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OVERNIGHTED
5/31/00

May 26, 2000

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

Dear Ms. Holobaugh:

The GLCCM IRB has taken vigorous steps to comply with your letter of April 13, 2000. We have responded to each and every one of the points you have raised. Our Administrator has attended "Human Subjects Research & IRB's Under Fire" presented by OPRR and the FDA. We have received consultations from two University-based IRB's that were recently found to be in compliance. All of our Board members have reviewed your comments and have read the Belmont report. We have decided to go beyond your recommendations and send our complete Policy to all perspective investigators so that they understand what is required for them to be in full compliance. We have revised and approved our policy and we have demonstrated our new expertise by requiring all of our Investigators of current projects to become fully compliant with current IRB and FDA policies. We have added a non-affiliated member who is an expert on IRB activities.

We understand that we face unique challenges in reviewing projects from around the United States, and we feel we are now meeting these challenges, with your guidance and with the advice from our consultants.

Our IRB is also unique because it primarily reviews projects in the emerging field of Complementary and Alternative medicine (CAM) and serves GLCCM members who are usually office-based and often not affiliated with a hospital. We believe that our Board members have more expertise in CAM than any IRB in the country. We now feel comfortable that we are familiar with the way IRB's are supposed to work, and we are hopeful that you agree.

We are sure that you realize that many prospective subjects are suffering from their illnesses and are impatiently waiting to enter into some of the studies under our IRB. We have received many inquiries about how long this process might take. We have acted as quickly and as thoroughly as we could. Please respond to this letter as promptly as you can. We appreciate the opportunity to make our IRB as good and as effective as it can be for the protection of human subjects in research projects.

In response to the⇨ ⇨ in the letter of April 13th :

⇨ ⇨ The IRB re-reviewed the consent forms of all active studies at the meeting on May 5th. All consent forms were found to be deficient with the acceptation of one. The Board directed that all investigators be contacted and advised to revise their consent forms to be in compliance with the newly approved consent form guidelines (copy enclosed).

⇨ ⇨ The request to remove the statement from the GLCCM web site, has been done, copy of letter from the GLCCM Executive Director is enclosed.

⇨ ⇨ The study M022 was placed on hold by the investigator for the reason of relocation. He informed the administrator when he was financially stable and was ready to restart the study. The reasons for placing studies on hold will be noted in future minutes, and also when they are reactivated.

⇨ ⇨ We have requested the name of the Chinese clinical investigator from Dr. Heimlich, to inform the investigator of his responsibility to obtain the appropriate Chinese government and local institutional approval for the research.

REQUEST FOR EXPLANATION: The chairman is a distinguished former Department Head at Tulane University School of Public Health. He gives valuable and continuing oversight to our IRB. Some of the responsibilities usually held by a Chairman have been delegated because the office of the IRB is in Ohio, not Louisiana and because we have found that our IRB functions better this way.

The Chairman does receive and review all studies in their entirety, his name is now listed on all informed consent forms as the IRB contact person, and the agendas are sent to him for approval before meetings. The Chairman will receive and review all adverse events.

Our response to the list at the end of the letter is as follows:

1. We are providing a list of projects that were active, on hold or pending before the restrictions were imposed on March 9, 2000. They have been identified as whether they would be subject to parts 50 and 56 of the FDA regulations.
2. For the studies that are subject to 50 &56 the following is being provided:
   A. A copy of the letter from the IRB notifying them of the FDA's restrictions for the IRB.
   B. Copies of the clinical investigator's letter, we have received to date, acknowledging that enrollment was suspended, and the investigator's plan to either (1) terminate (2) submit to another IRB and identify the new IRB, if these actions were planned.
   C. The following actions were taken by the IRB.
      i. The Secretary re-reviewed all protocols and provided a list to the Board as whether or not he felt the protocols needed an IND or IDE.

ii. The request for IND or IDE information was sent in the letter of April 18 to the investigators.

iii. The IRB reviewed the current informed consent of all projects. All inform consents were found to be deficient by the new IRB guidelines and/or 21CFR 50.25 with the exception of one. All will be requested to be revised and resubmitted.

iv. The investigators were requested to submit all advertising, including *anything* on a web site. During the May 5th IRB meeting the Board voted that the Board would approve no advertising until the investigators submit information on IND/IDE's. The investigators were instructed to remove references to GLCCM IRB approval on all advertising and web pages.

3. The GLCCM Executive Director, Jack Hank will review and /or approve the IRB's written procedures.

We also would like to respond to your comments. We have made the following changes:

I.A. Section II. We have removed the incorrect statement "Federal Drug Administration".

Section V.E. The Board voted on a membership term of 4 years, with optional renewals indefinitely. It was felt that it was important to maintain the expertise and knowledge gained by Board members in certain circumstances. The terms of the current Board members will be staggered so they do not all expire at the same time.

Section V.F. Examples of conflict of interest were added to this section.

Section V.H. has been addressed above.

Section V.I. (1) We have listed on the IRB roster, affiliated and non-affiliated. We have removed Affiliated by Laboratory. (2) We did not list whether the member is an ACAM member because ACAM is non-affiliated with GLCCM and the GLCCM IRB only reviews studies submitted by GLCCM members, ACAM has its own IRB. More explanation follows under item 2 below. (3) The roster has been moved to an appendix A in the Policy. A copy of the revised Policy is included.

Section VI. (1) We have added to the Policy how the Administrator processes research proposals submitted for initial review. (2) The deadlines have been inserted into the Policy. (3) We have added to the Policy that the administrator will return all incomplete submissions to the investigator. (4)The explanation of the tracking number has been included in the Policy.

Section VI. B. We have added more information on the community attitudes to the Policy.

Section VI. B2. We have added to the Policy the details on how the IRB will handle the conflicts of interest. The section of significant risk/non-significant risk devices was moved from the same section as the minimal risk/expedited review for clarification. We have clarified to the Board that we do not give all projects a degree of risk, and that significant and non-significant terms are for devices and minimal risk is for expedited reviews only. We will use a more frequent review date on studies the Board feels involves more than a small amount of risk. The maximum review interval is one year.

Section B.5. The information on required modifications to protocols has been inserted into the Policy.

Section B.6. We have clarified the community attitude determination.

Section VI.C We have clarified this section and VI B. and added that the Administrator will inform the investigator when the periodic report is due. We have clarified that the report will be sent to the Secretary. We have clarified that when a completed report is received of a suspended study, it will remain suspended until the next IRB meeting.
We have clarified that any incomplete progress report forms will be sent back to the investigator, thus slowing the approval process. We have included the progress report/continuing review form as you suggested we develop. It was not sent previously because we had given it to the FDA Investigator Hugh McClure, and had understood that you would receive a copy of it.

Section VI.E - We have clarified in the Policy that the expedited review will be reviewed by the Secretary unless there is a conflict of interest and also that if both the Secretary and Chairman have a conflict of interest it will be referred to another IRB member. We have clarified in the Policy the written procedure on the process of reporting an adverse event. We have developed an adverse event form, which is appendix F to the Policy and will be included in the investigator guidelines. We have also included in the Policy how conflict of interest will be handled.

Section VII.A.1. We have added to the Policy, a statement that information on IND/IDE's must be obtained before review of a study. It is also included on the new, Investigator Application Form.

Section VII. A.6. We have included the monitoring plan as appendix E.

Section VII. A. 10 We have included the emergency use of a test article as appendix D.

Section VII.A.12. We have moved this section and have changed the word regulations to policy.

Section VII.A. 12c.(1) We have informed Dr. Heimlich the Investigator of the foreign study that it was necessary to terminate the study S043 Study of Induced Malaria. We have included a copy of Dr. Heimlich's letter of reply for your information.

Section VII A 12 c (2) We have inserted how the IRB will assess community attitudes regarding specific proposed research, into the Policy.

Section VII. A. 12.d. We have added to the Policy that the Primary reviewer will receive a site report form from the investigator for review and may confer with a local consultant such as school board members to assess the community attitudes and qualifications of the sponsor, investigators, hospital, and/or institution.

Section VIIA. 13. We have corrected 21 CFR 312.7 or 21 CFR and 812.7 to 21 CFR 312.7.

Section VIII.A Detail of expedited review has been added to the Policy.

Section VIII.B. We have explained in the Policy that the Secretary will notify IRB members of expedited review approvals by placing them on the agenda of the next meeting.

Section VIII.C. We have added to the Policy that new co-investigators will be assessed by the Chief Investigator of the multi-center study by the site report form, and that the form will be reviewed by the designated reviewer before expedited approval.

Section VIII.D. We have added to the Policy, that all adverse events will be reviewed by the Chairman, who will determine if the project should be stopped or if more frequent continuing review will be required. Any instructions from the FDA will have precedence. All adverse events reported will be discussed on the agenda of the next IRB meeting.

Section IX. We have added to the Policy how the Administrator processes and tracks reports and studies that are received by the Secretary.

Section IX. A.2 We will document in the meeting minutes previously requested protocol changes that have been received by the IRB.

Section IX.A3 The meeting minutes will document how the periodic review of research is conducted.

1.B. We have explained in the Policy that GLCCM and ACAM are non-affiliated groups. The only reason for the IRB to meet at an ACAM meeting is that many of the IRB members attend ACAM meetings, so we save time and money by having the meetings at these locations. There is no relationship between ACAM and GLCCM. GLCCM does not review research by anyone who is not a GLCCM member. Dr. Rozema's presidency of ACAM is irrelevant and is no longer noted on the IRB roster. Neither ACAM nor GLCCM can override the decisions of the IRB.

2. We have removed Effie Buckley and Russell Jaffe from the non-affiliated classification. The Board voted for a new member Carol Weideman as a non-affiliated member. Her CV is enclosed.

3. We have responded to this above in the double arrows.

4. Introduction. (1) We have deleted this line. The Administrator had inserted the line referring to the FDA because of the questions arising whether the GLCCM IRB was FDA approved. The FDA inspector had previously instructed us that we could state the GLCCM IRB was "in applicable compliance of the FDA regulations." We have added the contact for the Center of Biologics to the Policy.

Page 2. We have revised the Guidelines to state if federal funding is required there will be specific guidelines to be followed.

Page 2. We did not include the rules sheet because it was not referred to in the warning letter and we thought you had it because the inspector had said everything he copied would be forwarded on. It is included in the Investigator Guidelines.

Page 2. We have added to page 4 the request for IND/IDE number.

Project/Protocol Information. Item 8

Informed Consent. Page 8 We have added to the consent form guidelines that consent forms and case histories must been retained by the investigator for a period of 2 years following the investigation is discontinued and the FDA is notified.

Termination of a project/Protocol. The paragraph has been divided to show the two different circumstances of termination and how the IRB will operate.

Continuing Review. We did have a continuing review form. It was not included, as we believed you had already reviewed it from the copies submitted by the FDA Inspector. We have included it as appendix F in the Policy.

Adverse Reactions. Page 10. We have added as appendix F to the Policy an Adverse Reaction Form which will be sent in Investigators packets. It will include the time frames in which reports must be submitted.

5. This has been addressed above in the double arrows.

6. A. This has been addressed above by the double arrows.
   B. We have corrected this. It was addressed above under Section VI. B2.
7. We have terminated the study. Also addressed above in the double arrows.

We have also included an article that will be sent to all investigators What Makes Clinical Research Ethical.

Sincerely,

L. Terry Chappell, M.D.
Secretary

LTC/bta