# GREAT LAKES COLLEGE OF CLINICAL MEDICINE
**Institutional Review Board**
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Overnighted

MAR. 2 0 2000

cc: Hugh McCune FDA C Carter



March 17, 2000

Ms. Patricia Holobaugh, (HFM-650)
Division of Inspections and Surveillance
Food And Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Thank you for the warning letter of March 9,2000, which we received on March 13, 2000. We appreciate the opportunity to bring our IRB into full compliance with FDA regulation. It is our sincere intention to do everything possible to make our IRB as good as it can be and to fully protect human subjects who elect to participate in research efforts. We hope that this detailed response will be satisfactory so that we can notify the investigators under our jurisdiction to resume enrollment of subjects as soon as possible.

*1. Failure to prepare detailed written procedures for conducting the review of research, including periodic review.*
*A. There are no detailed instructions as to how the IRB is to operate.*

The Basic Policy for Protection of Human Research Subjects for the Great Lakes College of Clinical Medicine has been completely rewritten to include all of the procedures required. This policy was discussed at the IRB meeting on 2/25/00 in Atlanta. It was felt that more time was needed. Copies were provided to all members. A conference all was arranged for 3/17/00 for the purpose of further discussion. After full discussion the procedures were approved by a vote of 11 to 0 in favor.

The organization of the Board is described Section V.
How many members are required in Section V. A.
How the members are selected and how applications are processed in V. E.
Who will receive pre-meeting materials to review and how it will be conducted in section VI
How the review is conducted and how decisions are made in section VI. D and Section X.
The criteria used for the basis to approve research in Section VII.

The frequency of continuing review and how it is conducted in Section VI. C
How controverted issues are decided by discussion, reference to FDA regulations and by majority vote as discussed in Sections VI. and VII.
Records maintenance in accordance with FDA requirements in Section IX.
Conflict of interest for projects in which an IRB member is involved in Section V.F.

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

Continuing review operations are described in detail in Section VI. C.
This was implemented at our 2/25/00 meeting – see minutes.
Investigators are sent guidelines to insure a concise report with the required information (copy attached.)

*C. Written Procedures should describe how the IRB will determine when an investigation involves an investigational product subject to FDA regulation.*

This has been addressed in Section VII. A 1.
The policy was implemented at the 2/25/00 meeting (see minutes)

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

This has been addressed in Section VI. B 2.

*E. The IRB should develop procedures for incorporating revisions to proposed research and for notifying the full IRB of those revisions...*

The procedures needed have been implemented. They are in Section VI. D.

*F. Written procedures should describe the extent to which the IRB will review web site advertisements for studies approved by the IRB...*

This has been implemented in Section VII. C.

*G. The written procedures should explain the role of the IRB Chair...*

Our procedures are unusual due to the fact that the IRB chairperson is not located at or near the IRB office. We have divided the responsibilities of the chairperson and secretary very carefully. This is spelled out in Section V. H. and Section VIII.

*H. There are no written procedures to describe how adverse reaction reports are reviewed by an "expedited" process or by the full IRB and*

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

These two items have been implemented in the Basic Policies in Section VI. E. and VIII. D.

*J. The IRB procedures should define whether the IRB will review proposed research to be conducted only in foreign countries...*

This has been implemented in Basic Policy, Section VII. A. 12. c.

*K. The written procedures should describe how the IRB will review proposed research and proposed consent forms...*

This information is now included in our Basic Policy Section VII. A. 13.

*L. The IRB should consider requiring investigators to include the IRB approval date on consent forms...*

This is on the agenda to be considered by the IRB at the May 5, 2000 meeting in Dallas.

2. *Failure to consider community attitudes and cultural backgrounds.*
The IRB required Dr. Heimlich to present his proposed research project in person. IRB members questioned Dr. Heimlich for at least 45 minutes on the history of this procedure, (it was used as a treatment for syphilis prior to antibiotics), the precautions to be taken, the recruitment of subjects, the qualifications of the facility to be utilized and other pertinent issues. The IRB was very comfortable that the potential benefit for subjects was far greater than the risk of this therapy and that this research was acceptable for Chinese citizens. Since his work was associated with an academic institution in China that commonly does international research, we assumed that the community standards and the consent translation were adequate. In the future, we will contact the foreign institution to check this. Our IRB's approach was no different than if the research was conducted in the U.S. One procedure that might now be different is that we have begun requiring a monitoring plan for projects. This was not required when the Heimlich project was approved. The preliminary results of this study have been encouraging and have received international scientific interest. We have added statements in our Policy in section VII.A.12.c to better define and document what is required of a foreign-based study. This will not come up frequently, since we are only serving members of GLCCM.

3. *Failure to include at least one IRB member who is not otherwise affiliated with the institution.*
We did not completely understand the definition of "affiliation" with the institution. We believed that we were adequately represented in this category by several members. Effie Buckley, R.N. has not been employed by Dr. Guilford or any other GLCCM member for one year. She is self-employed. She is not affiliated with GLCCM in any way other than the IRB. It is not easy to get someone to travel to 4 different cities a year for the IRB meetings. She has agreed to do this and we are grateful. We believe she qualifies as an unaffiliated member. Dr. Russ Jaffe might also be considered "unaffiliated". He is a speaker for GLCCM from time to time and owns a laboratory, but he is not connected to any promotion or sponsorship of GLCCM.
If the FDA requires us to get another unaffiliated member, we will ask Dr. Carter to nominate someone at our next meeting on May 5, 2000 in Dallas. If we do not hear from you, we will assume that Ms. Buckley and Dr. Jaffe are acceptable.

4. *Failure to insure that research is reviewed free from conflict of interest.*
We have tried to be careful about this, but obviously we missed the conflicts on these cases. It should be noted that at least in the case #M019, Dr. Kindness' lab was not involved until after the IRB approval. In our new Policies, Section V.F. we have defined such conflicts and outlined exactly how they will be dealt with in the future. Recent minutes reflect that we are following our new procedures by having IRB members with conflicts leave the room for discussion of the project and abstain from voting.

5. *Failure to exercise authority to require modification in (to secure approval) or disapprove all research activities covered by these regulations.*
A. *The IRB does not assure that studies subject to FDA regulations are ... IND IDE.*

The IRB Policy now requires that all investigators contact the FDA and get documentation as to whether an IND or IDE is required and the numbers must be supplied to the IRB. The IRB is gaining a great deal of knowledge about FDA requirements including when an IND or IDE is required, but we are making sure that the FDA is contacted before a study is approved. During our next year, we plan to send a least one member or staff to become certified through national meetings of the Public Responsibility in Medicine & Research (PRIM&R) and Applied Research Ethics National Association (ARENA). We also have become familiar with the FDA web site, which has been very helpful.

*B. The meeting minutes of March 13, 1999, document that an IND was required for a study required by Dr. Hauser. The IRB approved...*

This is in error. The IRB tabled Dr. Hauser's project. The project was not approved, and this is reflected in our minutes (copy enclosed). We are very aware that the IRB cannot supercede the authority of the FDA.

*C. Current IRB practices are inadequate to assure that studies "approved" pending modifications are not initiated before the IRB accepts the modified documents....*

This has been addressed in our revised Policy Section VI. D. We will be sure that all modifications are in place before an approval letter is issued.

*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 suggestions... were not included in the letter to Dr. Page.*

This is the only case when "suggestions" were specified and not put into the IRB letter. That will not be done under our new Policies. Dr. Page's study is no longer active.

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

This has been addressed under item 1. K. 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.*

*A. The consent form submitted with... "Gene Activated Therapy...for Cancer" was approved on September 20, 1997. The consent form... is deficient...*

*B. The study described in item 6A. above...*

*C. The English version of the consent form for the study titled, "Induced Malaria as Therapy ...is deficient...*

In order to insure that the IRB approves only consent forms that are in complete compliance with federal regulations, the IRB has prepared a checklist (attached) to be completed by our administrative secretary and reviewed in detail by the reviewer(s) of each project. In addition the consent form will be reviewed by the entire IRB as part of the approval process, as specified in Section X. In the past, we have frequently required that the investigators improve the informed consent, and we will be more diligent in the future. All of the IRB members will be given copies of the criticisms of the consent forms of Dr. Page and Dr. Heimlich for review at our next meeting on May 5, 2000 to be sure that everyone fully understands the problems with these consent forms. Dr. Page's project is inactive. Dr. Heimlich has been asked to speak to the revisions needed and listed under this item.

The required statement about the GLCCM IRB in the consent form will be returned to our legal council for revision to be sure that FDA guidelines that forbid waiver of liability for negligence are met. This will be accomplished so that a report can be presented to the IRB meeting on May 5, 2000.

*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.*

*A. The following research projects... "Effects of Intravenous Secretin Infusion in Autistic...," "Enzyme Potentiated Desensitization..." These studies do not qualify for expedited review...*

The types of projects that can be done by expedited review has been clarified and put into our Policies, Section VIII. We are not clear about the Enzyme Potentiated Desensitization project. It has been reviewed several times by the entire IRB Board and has been thoroughly analyzed. We understood that the FDA investigator agreed with us that the latter project was done properly.

*B. Research was reviewed and approved...*

*C. The IRB reviewed and approved...*

*D. There was no nonscientific member present when research was approved... Bob Smith...*

We misunderstood and thought that 8 of 16 members constituted a quorum. This has been corrected in Policies Section VI. A. We also did not realize that members excusing themselves for a conflict of interest had to be subtracted from the quorum calculations. This is now clear in Policies Section V.F.

We thought Bob Smith qualified as a nonscientific member since he had no professional or advanced degrees. We have two other nonscientific members and we will rely on one of them to attend each legally constituted meeting.

*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.*

Notification of investigators in writing of all decisions regarding approval or disapproval of research and continuing review is now specifically required in our Policies. In the past, we did not always perform the latter.

*9. Failure to conduct continuing review of research.*

*A. Continuing review is not conducted at convened meetings of the full IRB...*

*B. The IRB approved the continuation of studies even though the clinical investigator...*

The IRB now requires specific complete reports at designated intervals. The intervals are specified by the IRB at the time of approval based on the degree of risk. The Policies call for the discussion and review of each periodic report and then a determination of whether the project is to continue, how much risk is involved, and for how long the project is approved. This is described in Section VI. C. It was implemented at our last meeting on February 25, 2000. It should be noted that we were conducting our continuing reviews according to the instructions given us by our previous FDA investigator.

*10. Failure to properly identify and apply expedited review of procedures.*

This has been clarified in the new Policies, Section VIII. and has been fully implemented.

*11. Failure to have procedures to determine that risks to subjects are minimized.*

*A. The IRB did not determine whether medical devices used in studies proposed a significant risk...*

The IRB did determine that these devices posed non-significant risk to the subjects but it was not specified in the motion or in the minutes. Now the procedure to specify the degree of risk and the appropriate interval for review is spelled out in the Policies in Section VI. B 2. with references to the FDA information sheet in Appendix B of the Policies. The latter will be provided to IRB members for their reference during the IRB meetings.

*B. The IRB reviewed and approved the study titled "Induced Malaria..." ...*

This was addressed in Item 2.

*12. Failure to prepare adequate documentation of IRB activities.*

*A. There is no documentation of the manner in which the periodic review of research is conducted.*

This is now in Policies. Section VI. C.

*B. The current listing of IRB members does not objectively describe members' affiliations to the institution; see item 3, above.*

This has been revised with our current understanding in section V. I of our Policies.

*C. Meeting minutes do not always identify the title of the study... referred to by acronyms...*

We are now assigning numbers to projects for better identification.

*D. Meeting minutes do not identify which "updates" have been received ...*

This is addressed in Policies Section VI. C.

*E. Meeting minutes do not consistently document the details of recommended changes to protocols and consent forms.*

We will be more through in documenting recommended changes to protocols and consent forms. Our early IRB minutes were criticized by the FDA investigator as being too detailed. We now have a better understanding on exactly what needs to be included.

*F. Meeting minutes do not consistently record that previously requested protocol changes and or clarifications have been received by the IRB.*

We have corrected this with Policies VI. D.

*G. The IRB records do not document the IRB's determination that investigational devices are significant risk or non-significant risk devices.*

This has been corrected as noted in Item 11.

*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".*

This study was not acted upon. There was no motion. An oral report was given to the investigator at the meeting that the study was not ready and was not acceptable in its present form. The study was not resubmitted. In retrospect, perhaps we should have insisted on a motion so that we could have followed up with a letter. In part, we did not feel it was safe to give DHEA to subjects without determining they were deficient. The investigator orally told us that was not acceptable to him and the project was withdrawn.

*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...*

These documents are indeed in the file. Somehow, they did not get copied for the investigator, but they were there all along. Copies are attached.

*1. The 'Project Check List' for Dr. Page's study "Stimulated Autologous Immune Serum and Autologous Tumor Vaccine in the Treatment of Solid Refractory Tumors" does not document that the IRB conducted a review of an update on May 1, 1998.*

The project checklist was just a personal note, not part of the IRB official file.

Completion Date- all of these measures have been implemented and the deficiencies corrected except for the items noted that need to be taken before the entire board at our next meeting in Dallas on May 5, 2000. When these are completed, we will forward copies of the minutes to you.

Sincerely,

L. Terry Chappell, M.D.
Secretary

LTC/bta

Enclosures: IRB Basic Policy, IRB Guidelines for Investigators, 2/25/00 minutes, Letter sent to all investigators 3/14/00, 3/13/99 minutes, checklist for Informed consent, Heimlich's protocol and approval letter, sample letter for revisions.