21 CFR 56.108(c)]

- A. The following research projects are examples of studies approved after members submitted their votes by facsimile transmission: "Effects of Intravenous Secretin Infusion in Autistic and learning Compromised Individuals" and "Evaluation of the Effect of Immunotherapeutic Technique Enzyme Potentiated Desensitization (EPD) for a Considerable Variety of Illness/Conditions/diagnostic Conditions." This is not a complete listing. These studies do not qualify for expedited review, and should be discussed and voted on at convened meetings.
- B. Research was reviewed and approved during two meetings (May 1, 1998, and May 7, 1999) when the requirement of a majority of voting members was not met because one or more IRB members abstained from voting. The IRB should have a sufficient number of members present at each meeting so that a majority is retained when IRB members are excluded from deliberations and voting due to conflicts of interest.
- C. The IRB reviewed and approved research at the meetings held May 1, 1998, and November 20, 1998, when the requirement of a majority of voting members was not met, with six (6) and eight (8) of 16 members in attendance, respectively.
- D. There was no nonscientific member present when research was approved on November 20, 1998. Mr. Bob Smith does not represent the viewpoint of a nonscientific member due to his education, experience, and employment in a scientific position.

8. Failure to notify investigators in writing of its decision to approve or disapprove the proposed research activity, or of the modifications required to secure IRB approval of the research activity. [21 CFR 56.109(e)]

The IRB does not consistently notify clinical investigators in writing of the IRB decision to approve or disapprove research, including continuing review.

9. Failure to conduct continuing review of research. [21 CFR 56.109(f)]

- A. Continuing review is not conducted at convened meetings of the full IRB, nor are periodic reports discussed in any manner. The periodic reports are reviewed by Dr. Chappell, IRB secretary. No determination is made by the IRB as to whether the study should be amended, terminated, or allowed to continue as originally approved.
- B. The IRB approved the continuation of studies even though the clinical investigator submitted incomplete periodic reports. For example, on August 31, 1999, the IRB approved the continuation of the Study titled, "Low Level Laser Therapy for Treatment of Acute and Chronic Musculoskeletal Pain and Neurological Symptoms" even though the clinical investigator did not report how many subjects had been enrolled.

10. Failure to properly identify and apply expedited review procedures. [21 CFR § 56.110(b)]

On December 22, 1997, the IRB Secretary approved the study titled, "Clinical Relevance of Heavy Metal Removal by Calcium Disodium Ethylene Diamine Tetra Acetic Acid using an Appropriate Therapeutic Window in a Pediatric Population" through 'expedited review.' Such use of the term 'expedited review' is not permitted by FDA regulations. The IRB procedures should ensure that the use of expedited review is limited to the approval of minor changes in ongoing research as described in § 56.110 (b) and to the approval of categories of research listed in the enclosed Federal Register notice.

11. Failure to have procedures to determine that risks to subjects are minimized. [21 CFR § 56.111]

- A. The IRB did not determine whether medical devices used in studies pose a significant risk or nonsignificant risk to subjects. This determination was not made during IRB review of the following studies: "Low Level Laser Therapy for Treatment of Acute and Chronic Musculoskeletal Pain and Neurological Symptoms," "Ultraviolet Blood Irradiation," and "Class 3a Laser as an Acupuncture Device."
- B. The IRB reviewed and approved the study titled "Induced Malaria as Therapy for HIV Infection." The study includes the direct injection of blood from one person into the study subject, with vague descriptions of screening the malaria parasite donor for potential pathogens. Please explain how the IRB determined that risks to subjects were minimized and that the procedures are consistent with sound research design and do not unnecessarily expose subjects to risk.

12. Failure to prepare adequate documentation of IRB activities.
[21 CFR 56.115]

- FDA believes that the records that an IRB or an institution must maintain provide significant evidence of whether the procedures utilized by the IRB are adequately protecting the human subjects of the investigations that the IRB is reviewing.
- A. There is no documentation of the manner in which the periodic review of research is conducted.
 - B. The current listing of IRB members does not objectively describe members' affiliations to the institution; see item 3, above.
 - C. Meeting minutes do not always identify the title of the study which was discussed and voted on during a meeting. Many studies are referred to by acronyms, such as "AMG Project" or by the last name of the clinical investigator. For example, the minutes of March 26, 1996, identify only the "W.A. Shrader project" and the "Paula Bickle project."
 - D. Meeting minutes do not identify which "updates" have been received since the previous meeting. This is an example of the poor documentation of the IRB's periodic review of research.
 - E. Meeting minutes do not consistently document the details of recommended changes to protocols and consent forms.
 - F. Meeting minutes do not consistently record that previously requested protocol changes and/or clarifications have been received by the IRB.
 - G. The IRB records do not document the IRB's determination that investigational devices are significant risk or non-significant risk devices.
 - H. The minutes of the meeting of May 7, 1999, do not record the status of the IRB review of the study titled, "Comprehensive Nutrient Supplementation as an Adjunct to Chelation Therapy."
 - I. The file for the study titled, "Induced Malaria as Therapy for HIV Infection" does not contain the documents originally submitted in the study proposal, and does not contain a copy of the letter documenting when the study was initially approved by the IRB.
 - J. The "Project Check List" for Dr. Page's study "Stimulated Autologous Immune Serum and Autologous Tumor Vaccine in the Treatment of Refractory Solid Tumors" does not document that the IRB conducted a review of an update on May 1, 1998.

Based on the deficiencies found during this inspection, we have no assurance that your IRB procedures are adequately protecting the rights and welfare of the human subjects of research. For this reason, in accordance with 21 CFR 56.120(b)(1) and (2), and effective immediately,

- **no new studies** that are subject to Parts 50 and 56 of the FDA regulations are to be approved by your IRB, and
- **no new subjects** are to be admitted to ongoing studies that are subject to 21 CFR Parts 50 and 56 until you have received notification from this office that adequate corrections have been made.

These restrictions do not relieve the IRB of its responsibility for receiving and reacting to reports of unexpected and serious reactions and routine progress reports from ongoing studies.

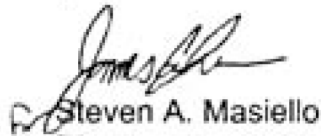
We acknowledge that the IRB promised to implement corrective actions. Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the procedures of your IRB into compliance with FDA requirements. Please include a copy of any revised documents, such as written procedures, with your response. Any plans of action must include projected completion dates for each action to be accomplished. In addition, please submit a copy of the written notification from the IRB to each of the affected clinical investigators notifying them of this suspension.

We will review your response and determine whether the actions are adequate to permit the IRB to resume unrestricted activities. Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions include, but are not limited to, the termination of all ongoing studies approved by your IRB and the initiation of regulatory proceedings for disqualification of your IRB.

Your written response should be addressed to:

Ms. Patricia Holobaugh (HFM-650)
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Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosures

1999 FDA Form 483

Federal Register Monday, November 9, 1998

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