Human Research Seminar Series

Common Findings of the IRB, OHRP, and FDA

Friday, February 1, 2013

Presented by:
David Wallach, CIP
IRB Director
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What are Findings?

Findings represent non-compliance with:
> IRB Policies & Procedures including reporting requirements
> SOPs – Departmental / Institutional
> Federal Regulations (FDA, OHRP)
> DSMC / DSMB reporting requirements
> Protocol, investigational plan, sponsor requirements

Do you have evidence of compliance through appropriate documentation practices?
How are Findings Discovered?

- IRB – Site visits
- OHRP/FDA – Inspections
- Sponsors – Monitoring visits

What’s All the Fuss About?

- Research is designed to generate knowledge for the scientific community leading to better ways to treat, prevent, diagnose and understand human disease.
- This only works by collecting accurate, reliable data while protecting the rights, safety, and welfare of subjects.
- The trust of research subjects (and the general public) is adversely affected by research "problems."
What’s the Worst that Could Happen?

- Research can be suspended or terminated by the IRB, institution, FDA, or OHRP.
- Loss of research grants/contracts.
- Investigator can be barred from conducting FDA regulated research: http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm
- Institution/employer may take action.
Research Oversight

FDA (Oversees Drugs/Devices/Biologics)

OHRP (Oversees Human Research)

Sponsor

Institution (Einstein IRB, Cancer Center, etc.)

External DSMB

Internal DSMC

PI

Research Team

FDA FY11 Clinical Investigator Inspections (n=611)

- No Action Indicated (NAI)
- Voluntary Action Indicated (VAI)
- Official Action Indicated (OAI)

6% 41% 53%
FDA’s Most Common Clinical Investigator Deficiencies

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – including informed consent issues

IRB’s Common Audit Findings

- Informed Consent & HIPAA Authorization
- Protocol Compliance/Deviations
- Regulatory (Non-Compliance with Regulations or IRB Policy)
- Documentation/Disorganized research records
Specifics: Informed Consent & HIPAA Authorization

- Incorrect language – Subject speaks only Spanish, yet English ICF signed.
- Expired Version
- Incorrect Version – Latest IRB-approved version not used (when the consent is revised via amendment)
- Incomplete – Specimen options blank, or checked off instead of initialed (per instructions), missing dates, missing staff signature
- HIPAA Authorization not obtained
- Signature lines completed incorrectly

Specifics: Informed Consent & HIPAA Authorization (cont’d)

- ICD/HIPAA dated by someone other than the subject
- IC documentation does not include either a time or a statement that the consent was obtained prior to initiation of study procedures
- Lack of documentation that the subject received a copy of the consent/HIPAA
FDA Warning Letter Excerpts

“Subject signed the consent form on [redacted]; however, the witness signed the consent on [a different date].”

“You failed to provide study subjects with a copy of their signed informed consent document.”

“Protocol section 9.3.2 requires that the … investigator retain the original consent forms … [but they] could not be located for 18 … subjects enrolled in the study. Copies were available in study binders….“

“Subjects signing the informed consent in most cases did not complete dates. It appears that the study coordinator …completed the date.”

How to Avoid

- Do not try to be “helpful” by dating the consent for subjects or investigators
- Take time to document the informed consent process – include the time that the consent was obtained and a statement that consent was obtained prior to study related procedures
- After giving a copy of the consent to the subject, document
Specifics: Protocol Compliance/Deviations

- Entrance criteria weren’t met (or documentation missing)
- DSMC/DSMP details (listed members and plan) in original protocol application different from current practice

Specifics: Protocol Compliance/Deviations (cont’d)

- A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change.
- Protocol deviation is also used to refer to any other, unplanned, instance(s) of protocol noncompliance.
- For example:
  - Situations in which the investigator failed to perform tests or examinations as required by the protocol or
  - Failure on the part of study subjects to complete scheduled visits as required by the protocol.

Source: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133569.htm
FDA Warning Letter Excerpts

“An ultrasound was not done at six months for subject.”
“Numerous assessments were not completed as required by the protocol.”
“Physical exam at six months was not done for subject.”
“You did not conduct certain follow up visits or document efforts to locate missing subjects.”
“Although laboratory samples were taken for certain tests, including the hematology, biochemistry, coagulation and/or the test,…these laboratory samples were not performed within the protocol specified time periods…”

How to Avoid Unplanned Deviations

• Know the protocol, follow it exactly*
  > *Changes in approved research may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
• Pay attention to monitor visit letters / reports
• Perform timely self-monitoring of protocol adherence
• Carefully monitor those activities that are delegated to others
• Educate and reeducate when necessary
Unplanned Deviations that Have Already Occurred

- Sometimes, despite your best efforts, deviations will occur. Here’s what you need to do:
  > Document and submit to the IRB and notify sponsor
  > If serious or multiple deviations occur:
    - Find the root cause and develop a corrective action plan
    > Monitor the effectiveness of the corrective action plan

Specifics: Regulatory (Non-Compliance with Regulations or IRB Policy)

- Key Personnel (KP) – study staff changes since last continuing review, yet an amendment has not been submitted
  > KP no longer working on study yet listed
  > KP working on study yet not listed
- Hospitalizations noted in source documents yet never submitted to the IRB
- AE report found in research records but not submitted to the IRB
- AEs submitted late.
FDA Warning Letter Excerpts

Failure to comply with IRB reporting requirements:

"Your IRB requires that a written report of the death of any research subject be made within ___ business days...five or more subject deaths have not been reported to the IRB."

How to Avoid

- Know your AE reporting policies:
  > Sponsor’s policy
  > IRB policy
- Submit reports & complete notifications with timeliness
- If you are unsure about reporting criteria, call the IRB
- Make sure that your report is complete prior to submission (evaluated by PI/Co-I, personally signed and dated).
- Keep track of AE reports and submit a follow-up report when new information becomes available.
Specifics: Documentation/Disorganized Research Records

- Inconsistent/missing source documents (e.g. online log, individual records, entrance criteria check sheet)
- Improper documentation – use of pencil, white-out, crossed out data are not legible or initialed/dated; corrections not initialed/dated
- Incomplete records (e.g. headers on worksheets/data collection tools)
- Study drug accountability not documented
- Revisions to source or CRF without initials/date
- CRF does not match source documentation (or revisions to CRF not supported by rationale in source)
- Documented assessments of study labs/procedures missing
- PI signature and/or date missing on essential documents (eligibility, consent note, queries, CRFs, adverse event submissions)

FDA Warning Letter Excerpts

“Records…were written in pencil, and many entries are illegible.”

“Entries were obscured by correction fluid.”

“There is no documentation of the name or initials of the person making entries in the records.”

“Source data for various assessments could not be located.”

“There is no record of who administered the study drug…Without a record of who administered the study drug, you cannot assure that these injections were performed by a member of the blinded study team.”
FDA Warning Letter Excerpts (cont’d)

“There was no supporting data...to confirm information contained in their case histories to demonstrate their eligibility...”

“The CRF contained blank fields.”

“Number of discrepancies were noted between source documents and data recorded on the CRFs...[CRF] indicates that a pericardial effusion was present, but echocardiogram report...states that no pericardial effusion was present.”

How to Avoid

- Don’t use pencil or white out
- Don’t obscure original entries, line through (once), initial & date
- Write the corrected entry and the reason for the correction is generally included
- Maintain accurate records of study related activities
- Ensure that there is a source for each CRF entry
- Maintain source data with research record
- Ensure the timely review of study labs/procedures
  > Assessment, initials/date of Investigator (documented in subject chart)
How Do You Avoid … (#1)

- “That’s not what I thought the protocol said.”
- “That’s not what we meant to write.”
- “We changed the screening procedures because we found that some of the tests were unnecessary.”

*Re-read the IRB approved protocol often and follow it exactly (particularly for investigator initiated protocols).*

How Do You Avoid … (#2)

- “Let me see if anyone knows whose handwriting that is.”
- “I always give the subjects one bottle of medication at week 2, so I must have done that and not written it down.”

*Maintain adequate records: A 3rd party reviewer should be able to reconstruct the conduct of the trial based on your records. What was done, by whom, when? Review records with a critical eye.*
How Do You Avoid … (#3)

• “His wife signed the research consent because the subject was sedated; he had already told me he wanted to participate.”

Unless the IRB has specifically allowed a Legally Authorized Representative to consent to the research on behalf of the subject, the subject must personally consent to the research and sign the research consent form. The permissibility of a relative consenting to research is different from clinical care.

How Do You Avoid … (#4)

• “I didn’t know the application said that we would talk to the patient about the study at the pre-op visit. We got consent in the holding area before surgery.”
• “I didn’t know the application said that we would get consent during a prenatal visit. We got consent at the time of epidural.”

Refer to the original IRB application and know how the consent process was described. This is the approved process and should describe who obtains consent and where and when it may be obtained.
How Do You Avoid … (#5)

• “The patient doesn’t speak English but I speak Spanish so I read the English ICD to the subject in Spanish and the subject signed it. He asked a lot of questions and demonstrated that he understood.”

Use IRB-approved translated ICDs. Per federal regulations, “The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.”

How Do You Avoid … (#6)

• “We had a committee but two of the three people left Montefiore so they didn’t meet.”
• “The committee met and looked at everything and said it was all fine.”

If you study has a DSMC (data safety monitoring committee charged with periodically reviewing the study data), ensure that this occurs and that the review and findings are documented and submitted to the IRB.
Questions?

• Any questions, please contact the Einstein IRB
• East Campus:
  > Jackie Rowan, QA Coordinator
  > 718-430-2268
  > jacqueline.rowan@einstein.yu.edu
• West Campus:
  > Kathleen O'Connor, QM Analyst
  > 718-920-4151 x228
  > koconno@montefiore.org

Einstein IRB Contact Information

East Campus IRB
• Belfer Building, Room 1002
  1300 Morris Park Avenue
  Bronx, NY 10461
• Phone: 718-430-2237
• Fax: 718-430-8817

West Campus IRB
• 3308 Rochambeau Ave
  Bronx, NY 10467
• Phone: 718-798-0406
• Fax: 718-798-5687

Website: [http://www.einstein.yu.edu/irb](http://www.einstein.yu.edu/irb)
Includes: Policies and Procedures,
Submission Guidelines, Forms,
and Educational Materials
Dear Dr. Horowitz:

Between August 16, 2010, and September 3, 2010, Mr. Matthew Watson and Mr. Anthony Thomas, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol (b)(4), entitled "(b)(4)" of the investigational drug (b)(4), performed for (b)(4).

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your September 14, 2010, written response to the Form FDA 483, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Mr. Watson presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to retain records required to be maintained under 21 CFR part 312 until 2 years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)].

On October 1, 2009, the sponsor discontinued your participation in Protocol (b)(4). FDA was notified in a letter dated October 5, 2009, that your participation in Protocol (b)(4) was discontinued. As explained above, between August 16, 2010, and September 3, 2010, Mr. Watson and Mr. Thomas, representing FDA, conducted an inspection and met with you to review your
conduct of Protocol (b)(4). At the time of the inspection, which was less than two years after your investigation was discontinued and FDA was notified, the inspection revealed that you failed to retain the following records:

a. Electronic case report forms (eCRFs). During FDA’s inspection, you stated that your study coordinator used a sponsor-provided laptop to enter data into the eCRF for each subject. You also stated that during the closeout visit conducted by the sponsor’s monitor, the monitor took the sponsor-provided laptop computer containing the eCRFs. In your September 14, 2010, written response to Form FDA 483 (your written response), you further explained that the actual eCRF data disks were never obtained from the sponsor. However, it was your responsibility as the investigator to retain copies of the eCRFs for two years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)].

b. The Enrollment and Patient Status Log and the Screening/Enrollment Log. During FDA’s inspection, your study coordinator obtained copies of these two logs from the sponsor. However, it was your responsibility as the investigator to retain copies of the logs for two years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)].

We acknowledge that in your written response you stated that you intend to “be more vigilant in documentation oversight than in the past.” However, you did not specify the corrective actions you will take to address these violations or to prevent this type of violation from reoccurring in the future.

2. You failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

FDA found discrepancies and deficiencies in records for both of the subjects enrolled in Protocol (b)(4), which raises significant questions about the reliability of data at your site. Specifically:

a. The study flowsheets appear to document post-dialysis vital signs rather than pre-dialysis vital signs. The protocol required that vital-sign assessments, including body temperature, sitting blood pressure and sitting pulse measurements, be performed pre-dialysis at every visit. During FDA’s inspection, your study coordinator stated that she transcribed vital-sign data from the dialysis center’s Patient Treatment Records onto the study flowsheets, and then used the flowsheets to enter the data into the eCRFs. However, a comparison of the Patient Treatment Records and the flowsheets suggests that for some visits, your study coordinator recorded the post-dialysis vital-sign data on the study flowsheets rather than the pre-dialysis vital-sign data, as required by the protocol (see table below for examples). This discrepancy raises questions about the reliability of the data at your site, in part because the Study Coordinator used the flowsheets to enter data into the eCRFs.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Visit #</th>
<th>Patient Treatment Record (pre-dialysis)</th>
<th>Patient Treatment Record (post-dialysis)</th>
<th>Study Flowsheet</th>
</tr>
</thead>
<tbody>
<tr>
<td>00013</td>
<td>Washout Week 1</td>
<td>Sitting Blood Pressure (BP) 163/103</td>
<td>Standing BP 118/69*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Body Temp 94.8°F Heart Rate (HR) 90</td>
<td>Body Temp 98.2°F HR 92</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sitting BP 118/69* Body Temp 98.2°F</td>
<td>Sitting Pulse 92</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sitting BP</td>
<td></td>
</tr>
</tbody>
</table>
For Subject 00013’s Washout Week 1 visit, the study coordinator appears to have recorded the post-dialysis standing blood pressure measurement on the flowsheet.

** For Subject 00016’s Screening visit, the study coordinator appears to have recorded both the pre- and post-dialysis body temperatures on the flowsheet. Without a copy of the eCRF, we cannot determine whether the pre- or post-dialysis temperature was recorded in this subject’s eCRF.

b. There are discrepancies between the Enrollment and Patient Status Log and the Screening/Enrollment Log referenced in 1.b. above. For example, the Enrollment and Patient Status Log for Subject 00013 shows March 2, 2009, as the date of informed consent; however, the Screening/Enrollment Log shows February 23, 2009, as the date of consent. Likewise for Subject 00016, the Enrollment and Patient Status Log shows March 9, 2009, as the date of informed consent; however, the Screening/Enrollment Log shows March 2, 2009, as the date of consent.

We note that in your written response, you stated that you intend to “be more vigilant in documentation oversight than in the past.” However, it was your responsibility as the investigator to ensure that adequate and accurate records were prepared and maintained as required by 21 CFR 312.62(b). Furthermore, you did not specify the corrective actions you will take to address these violations or to prevent this type of violation from reoccurring in the future.

3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

Section 7 of the protocol lists all of the required assessments in the protocol, and specifies when those assessments were to be performed. It appears that the following protocol-required assessments were not performed:

a. For both subjects, there was no documentation showing that the blood pressure measurements were taken in accordance with the protocol. The protocol specified that each subject’s blood pressure should be measured three times, and the mean of those three measurements should be used as the subject’s blood pressure measurement, at every visit.
There was no documentation to show that subjects’ blood pressures were measured in accordance with these protocol requirements at any of the subjects’ visits.

b. For Subject 00016:

i. Laboratory Reports show that the protocol-required hematology test results were not calculated at Visits 4 (Baseline) and 8.

ii. There was no documentation available to show that the protocol-required laboratory evaluations were conducted at Visit 13.

c. For Subject 00013:

i. There was no documentation available to show that the protocol-required physical examination was conducted at Visit 1 (Screening).

ii. There was no documentation available to show that the protocol-required laboratory evaluations were conducted at Visits 1 (Screening) and 4.

 Failure to perform study-related assessments may jeopardize subjects’ rights, safety, and welfare, and may compromise the reliability of the data at your site. Based on the documentation available at the time of the inspection, it appears that you did not ensure that these assessments were conducted in accordance with the protocol. It was your responsibility as the investigator to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

We acknowledge that it is possible that the eCRFs provide documentation that you measured blood pressure in accordance with the protocol, conducted the protocol-required laboratory evaluations at Visit 13 for Subject 00016, and conducted the protocol-required physical examination at Visit 1 and laboratory evaluations at Visits 1 and 4 for Subject 00013. However, as explained above, you failed to retain copies of the eCRFs in violation of 21 CFR 312.62(c). Moreover, to the extent that the eCRFs do not provide documentation that these assessments were conducted in accordance with the protocol, such deficiencies would suggest that, even if you conducted these assessments according to the protocol, you failed to prepare and maintain adequate and accurate case histories, as required by 21 CFR 312.62(b).

4. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

Each time the study drug was dispensed to a subject, the protocol required that the drug label be removed from the packaging and affixed to the Drug Label Form for that subject. However, the Drug Label Form for Subject 00013 did not include labels for the two drugs (medication randomization numbers3 1010589 and 1020640) that, according to the Drug Accountability Log, were dispensed to the subject on May 22, 2009.

We note that in your written response, you stated that you “agree that there was [sic] inadequate drug dispensing records in the paperwork,” but that you believed ”it was better documented in the eCRF.” However, it was your responsibility as the investigator to maintain adequate records of the disposition of the drug [21 CFR 312.62(a)]. As explained above, it was also your responsibility as the investigator to retain copies of the eCRFs for two years after the investigation was discontinued and FDA was notified [21 CFR 312.62(c)]. In addition, in your written response, you did not specify any corrective actions that you will take to address these violations or to prevent this type of violation from reoccurring in the future.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{Sincerely yours,}
Leslie K. Ball, M.D.
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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1 Mr. Thomas was present at the inspection from August 16, 2010, through August 20, 2010.
2 We note that on some of your study records, the number for this subject is recorded as “0013” instead of “00013.”
3 On the drug labels affixed to the Drug Label Form, the medication randomization number was referred to as the “Med. #.” On the Drug Accountability Log, this same number was referred to as the “Lot number.”

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Leslie K Ball
03/21/2011
Dear Dr. Sanderlin:

This letter describes some of the results of a Food and Drug Administration (FDA, the Agency) inspection conducted between June 21, 2012, and July 18, 2012. The FDA investigator met with you to review your conduct of a clinical study entitled *A Multi-Center, Actual Use Clinical Trial of the OraQuick ADVANCE® HIV 1/2 Antibody Test Over-the-Counter Product Performance in Untrained Users, Protocol OQ-OTC-5*. The FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational devices.

At the end of the inspection, the FDA investigator met with you to discuss the items listed on the Form FDA 483, Inspectable Observations. Based on the Form FDA 483 and other information available to the Agency, we have determined that you violated regulations governing the proper conduct of clinical studies involving investigational devices, as published in Title 21, Code of Federal Regulations (CFR) Part 812, (available at http://www.gpoaccess.gov/cfr/index.html). The applicable provisions of the CFR are cited for the violation listed below.

You failed to ensure that the investigation was conducted according to the investigational plan, the signed agreement, applicable FDA regulations, and conditions of approval imposed by the Institutional Review Board (IRB) or FDA, this, in order to protect the rights, safety, and welfare of the subjects under your care. [21 CFR §§ 812.100 and 812.110(b)].

The Protocol’s Study Design, Section III.L, *Follow-up for HIV Positive Test Results*, requires the clinical investigator to “comply with all federal, state, and local regulations regarding the reporting of newly-identified HIV positive laboratory results to the Centers for Disease Control and Prevention...
Eighteen (18) study subjects in Houston, Texas were confirmed HIV positive using FDA-approved methods at the central laboratory, with the first subject being confirmed HIV positive in December 2010, more than 18 months ago. The table below identifies each newly-diagnosed HIV positive subject and the date you signed the central lab report form with a positive HIV test result. Also listed below is the date of Visit 3 for the subjects. According to the protocol, review of the subject’s self test data and laboratory results occurred during Visit 3. All of these subject visits occurred more than one year ago.

<table>
<thead>
<tr>
<th>Subject #/Initials</th>
<th>Date the central lab positive HIV test result form was signed by CI</th>
<th>Date of Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b)(6)</td>
<td>12/23/2010</td>
<td>12/23/2010</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>1/24/2011</td>
<td>1/24/2011</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>2/21/2011</td>
<td>2/21/2011</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>2/24/2011</td>
<td>2/24/2011</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>4/18/2011</td>
<td>4/18/2011</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>7/1/2011</td>
<td>7/1/2011</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>7/1/2011</td>
<td>7/1/2011</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>7/18/2011</td>
<td>7/18/2011</td>
</tr>
</tbody>
</table>

The inspection revealed no documentation that you had reported the subjects with HIV positive laboratory results in accordance with state requirements, specifically, the Texas Administrative Code Title 25, Part 1, Chapter 97, Subchapter F, Rule 97.133, which requires you to submit to the State of Texas information for any specimen derived from a human body that yields microscopic, cultural, serological or any other evidence of HIV. According to the Texas Department of State Health Services’ “Technical Assistance Bulletin: Reporting Rapid HIV Test Results” dated March 2010, you are to report positive HIV test results on the Form STD-27 (Department of State Health Services Confidential Report of Sexually Transmitted Diseases Form), and the completed forms are to be sent to the local or regional health authority within seven days of receiving the positive test result. Contrary to what your staff told FDA during the inspection, the CDC does not accept direct reports from individuals. Instead, state health departments, such as the Texas Department of State Health Services, upon receipt of HIV positive laboratory results from within the state, report such surveillance data to the CDC using an electronic HIV/AIDS reporting system.

Within fifteen (15) business days of receipt of this letter, please provide written documentation to confirm that you reported the eighteen (18) subjects with HIV positive laboratory results to the Texas Department of State Health Services, along with the dates on which you made these reports. If you did not report some or all of the HIV positive laboratory results to the Texas Department of State Health Services, please provide details regarding that information as well.

Please provide specific actions you will take to prevent the recurrence of similar violations in current and future studies for which you are the clinical investigator. Failure to respond to this letter and to take appropriate corrective action could result in FDA taking regulatory action without further notice to you.

The seriousness of the violation referenced in this letter, and its potential public health implications,
has caused us to issue this letter prior to a complete review of all of the violations listed on the Form FDA 483 and, as a result, this letter is not intended to be an all-inclusive list of deficiencies. We are continuing to review information from the two recent inspections conducted at your site (March 27, 2012 through March 29, 2012 and the inspection noted in the first paragraph of this letter). It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations.

Please send your written response to:

Janet White
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1488
Telephone: 301-827-6323

We also request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

/S/
Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: District Director
  Food and Drug Administration
  4040 North Central Expressway, Suite 300
  Dallas, Texas 75204

  Texas Department of State Health Services
  PO Box 149347
  Austin, Texas 78714-9347
Dear Dr. Boyce:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between August 24 and September 15, 2011, by Krista Flores, representing the FDA, to review your conduct of a clinical investigation [Protocol (b)(4)] entitled (b)(4) of the investigational drug (b)(4) performed for (b)(4).

This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Flores presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 5, 2011, written response to the Form FDA 483.

From our review of the establishment inspection report, the documents submitted with that report, and your October 5, 2011, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. You failed to assure that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of the proposed clinical study [21 CFR 312.66].

   As a clinical investigator, you are required to assure that an IRB that complies with 21 CFR part 56 reviews and approves a proposed clinical investigation. You failed to assure that an IRB that complies with 21 CFR part 56 reviewed and approved a proposed clinical study. Specifically:

      a. Subject 23/015852 was enrolled on May 19, 2010;
      b. Subject 24/001699 was enrolled on May 23, 2010;
      c. Subject 25/015964 was enrolled on June 23, 2010;
      d. Subject 26/001970 was enrolled on July 5, 2010; and
      e. Subject 27/016052 was enrolled on July 26, 2010.


In your written response to the Form FDA 483, you note that the protocol and revised informed consent document were submitted to the IRB on April 7, 2010, for continuing review approval; and that, in response, the IRB communicated stipulations required to be met prior to IRB approval. Specifically, you noted that the IRB's letter stipulated that subinvestigators needed to complete updated training in Good Clinical Practice (GCP) and to sign a conflict of interest statement before IRB approval could be granted. You further note that your study coordinator was delegated the responsibility of ensuring that the IRB's stipulations were addressed, and that IRB approval was obtained. You indicate that your failure to obtain IRB approval was the result of the actions of your study coordinator, and that you were not aware that IRB approval of your clinical investigation had expired until after all five of the above listed subjects were enrolled.

We acknowledge that you have provided a corrective action plan that includes placing expiration/renewal dates for studies on your personal calendar; seeing the actual IRB approval letter and approved informed consent; using a clinical research associate meeting form to inquire if the clinical research associate has any concerns about documents or processes; and conducting a clinical study with two coordinators.

Your response is incomplete because you have not provided documentation of procedures to ensure that IRB review and approval are obtained. Without this information, we cannot conduct an informed evaluation of the potential use of your corrective actions to prevent the recurrence of this type of violation in the future. Moreover, it was your responsibility as a clinical investigator to ensure that an IRB that complied with 21 CFR part 56 was responsible for the initial and continuing review and approval of Protocol (b)(4). Please note that, although you indicate that your current employer closely monitors protocols nearing expiration of IRB approval, it remains your responsibility as a clinical investigator to ensure IRB review and approval.

Your failure to ensure IRB approval of Protocol (b)(4) raises concerns about the extent to which subjects’ rights and welfare were protected at your site.

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the signed and dated consent forms. You have failed to maintain adequate and accurate case histories by using informed consent forms that inaccurately indicated they had been approved by the IRB. Specifically:

Informed consent forms for the five subjects enrolled at your site after IRB approval for your study had expired (Subjects 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052) were found to have stamps on the documents inaccurately indicating that they had been approved by the IRB. The stamps on these informed consent forms inaccurately showed an IRB approval date of May 11, 2010, and an IRB approval expiration date of May 9, 2011.

According to your September 15, 2011, affidavit, you were not aware until August 30, 2010, that IRB approval had expired on May 11, 2010, and you were informed by your site manager on September 9, 2010, that your study coordinator had purchased a custom-made stamp at Office Depot, which he had used to stamp the informed consent documents that were used to enroll five subjects after the study’s IRB expiration date.

In your written response to the Form FDA 483, you indicate that the above finding was the “egregious act of one rogue employee.” We acknowledge that your written response provided a corrective action plan that includes placing expiration/renewal dates for studies on your personal calendar; seeing the actual IRB approval letter and approved informed consent prior to enrolling subjects in any study; using a clinical research associate meeting form to inquire if the clinical research associate has any concerns about documents or processes; and conducting a clinical study with two coordinators.

Your response is incomplete because you have not provided documentation of procedures for regulatory oversight of studies that you conduct. Without this information, we cannot conduct an informed evaluation of the potential use of your corrective actions to prevent the recurrence of this type of violation in the future. Moreover, it was your responsibility as a clinical investigator to prepare and maintain adequate and accurate case histories for Protocol (b)(4). Please note that, although you indicate that your current employer has internal processes for helping to ensure that updated informed consent documents are used, it remains your responsibility as a clinical investigator to prepare and maintain adequate and accurate case histories.

You failed to prepare and maintain adequate and accurate case histories because the case histories for your
study included informed consent documents that inaccurately indicated they had been approved by the IRB. By doing so, as also noted below, you may have caused Subjects 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052 to be misled regarding the status of IRB approval of the informed consent documents they were signing, thus raising concerns about the adequacy of human subject protections at your site.

3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol (b)(4) requires, among other things, that postoperative day (POD) visits occur and electrocardiograms (ECGs) be recorded at specified times. You failed to adhere to these requirements. Specifically:

a. The protocol requires that the office visit on POD 28 occur no earlier than 28 full days after study drug administration. For six subjects (20/001483, 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052) out of the nine subjects whose POD 28 assessments were reviewed during the inspection, POD 28 assessments either were not performed or were performed earlier than 28 full days after study drug administration.

b. The protocol requires that standard 12-lead ECGs be recorded at 24 hours and 96 hours after completion of surgery and at discharge. For seven subjects (17/015693, 18/001401, 21/015769, 23/015852, 25/015964, 26/001970, and 27/016052) out of the nine subjects whose ECG records were reviewed during the inspection, ECGs were not performed at certain required times.

In your written response to the Form FDA 483, you concur with the findings noted in Item 3a. above, as they relate to Subjects 20/001483, 23/015852, 24/001699, and 25/015964. Regarding the missing ECGs (see the findings in Item 3b. above), you state in your written response that the reason why ECGs were missing is that hospital staff and the study coordinator did not obtain ECGs as required by the protocol.

We acknowledge that you have provided a corrective action plan to prevent future recurrence of similar violations. As part of your corrective action plan, you state that you will continue to ensure that hospital and research staff are aware of the importance of following study procedures, and that you will escalate findings of noncompliance to a written report when appropriate. Furthermore, in your response, you state that your current employer has an internal process for reporting protocol deviations, and that coordinators must report deviations to the regulatory team for submission to the IRB.

Your response is incomplete because you have not provided documentation of procedures that you will use for oversight of studies that you conduct. Without this information, we cannot conduct an informed evaluation of the potential use of your corrective actions to prevent the recurrence of this type of violation in the future. Moreover, as the clinical investigator, you were ultimately responsible for ensuring that Protocol (b)(4) was conducted according to the investigational plan.

Your failure to ensure that Protocol (b)(4) was conducted according to the investigational plan, raises concerns about the extent to which the rights, safety, and welfare of subjects were protected, and about the validity and integrity of the data at your site. Of note, obtaining data for the POD 28 assessment prior to 28 full days after study drug administration may have affected the primary efficacy endpoint of first occurrence of the composite of all-cause death, nonfatal stroke, or need for mechanical support for severe left ventricular dysfunction (SLVD) occurring during and following (b)(4) surgery through POD 28. In addition, failure to obtain protocol-required ECGs in seven of the nine subjects undergoing cardiac surgery is a significant safety concern, and further raises concerns about the validity and integrity of the data collected at your site.

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.27].

As a clinical investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR part 50. Except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. You failed to properly document informed consent. Specifically:

The informed consent form signed by Subject 26/001970 was not dated.

In addition, as noted above, the informed consent forms for the five subjects enrolled at your site after IRB approval for your study had expired (Subjects 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052) were not approved by the IRB, and were found to have stamps on the documents inaccurately indicating that they had been approved by the IRB.

In your written response to the Form FDA 483, you acknowledge that the informed consent form for subject
26/001970 was not dated. As a corrective action, you state that you will emphasize to your research staff the importance of dating documents as required. Furthermore, you state that a second research staff person will inspect the informed consent forms for completeness. In your written response, you also provide corrective actions related to the use of informed consent documents that were not approved by the IRB, including placing expiration/renewal dates for studies on your personal calendar; seeing the actual IRB approval letter and approved informed consent prior to enrolling subjects in any study; using a clinical research associate meeting form to inquire if the clinical research associate has any concerns about documents or processes; and conducting a clinical study with two coordinators.

Your response is incomplete because you have not provided documentation of procedures that you will use for oversight of studies that you conduct, or of training that study staff have received on the new procedures. Without this information, we cannot conduct an informed evaluation of the potential use of your corrective actions to prevent the recurrence of this type of violation in the future. Moreover, as the clinical investigator, you were ultimately responsible for ensuring that informed consent was obtained in accordance with 21 CFR part 50. Of note, your use of informed consent forms that inaccurately indicated they had been approved by the IRB, may have caused Subjects 23/015852, 24/001699, 25/015964, 26/001970, and 27/016052 to be misled regarding the status of IRB approval of the informed consent documents they were signing.

Your failure to obtain informed consent in accordance with 21 CFR part 50 prior to involving subjects in research, raises significant concerns about your protection of study subjects enrolled at your site in the study mentioned above.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity, M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
/S/
Thomas N. Moreno, M.S.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Betty Tuller, Ph.D.
(b)(6)

Dear Dr. Tuller:
Between January 18, 2011, and February 14, 2011, Mr. Sean Creighton, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drug (b)(4):

(b)(4)

The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of Title 21, Code of Federal Regulations (CFR) Part 312 if the criteria in 21 CFR 312.2(b)(1) are met. However, the studies listed above do not meet these criteria because they involved a route of administration or dosage level that significantly increased the risks (or decreased the acceptability of the risks) associated with the use of this drug product [21 CFR 312.2(b)(iii)]. Therefore, these studies were subject to 21 CFR Part 312 [21 CFR 312.2(a)] and should have been conducted under an Investigational New Drug (IND) application [21 CFR 312.20]. As a result, your conduct as the clinical investigator for these studies was required to conform to the requirements in 21 CFR Part 312.

During the time you conducted these studies, you were working at the following address: Florida Atlantic University, Center for Complex Systems and Brain Sciences, 777 Glades Road, Boca Raton, FL 33431.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We are aware that at the conclusion of the inspection, Mr. Creighton presented and discussed with you the inspectional findings. We wish to emphasize the following:

1. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

As the investigator, it was your responsibility to obtain informed consent in accordance with 21 CFR Part 50 [21 CFR 312.60]. 21 CFR 50.25(a) describes the basic information that must be provided to each subject when seeking informed consent. However for four of the five studies listed above (b)(4) and (b)(4), you failed to ensure that subjects were provided with all of the basic information required by 21 CFR 50.25(a).

Specifically, the informed consent documents used for these four studies failed to include the following required elements:

   a. Identification of any procedures which are experimental [CFR 50.25(a)(1)].
b. A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject [21 CFR 50.25(a)(4)].

c. A statement noting the possibility that the Food and Drug Administration may inspect the records [21 CFR 50.25(a)(5)].

d. An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs; and, if so, what they consist of, or where further information may be obtained [21 CFR 50.25(a)(6)].

e. A description of any reasonably foreseeable risks or discomforts to the subject [21 CFR 50.25 (a)(2)].

The informed consent documents for these studies indicate that "Risks from the (b)(4) are primarily hypoglycemia." However, according to the (b)(4) label found in study records at your site, the risks associated with the use of (b)(4) products also include, but are not limited to, hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. (b)(4) administered (b)(4) has a rapid onset of action. Therefore, this modality of (b)(4) therapy should be used with caution in subjects at risk for hypokalemia (e.g., patients using potassium-lowering medications and patients taking medications sensitive to serum potassium concentrations), and potassium should be monitored frequently when (b)(4) is administered (b)(4) to avoid fatal hypokalemia.

You failed to inform subjects of the reasonably foreseeable risk of developing hypokalemia and its complications. This is a critical omission in the information provided to subjects when seeking informed consent, and represents a significant human subject protection concern.

Your failure to inform subjects of the reasonably foreseeable risk of hypokalemia and its complications, along with your failure to inform subjects of the additional required elements of consent listed above, denied the subjects an opportunity to assess the risks and benefits of their participation in the clinical investigations. Additionally, by not providing the subjects under your care with the information they were entitled to receive to assist them in making an informed decision about whether to participate in the studies, you compromised the rights, safety, and welfare of those subjects.

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

As the clinical investigator, you were required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62 (b)]. Case histories include information related to subjects' enrollment and participation in, and completion of, the study. However, during the inspection, you indicated to Mr. Creighton that you did not keep records of how many subjects were enrolled, how many subjects withdrew from the study, and how many subjects completed the study. As a result, it appears that you failed to maintain adequate and accurate case histories as required by 21 CFR 312.62(b).

Your failure to maintain adequate and accurate case histories, including information related to subject enrollment and completion of the study, impacts the ability to accurately characterize subject participation in your studies; raises concerns about subject safety and data integrity; and compromises the interpretation and validity of the investigational endpoints.

3. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].

As the clinical investigator, you were required to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66]. Our investigation revealed that you collected lists of adverse events that occurred during the conduct of the five studies listed above, between 2004 and 2009, including some adverse events that resulted in hospitalization of subjects. However, during the course of our investigation, you indicated to Mr. Creighton that you did not keep records of how many subjects were enrolled, how many subjects withdrew from the study, and how many subjects completed the study. As a result, it appears that you failed to maintain adequate and accurate case histories as required by 21 CFR 312.62(b).

Your failure to ensure that the IRB was notified of all unanticipated problems involving risk to subjects, raises concerns about the extent to which subjects’ rights, safety, and welfare were
protected. Without a complete listing of the unanticipated problems involving risks to the subjects, the IRB was unable to make an informed determination regarding the continued safety of the subjects enrolled in your investigations.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

/s/
Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
August 14, 2012

Stephen R. Forrest, Ph.D.
Vice President of Research
University of Michigan
Office of Vice President of Research
4080 Fleming Building
Ann Arbor, MI 48109-1340

RE: Human Research Subject Protections Under Federalwide Assurance (FWA)- 4969

Dear Dr. Forrest:

Thank you for your July 10, 2012 report in response to our May 31, 2012 request for information related to our evaluation of the University of Michigan (UM) system for protecting human research subjects as part of our program to evaluate human subjects protection programs of institutions that receive Department of Health and Human Services (HHS) support for research.

(A) Based on our review of your response, we make the following determinations:

1) We have determined that many of the informed consent documents provided in your response do not appear to include all the pertinent alternatives to participation in the research, as required by HHS regulations at 45 CFR 46. 46116(a)(4) which require that when seeking informed consent specific information shall be provided to each subject, including a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Specifically, we note that the informed consent documents for the following protocols did not include appropriate information regarding the option of obtaining the research intervention outside of the research:

   b. HUM00000408: The Effect of Chronic Macrolide Administration on the Frequency and Severity of COPD Exacerbations.
   c. HUM00001093: Sublobar resection versus Sublobar resection plus brachytherapy.
Your response stated that some of the studies were conducted under an FDA IND, and it would be inappropriate to offer this experimental therapy outside of the study and that the consent forms for some of these studies did not include the investigational intervention as it is not part of standard of care. HHS regulatory requirements at 45 CFR 46.116(a)(4) do not specify that only information about standard of care interventions must be provided to subjects, but must include a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Your response also stated that offering as an option the use of some over the counter interventions could be viewed as encouraging self-medication without medical supervision, which could potentially be harmful, or that it would be inappropriate to offer an unproven therapy as a treatment option outside of the study. We note that the forms could have advised subjects to obtain such treatments only under medical supervision, if indeed, for the particular treatment in question, such supervision would be appropriate.

2) We determine that the consent form provided for a study indicate that subjects may be coerced into participating in open-ended, future research involving their biospecimens, in contravention of the regulatory requirements at 45 CFR 46.116. We note the following in this specific protocol: HUM00033520: Pilot Study of the Safety, Feasibility, and Potential Efficacy of Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG)

   -- Page 4: “Your samples and data will be used by the researchers carrying out this study, but they also may be used by other researchers, both during the study and after it ends. Your samples and data will be stored indefinitely.”
--Page 12: “If you do not agree to have your samples and data sent to the Repositories, you may not participate in this study.” Subjects cannot participate in this research study without agreeing to participate in future, non-specified research studies.

Your response notes that standard of care therapy was not withheld from potential subjects if they did not participate; there were no urgent timelines placed upon potential subjects in which to make a decision; and agreeing to participate in the biobanking portion of the study did not expose the potential subject to any greater risk than the non-biobanking portion of the study since no genetic testing is planned. However, we note that the study did hold out the prospect of direct benefit to the subjects which may be difficult for them to obtain without their agreement to participate in the biobanking portion of the study. Thus, they are being denied the right they have to participate in the study “alone,” without participating in the unrelated open-ended future biospecimen research. The level of risks presented by biospecimen research is not relevant to this issue. Even if such research is very low risk, subjects, just because they are enrolling in a particular clinical trial, do not generally give up their autonomy regarding deciding whether their identifiable biospecimens can be used for wholly open-ended and unspecified future research. (See http://www.hhs.gov/ohrp/detrm_letrs/YR08/apr08b.pdf for a prior determination letter regarding this issue)

(B) [Redacted]

Please provide us with responses to the above determinations, questions and concerns by September 21, 2012, including a corrective action plan for each of our determinations. Feel free to contact me if you would like guidance in developing a corrective action plan.

(C) At this time, we offer the following additional guidance:
1) We recommend that when approving consent forms, IRBs ensure that when the study is not expected to provide any direct benefits to subjects that the form clearly state this.” This will help ensure that consent forms accurately describe the benefits to the subject or others that may reasonably be expected from the research, as required by HHS regulatory requirements at 45 CFR 46.116(a)(3).

2) We note that the consent form for the study HUM00000392: Micronutrient prevention of noise-induced hearing loss at the Spanish (NATO) Air Force Base and cutlery stamping factories of Albacete contained numerous errors. We recommend that they be corrected.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please feel free to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc:
Ms. Judith A. Nowack, Associate Vice President for Research, UM
Dr. Alan Sugar M.D., IRB Chairperson IRBMED B-2 #6
Dr. Richard Redman, IRB Chairperson IRB #2 & #3, UM
Dr. Robert W. Hymes, IRB Chairperson Dearborn IRB #4, UM
Dr. Marianne McGrath, IRB Chairperson Flint IRB #5, UM
Dr. Michael Geisser, IRB Chairperson IRBMED A-2 #7 & #8 & C-1#9, UM
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration
Dr. Joanne Less, Food and Drug Administration
Dr. Sherry Mills, OER, National Institutes of Health
Dr. Joe Ellis, OER, National Institutes of Health
August 16, 2012

James S. Economou, M.D., Ph.D.
Vice Chancellor for Research
University of California Los Angeles
2147 Murphy Hall, Box 951405
Los Angeles, CA 90095-1405

RE: Human Research Protections Under Federalwide Assurance FWA-4642

Research Project: Respirator Effects In Impaired Workers
Principal Investigator: Philip Harber MD MPH
HHS Protocol Number: R01 2R01OH008119

Research Project: Occupational Medicine Activities and Skills: An Empiric Study
Principal Investigator: Philip Harber MD MPH
HHS Protocol Number: R01 5R01OH008647

Dear Dr. Economou:

Thank you for your November 29, 2011 report in response to our October 31, 2011 request that the University of California Los Angeles (UCLA) evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) and your August 6, 2012 letter in response to our June 11, 2012 questions and concerns letter. Based on review of your response, we make the following determinations:

A. Determinations Regarding the Above-Referenced Research:

1. A complainant alleged that UCLA failed to ensure that there were adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, as required by HHS regulations at 45 CFR 46.111(a)(7). In specific, the complainant alleged that, for the above studies:
(a) Research files that were clearly identified as containing subject data were removed from locked file cabinets and placed in easily accessible cardboard boxes.

According to your reports, in late December 2010, the principal investigator for the above-referenced studies unexpectedly left UCLA Department of Family Medicine, and retired from UCLA in March 2011. As a result of this unexpected departure, sometime in June 2011 the Department of Family Medicine took over responsibility for the principal investigator’s records. According to your reports, the Department of Family Medicine Chief Administrative Officer asked the Human Resources (HR) Director to clear out the principal investigator’s office and secure study files. In response to this directive, the HR Director removed the contents of the file cabinets and placed the contents in cardboard boxes. According to your responses, these boxes were - and are currently - maintained in a locked interior office space within a suite with access that is limited. You indicated in your August 6, 2012 response that access to the locked interior space is limited by the use of a master key. This master key is maintained with the front desk receptionist.

We acknowledge your statement that “Although this action [UCLA Department of Family Medicine HR Director actions] was taken without IRB review, the research was at that time [June 2011] no longer under an active approved protocol.”

(b) Research files were individually handled and looked at by the HR Director and her assistant and were comingled with patient and administrative files.

In your 2011 report, you acknowledged that the HR Director and her assistant “individually handled” the files as alleged, but that such handling was solely for the purpose of removal and transfer of the files from the file cabinets into boxes for safe keeping. According to your response, the files were not clearly marked by the investigator and, as a result, it was difficult for the Department of Family Medicine to determine whether the files were research records, patient clinical files, or miscellaneous documents. The UCLA Department of Family Medicine provided assurance that the files were not reviewed other than to transfer the files from the cabinets into boxes and to categorize them.

(c) Computers that had been secured were left open and accessible.
(d) Hard drives with data were left open and accessible.

According to the 2011 response, UCLA found no evidence that the computers and hard drives were “left open and accessible” or of any security breach of electronic data. UCLA stated that when the principal investigator was still employed at UCLA, computers and hard drives were password protected and maintained in a locked interior office space within a suite. Upon the departure of the investigator, the
computers and hard drives remained in the same locked interior office space with limited access.

(e) There is a single fax machine in an open area in the family medicine Oppenheimer Building suite and that identifiable private research materials from the fax are spread on an adjacent table and open to view by many staff, visitors, etc. In your 2011 response, you explained that the Department of Family Medicine Suite is: (a) located on the 18th floor of a business building; (b) houses faculty researchers and their staffs; and (c) neither a public nor a patient care area. In this same response, you stated that the single fax machine, which is dedicated to this department, is in a sequestered area in the suite and accessible only to authorized personnel. The complainant disagreed with this assessment. The complainant maintained that the fax machine is not in a sequestered area, as explained by UCLA, rather it is located in the most heavily used area in the suite and that there is no access control over the fax machine other than the main door to the suite. According to the complainant, fax materials were commonly left on the table in front of the mailboxes or the materials were placed in the open mailboxes of individual faculty/staff without any protection. According to the complainant, s/he regularly saw medical treatment reports for a breast cancer research project that were left on a table.

Your August 6, 2012 report included a floor plan of the Department of Family Medicine Suite. According to the floor plan, there is a single main double-door entry into the suite from the building hallway. According to the plan, a person must walk approximately 60 feet from the main entry to reach the fax machine. The entry way for each cubicle in proximity to the fax machine does not directly face the fax machine.

Moreover, you provided assurance that UCLA Department of Family Medicine staff who handle protected health information are required to complete required Health Insurance Portability and Accountability Act (HIPAA) training and that the practice of receiving/transmitting restricted information by facsimile is consistent with the UCLA health Compliance Policy “Facsimile Transmission of Restricted Information.” Lastly, according to your 2011 response, you found no evidence indicating that there has been any breach of subject safety or confidentiality of data.

(f) Anyone can enter the Department of Family Medicine Suite. No one checks the identity of people walking into the suite.

According to your August 6, 2012 report, this suite, which houses faculty researchers and their staff, is open from 8:00 am – 5:00 pm Monday – Friday. Although there are no formal procedures for granting outside visitors access to the suite, there is a front desk receptionist. You stated that in the unlikely event that there would be an
unknown or unidentified person in the suite, the receptionist, faculty or staff would ask the person to identify him/herself and state the purpose of the visit.

Based on the information outlined above, we found that these allegations could not be proven. No evidence was presented to us indicating that UCLA failed to ensure that there were adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, as required by HHS regulations at 45 CFR 46.111(a)(7).

2. The same complainant alleged that when the above-referenced allegations were brought to the attention of the UCLA institutional review board (IRB) and institutional officials, they were not investigated, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

According to your response, allegations regarding research data security, security of personal identifying information, and protected health information were brought to the attention of the UCLA IRB in May 2011. We note further, however, that according to your response these allegations were within the context of another study of the same investigator funded by the Department of Energy (DOE). Upon receiving these allegations, the UCLA Office of the Human Research Protection Program (OHRPP) Quality Improvement Unit (QIU) conducted an investigation into the allegations as they related to the DOE funded research and was in the process of preparing a report for the complainant and the UCLA Institutional Official when UCLA received our October 31, 2011 letter.

According to UCLA, in response to the October 31, 2011 letter from our office, the UCLA OHRPP QIU conducted an expanded investigation and returned to the Department of Family Medicine to seek additional information and to examine the security on the premises relative to the confidentiality of the date for these projects.

Based on the responses provided, we found that this allegation could not be proven. No evidence was presented to us indicating that UCLA failed to investigate the allegations referenced above as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).
The remaining questions and concerns from our June 11, 2012 letter have been adequately addressed.

At this time, there should be no need for further involvement by our office in this matter. Please notify us if you identify new information which might alter this determination.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Sharon K. Friend, Director, OHRPP, University of California, Los Angeles (UCLA)
Dr. Daniel Clemens, IRB Chair, UCLA MIRB1
Dr. Fairooz Kabbinavar, IRB Chair, UCLA MIRB2
Dr. Nancy Levine, IRB Chair, UCLA IRB #3
Dr. James McGough, IRB Chair, UCLA IRB #4
Dr. Alison Moore, IRB Chair, UCLA IRB #5
Mr. Ron Otten, Center for Disease Control and Prevention
October 16, 2012

James S. Economou, M.D., Ph.D.
Vice Chancellor for Research
University of California Los Angeles
2147 Murphy Hall, Box 951405
Los Angeles, CA 90095-1405

RE: Human Research Protections Under Federalwide Assurance FWA-4642

Research Project: Diabetes Prevention Program Outcomes Study
Principal Investigator: Dr. Karol E. Watson
HHS Protocol Number: U01 DK 048443

Dear Dr. Economou:

Thank you for your March 29, 2012 report in response to our January 10, 2012 request that the University of California Los Angeles (UCLA) evaluate indications of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). Based on review of your response, we make the following determinations:

A. Determinations Regarding the Above-Referenced Research:

(1) We have determined that changes to the above-referenced research were initiated without institutional review board (IRB) review and approval, in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii), which require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. Specifically, we note that a UCLA Office of the Human Research Protection Program (OHRPP) Quality Improvement Unit (QUI) records review found that serious adverse events (SAEs), which were documented by the investigator, but not by the study staff, were not consistently reported to the Diabetes Prevention Outcomes Study (DPPOS) Data Coordinating Center (DCC) in accordance with the IRB-approved protocol.
Corrective Actions: According to your response, the following corrective actions have been, or will be, implemented to address this noncompliance:

(a) Replacing the previous program coordinator with two research staff members;
(b) Retraining of research staff members on the timely identification and reporting of (SAEs);
(c) The development of new forms to avoid similar non-reporting in the future;
(d) Creation or modification of spreadsheets, checklists, procedures and forms to better capture possible SAEs.

We have determined that the corrective actions noted above adequately address our determination and are appropriate under the UCLA FWA.

(2) We received indications that the study investigator failed to report unanticipated problems or noncompliance to the IRB, institutional officials, and OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). Specifically, we were concerned that the above referenced SAEs were not reported to the IRB, institutional officials, and OHRP.

According to your response, the OHRPP QIU reviewed the UCLA IRB records for this study for the past seven years and participant research records at the UCLA clinical center. This review revealed that all unanticipated problems or noncompliance associated with this study were reported to the IRB, institutional officials, and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). Moreover, we note that the OHRPP QIU records review found that the above-referenced SAEs - SAEs that were not reported to the DPPOS DCC in accordance with the IRB approved protocol -did not constitute unanticipated problems or noncompliance. As a result, the SAEs did not need to be reported to the UCLA IRB under the requirements of the HHS protection of human subjects regulations. Based on information provided in your correspondence, we have determined that this indication of noncompliance is unproven. From the evidence presented to us, the investigator reported all unanticipated problems or noncompliance associated with this study to the IRB, institutional officials and OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

At this time, there should be no need for further involvement by our office in this matter. Please notify us if you identify new information which might alter this determination.
We appreciate the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Sharon K. Friend, Director, OHRPP, University of California, Los Angeles (UCLA)
Dr. Fairooz Kabbinavar, IRB Chair, UCLA MIRB1 & 2
Dr. Nancy Levine, IRB Chair, UCLA IRB #3
Dr. James McGough, IRB Chair, UCLA IRB #4
Dr. Alison Moore, IRB Chair, UCLA IRB #5
Dr. Karol E. Watson, UCLA

cc without enclosures:
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
Dr. Griffin P. Rodgers, Director, NIDDK
The New England
Journal of Medicine

Volume 274 JUNE 16, 1966 Number 24

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SPECIAL ARTICLE
ETHICS AND CLINICAL RESEARCH*
HENRY K. BEECHER, M.D.†

BOSTON

HUMAN experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects when it must be apparent that they would not have been available if they had been truly aware of the uses that would be made of them. Evidence is at hand that many of the patients in the examples to follow never had the risk satisfactorily explained to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered as a direct result of experiments described here. There is a belief prevalent in some sophisticated circles that attention to these matters would “block progress.” But, according to Pope Pius XII,† “... science is not the highest value to which all other orders of values... should be subordinated.”

I am aware that these are troubling charges. They have grown out of troubling practices. They can be documented, as I propose to do, by examples from leading medical schools, university hospitals, private hospitals, governmental military departments (the Army, the Navy and the Air Force), governmental institutes (the National Institutes of Health), Veterans Administration hospitals and industry. The basis for the charges is broad.‡

I should like to affirm that American medicine is sound, and most progress in it soundly attained. There is, however, a reason for concern in certain areas, and I believe the type of activities to be mentioned will do great harm to medicine unless soon corrected. It will certainly be charged that any mention of these matters does a disservice to medicine, but not one so great, I believe, as a continuation of the practices to be cited.

Experimentation in man takes place in several areas: in self-experimentation; in patient volunteers and normal subjects; in therapy; and in the different areas of experimentation on a patient not for his benefit but for that, at least in theory, of patients in general. The present study is limited to this last category.

REASONS FOR URGENCY OF STUDY

Ethical errors are increasing not only in numbers but in variety – for example, in the recently added problems arising in transplantation of organs.

There are a number of reasons why serious attention to the general problem is urgent.

Of transcendent importance is the enormous and continuing increase in available funds, as shown below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Massachusetts General Hospital</th>
<th>National Institutes of Health*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1945</td>
<td>$500,000†</td>
<td>$501,800</td>
</tr>
<tr>
<td>1955</td>
<td>$2,222,816‡</td>
<td>$36,003,200</td>
</tr>
<tr>
<td>1965</td>
<td>$8,384,342‡</td>
<td>$436,600,000</td>
</tr>
</tbody>
</table>

*National Institutes of Health figures based upon decade averages, excluding funds for construction, kindly supplied by Dr. John Sherman, of National Institutes of Health.
†Approximation, supplied by Mr. David C. Crockett, of Massachusetts General Hospital.
‡At the Brook Lodge Conference on “Problems and Complexities of Clinical Research” I commented that “what seem to be breaches of ethical conduct in experimentation are by no means rare, but are almost, one fears, universal.” I thought it was obvious that I was by “universal” referring to the fact that examples could easily be found in all categories where research in man takes place to any significant extent. Judging by press comments, that was not obvious; hence, this note.

*From the Anaesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital.
†Dorothy Professor of Research in Anaesthesia, Harvard Medical School.
tenure post, to a professorship in a major medical school, unless he has proved himself as an investigator. If the ready availability of money for conducting research is added to this fact, one can see how great the pressures are on ambitious young physicians.

Implementation of the recommendations of the President’s Commission on Heart Disease, Cancer and Stroke means that further astronomical sums of money will become available for research in man.

In addition to the foregoing three practical points there are others that Sir Robert Platt has pointed out: a general awakening of social conscience; greater power for good or harm in new remedies, new operations and new investigative procedures than was formerly the case; new methods of preventive treatment with their advantages and dangers that are now applied to communities as a whole as well as to individuals, with multiplication of the possibilities for injury; medical science has shown how valuable human experimentation can be in solving problems of disease and its treatment; one can therefore anticipate an increase in experimentation; and the newly developed concept of clinical research as a profession (for example, clinical pharmacology) — and this, of course, can lead to unfortunate separation between the interests of science and the interests of the patient.

**Frequency of Unethical or Questionably Ethical Procedures**

Nearly everyone agrees that ethical violations do occur. The practical question is, how often? A preliminary examination of the matter was based on 17 examples, which were easily increased to 50. These 50 studies contained references to 186 further likely examples, on the average 3.7 leads per study; they at times overlapped from paper to paper, but this figure indicates how conveniently one can proceed in a search for such material. The data are suggestive of widespread problems, but there is need for another kind of information, which was obtained by examination of 100 consecutive human studies published in 1964, in an excellent journal; 12 of these seemed to be unethical. If only one quarter of them is truly unethical, this still indicates the existence of a serious situation. Pappworth, in England, has collected, he says, more than 500 papers based upon unethical experimentation. It is evident from such observations that unethical or questionably ethical procedures are not uncommon.

**The Problem of Consent**

All so-called codes are based on the bland assumption that meaningful or informed consent is readily available for the asking. As pointed out elsewhere, this is very often not the case. Consent in any fully informed sense may not be obtainable. Nevertheless, except, possibly, in the most trivial situations, it remains a goal toward which one must strive for sociologic, ethical and clear-cut legal reasons. There is no choice in the matter.

If suitably approached, patients will accede, on the basis of trust, to about any request their physician may make. At the same time, every experienced clinician investigator knows that patients will often submit to inconvenience and some discomfort, if they do not last very long, but the usual patient will never agree to jeopardize seriously his health or his life for the sake of “science.”

In only 2 of the 50+ examples originally compiled for this study was consent mentioned. Actually, it should be emphasized in all cases for obvious moral and legal reasons, but it would be unrealistic to place much dependence on it. In any precise sense statements regarding consent are meaningless unless one knows how fully the patient was informed of all risks, and if these are not known, that fact should also be made clear. A far more dependable safeguard than consent is the presence of a truly responsible investigator.

**Examples of Unethical or Questionably Ethical Studies**

These examples are not cited for the condemnation of individuals; they are recorded to call attention to a variety of ethical problems found in experimental medicine, for it is hoped that calling attention to them will help to correct abuses present. During ten years of study of these matters it has become apparent that thoughtlessness and carelessness, not a willful disregard of the patient’s rights, account for most of the cases encountered. Nonetheless, it is evident that in many of the examples presented, the investigators have risked the health or the life of their subjects. No attempt has been made to present the “worst” possible examples; rather, the aim has been to show the variety of problems encountered.

References to the examples presented are not given, for there is no intention of pointing to individuals, but rather, a wish to call attention to widespread practices. All, however, are documented to the satisfaction of the editors of the Journal.

*Known Effective Treatment Withheld*

**Example 1.** It is known that rheumatic fever can usually be prevented by adequate treatment of streptococcal respiratory infections by the parenteral administration of penicillin. Nevertheless, definitive treatment was withheld, and placebos were given to a group of 109 men in service, while benzathine penicillin G was given to others.

The therapy that each patient received was determined automatically by his military serial number arranged so that more men received penicillin than received placebo. In the small group of patients studied 2 cases of acute rheumatic fever and 1 of acute nephritis developed in the control patients, whereas these complications did not occur among those who received the benzathine penicillin G.

**Example 2.** The sulfonamides were for many years the only antibacterial drugs effective in shortening the duration of acute streptococcal pharyngitis and in reducing its suppurrative complications. The investigators in this study undertook to determine if the occurrence of the serious nonsuppurrative com-

*Reduced here to 22 for reasons of space.*

lications, rheumatic fever and acute glomerulonephritis, would be reduced by this treatment. This study was made despite the general experience that certain antibiotics, including penicillin, will prevent the development of rheumatic fever.

The subjects were a large group of hospital patients; a control group of approximately the same size, also with exudative Group A streptococcus, was included. The latter group received only non-specific therapy (no sulfadiazine). The total group denied the effective penicillin comprised over 500 men.

Rheumatic fever was diagnosed in 5.4 per cent of those treated with sulfadiazine. In the control group rheumatic fever developed in 4.2 per cent.

In reference to this study a medical officer stated in writing that the subjects were not informed, did not consent and were not aware that they had been involved in an experiment, and yet admittedly 25 acquired rheumatic fever. According to this same medical officer more than 70 who had had known definitive treatment withheld were on the wards with rheumatic fever when he was there.

Example 3. This involved a study of the relapse rate in typhoid fever treated in two ways. In an earlier study by the present investigators chloramphenicol had been recognized as an effective treatment for typhoid fever, being attended by half the mortality that was experienced when this agent was not used. Others had made the same observations, indicating that to withhold this effective remedy can be a life-or-death decision. The present study was carried out to determine the relapse rate under the two methods of treatment; of 408 charity patients 251 were treated with chloramphenicol, of whom 20, or 7.97 per cent, died. Symptoms of treatment was given, but chloramphenicol was withheld in 157, of whom 36, or 22.9 per cent, died. According to the data presented, 23 patients died in the course of this study who would not have been expected to succumb if they had received specific therapy.

Study of Therapy

Example 4. TriA (trimetrexate) was introduced for the treatment of infection with gram-positive organisms. Spotty evidence of hepatic dysfunction emerged, especially in children, and so the present study was undertaken on 50 patients, including mental defective or juvenile delinquents who were inmates of a children's center. No disease other than acne was present; the drug was given for treatment of this. The ages of the subjects ranged from thirteen to thirty-nine years. "By the time half the patients had received the drug for four weeks, the high incidence of significant hepatic dysfunction. . . led to the discontinuation of administration to the remainder of the group at three weeks." (However, only two weeks after the start of the administration of the drug, 54 per cent of the patients showed abnormal excretion of bromsulfalein.) Eight patients with marked hepatic dysfunction were transferred to the hospital "for more intensive study." Liver biopsy was carried out in these 8 patients and repeated in 4 of them. Liver damage was evident. Four of these hospitalized patients, after their liver-function tests returned to normal limits, received a "challenge" dose of the drug. Within two days hepatic dysfunction was evident in 3 of the 4 patients. In 1 patient a second challenge dose was given after the first challenge and again led to evidence of abnormal liver function. Floculation tests remained abnormal in some patients as long as five weeks after discontinuation of the drug.

Physiologic Studies

Example 5. In this controlled, double-blind study of the hematologic toxicity of chloramphenicol, it was recognized that chloramphenicol is "well known as a cause of aplastic anemia" and that there is a "prolonged morbidity and high mortality of aplastic anemia." When carried chloramphenicol-induced aplastic anemia can be related to dose . . . . The aim of the study was "further definition of the toxicity of the drug . . . ."

Forty-one randomly chosen patients were given either 2 or 6 gm. of chloramphenicol per day; 12 control patients were used. "Toxic bone-marrow depression, predominantly affecting erythropoiesis, developed in 2 of 20 patients given 2.0 gm. and in 18 of 21 given 6 gm. of chloramphenicol daily." The smaller dose is recommended for routine use.

Example 6. In a study of the effect of thymectomy on the survival of skin homographs 18 children, three and a half months to eighteen years of age, about to undergo surgery for congenital heart disease, were selected. Eleven were to have total thymectomy as part of the operation, and 7 were to serve as controls. As part of the experiment, full-thickness skin homographs from an unrelated adult donor were sutured to the chest wall in each case. (Total thymectomy is occasionally, although not usually part of the primary cardiovascular surgery involved, and whereas it may not greatly add to the hazards of the necessary operation, its eventual effects in children are not known.) This work was proposed as part of a long-range study of "the growth and development of these children over the years." No difference in the survival of the skin homograph was observed in the 2 groups.

Example 7. This study of cyclopropane anesthesia and cardiac arrhythmias consisted of 31 patients. The average duration of the study was three hours, ranging from two to four and a half hours. "Minor surgical procedures" were carried out in all but 1 subject. Moderate to deep anesthesia, with endotracheal intubation and controlled respiration, was used. Carbon dioxide was injected into the closed respiratory system until cardiac arrhythmias appeared. Toxic levels of carbon dioxide were achieved and maintained for considerable periods. During the cyclopropane anesthesia a variety of pathologic cardiac arrhythmias occurred. When the carbon dioxide tension was elevated above normal, ventricular extrasystoles were more numerous than when the carbon dioxide tension was normal, ventricular arrhythmias being continuous in 1 subject.
for ninety minutes. (This can lead to fatal fibrillation.)

Example 8. Since the minimum blood-flow requirements of the cerebral circulation are not accurately known, this study was carried out to determine "cerebral hemodynamic and metabolic changes . . . before and during acute reductions in arterial pressure induced by drug administration and/or postural adjustments." Forty-four patients whose ages varied from the second to the tenth decade were involved. They included normotensive subjects, those with essential hypertension and finally a group with malignant hypertension. Fifteen had abnormal electrocardiograms. Few details about the reasons for hospitalization are given.

Signs of cerebral circulatory insufficiency, which were easily recognized, included confusion and in some cases a nonresponsive state. By alteration in the tilt of the patient "the clinical state of the subject could be changed in a matter of seconds from one of alertness to confusion, and for the remainder of the flow, the subject was maintained in the latter state." The femoral arteries were cannulated in all subjects, and the internal jugular veins in 14.

The mean arterial pressure fell in 37 subjects from 109 to 48 mm. of mercury, with signs of cerebral ischemia. "With the onset of collapse, cardiac output and right ventricular pressures decreased sharply."

Since signs of cerebral insufficiency developed without evidence of coronary insufficiency the authors concluded that "the brain may be more sensitive to acute hypotension than is the heart."

Example 9. This is a study of the adverse circulatory responses elicited by intra-abdominal maneuvers:

When the peritoneal cavity was entered, a deliberate series of maneuvers was carried out [in 68 patients] to ascertain the effective stimuli and the areas responsible for development of the expected circulatory changes. Accordingly, the surgeon rubbed localized areas of the parietal and visceral peritoneum with a small ball sponge as discreetly as possible. Traction on the mesenteries, pressure in the area of the celiac plexus, traction on the gallbladder and stomach, and occlusion of the portal and caval veins were the other stimuli applied.

Thirty-four of the patients were sixty years of age or older; 11 were seventy or older. In 44 patients the hypotension produced by the deliberate stimulation was "moderate to marked." The maximum fall produced by manipulation was from 200 systolic, 105 diastolic to 42 systolic, 20 diastolic; the average fall in mean pressure in 25 patients was 53 mm. of mercury.

Of the 50 patients studied, 17 showed either atrioventricular dissociation with nodal rhythm or nodal rhythm alone. A decrease in the amplitude of the T wave and elevation or depression of the ST segment were noted in 25 cases in association with manipulation and hypotension or, at other times, in the course of anesthesia and operation. In only 1 case was the change pronounced enough to suggest myocardial ischemia. No case of myocardial infarction was noted in the group studied although routine electrocardiograms were not taken after operation to detect silent infarcts. Two cases in which electrocardiograms were taken after operation showed T-wave and ST-segment changes that had not been present before.

These authors refer to a similar study in which more alarming electrocardiographic changes were observed. Four patients in the series sustained silent myocardial infarctions; most of their patients were undergoing gallbladder surgery because of associated heart disease. It can be added further that in the 34 patients referred to above as being sixty years of age or older, some doubtless had heart disease that could have made risky the maneuvers carried out. In any event, this possibility might have been a deterrent.

Example 10. Starling's law — "that the heart output per beat is directly proportional to the diastolic filling" — was studied in 30 adult patients with atrial fibrillation and mitral stenosis sufficiently severe to require valvulotomy. "Continuous alterations of the length of a segment of left ventricular muscle were recorded simultaneously in 13 of these patients by means of a mercury-filled resistance gauge sutured to the surface of the left ventricle." Pressures in the left ventricle were determined by direct puncture simultaneously with the segment length in 13 patients and without the segment length in an additional 13 patients. Four similar unanesthetized patients were studied through catheterization of the left side of the heart transeptally. In all 30 patients arterial pressure was measured through the catheterized brachial artery.

Example 11. To study the sequence of ventricular contraction in human bundle-branch block, simultaneous catheterization of both ventricles was performed in 22 subjects; catheterization of the right side of the heart was carried out in the usual manner; the left side was catheterized transbronchially. Extrasystoles were produced by tapping on the epicardium in subjects with normal myocardium while they were undergoing thoracotomy. Simultaneous pressures were measured in both ventricles through needle puncture in this group.

The purpose of this study was to gain increased insight into the physiology involved.

Example 12. This investigation was carried out to examine the possible effect of vagal stimulation on cardiac arrest. The authors had in recent years transected the homolateral vagus nerve immediately below the origin of the recurrent laryngeal nerve as palliation against cough and pain in patients with carcinoma. Having been impressed with the number of reports of cardiac arrest that seemed to follow vagal stimulation, they tested the effects of intrathoracic vagal stimulation during 30 of their surgical procedures, concluding, from these observations in patients under satisfactory anesthesia, that cardiac irregularities and cardiac arrest due to vagovagal reflex were less common than had previously been supposed.

Example 13. This study presented a technic for determining portal circulation time and hepatic
blood flow. It involved the transcutaneous injection of the spleen and catheterization of the hepatic vein. This was carried out in 43 subjects, of whom 14 were normal; 16 had cirrhosis (varying degrees), 9 acute hepatitis, and 4 hemolytic anemia.

No mention is made of what information was divulged to the subjects, some of whom were seriously ill. This study consisted in the development of a technic, not of therapy, in the 14 normal subjects.

Studies to Improve the Understanding of Disease

Example 14. In this study of the syndrome of impending hepatic coma in patients with cirrhosis of the liver certain nitrogenous substances were administered to 9 patients with chronic alcoholism and advanced cirrhosis: ammonium chloride, ammonium citrate, urea or dietary protein. In all patients a reaction that included mental disturbances, a "flapping tremor" and electroencephalographic changes developed. Similar signs had occurred in only 1 of the patients before these substances were administered:

The first sign noted was usually clouding of the consciousness. Three patients had a second or a third course of administration of a nitrogenous substance with the same results. It was concluded that marked resemblance between this reaction and impending hepatic coma, implied that the administration of these [nitrogenous] substances to patients with cirrhosis may be hazardous.

Example 15. The relation of the effects of ingested ammonia to liver disease was investigated in 11 normal subjects, 6 with acute virus hepatitis, 26 with cirrhosis, and 8 miscellaneous patients. Ten of these patients had neurologic changes associated with either hepatitis or cirrhosis.

The hepatic and renal veins were cannulated. Ammonium chloride was administered by mouth. After this, a tremor that lasted for three days developed in 1 patient. When ammonium chloride was ingested by 4 cirrhotic patients with tremor and mental confusion the symptoms were exaggerated during the test. The same thing was true of a fifth patient in another group.

Example 16. This study was directed toward determining the period of infectivity of infectious hepatitis. Artificial induction of hepatitis was carried out in an institution for mentally defective children in which a mild form of hepatitis was endemic. The problem was the intramuscular injection or oral administration of the virus, but nothing is said regarding what was told them concerning the appreciable hazards involved.

A resolution adopted by the World Medical Association states explicitly: "Under no circumstances is a doctor permitted to do anything which would weaken the physical or mental resistance of a human being except from strictly therapeutic or prophylactic indications imposed in the interest of the patient." There is no right to risk an injury to 1 person for the benefit of others.

Example 17. Live cancer cells were injected into 22 human subjects as part of a study of immunity to cancer. According to a recent review, the subjects (hospitalized patients) were "merely told they would be receiving 'some cells'" — "... the word cancer was entirely omitted. ...

Example 18. Melanoma was transplanted from a daughter to her volunteering and informed mother, "in the hope of gaining a little better understanding of cancer immunity and in the hope that the production of tumor antibodies might be helpful in the treatment of the cancer patient." Since the daughter died on the day after the transplantation of the tumor into her mother, the hope expressed seems to have been more theoretical than practical, and the daughter's condition was described as "terminal" at the time the mother volunteered to be a recipient. The primary implant was widely excised on the twenty-fourth day after it had been placed in the mother. She died from metastatic melanoma on the four hundred and fifty-first day after transplantation. The evidence that this patient died of diffuse melanoma that metastasized from a small piece of transplanted tumor was considered conclusive.

Technical Study of Disease

Example 19. During bronchoscopy a special needle was inserted through a bronchus into the left atrium of the heart. This was done in an unspecified number of subjects, both with cardiac disease and with normal hearts.

The technic was a new approach whose hazards were at the beginning quite unknown. The subjects with normal hearts were used, not for their possible benefit but for that of patients in general.

Example 20. The percutaneous method of catheterization of the left side of the heart has, it is reported, led to 8 deaths (1.09 per cent death rate) and other serious accidents in 732 cases. There was, therefore, need for another method, the transcatheter approach, which was carried out in the present study in more than 500 cases, with no deaths.

Granted that a delicate problem arises regarding how much should be discussed with the patients involved in the use of a new method, nevertheless where the method is employed in a given patient for his benefit, the ethical problems are far less than when this potentially extremely dangerous method is used "in 15 patients with normal hearts, undergoing bronchoscopy for other reasons." Nothing was said about what was told any of the subjects, and nothing was said about the granting of permission, which was certainly indicated in the 15 normal subjects used.

Example 21. This was a study of the effect of exercise on cardiac output and pulmonary-artery pressure in 8 "normal" persons (that is, patients whose diseases were not related to the cardiovascular system), in 8 with congestive heart failure severe enough to have recently required complete bed rest, in 6 with hypertension, in 2 with aortic insufficiency, in 7 with mitral stenosis and in 5 with pulmonary emphysema.

Intracardiac catheterization was carried out, and the catheter then inserted into the right or left main branch of the pulmonary artery. The brachial artery
was usually catheterized; sometimes, the radial or femoral arteries were catheterized. The subjects exercised in a supine position by pushing their feet against weighted pedals. "The ability of these patients to carry on sustained work was severely limited by weakness and dyspnea." Several were in severe failure. This was not a therapeutic attempt but rather a physiologic study.

**Bizarre Study**

**Example 22.** There is a question whether ureteral reflux can occur in the normal bladder. With this in mind, vesicourethrography was carried out on 26 normal babies less than forty-eight hours old. The infants were exposed to x-rays while the bladder was filling and during voiding. Multiple spot films were made to record the presence or absence of ureteral reflux. None was found in this group, and fortunately no infection followed the catheterization. What the results of the extensive x-ray exposure may be, no one can yet say.

**Comment on Death Rates**

In the foregoing examples a number of procedures, some with their own demonstrated death rates, were carried out. The following data were provided by 3 distinguished investigators in the field and represent widely held views.

**Cardiac catheterization:** right side of the heart, about 1 death per 1000 cases; left side, 5 deaths per 1000 cases. "Probably considerably higher in some places, depending on the portal of entry." (One investigator had 15 deaths in his first 150 cases.) It is possible that catheterization of a hepatic vein or the renal vein would have a lower death rate than that of catheterization of the right side of the heart, for if it is properly carried out, only the atrium is entered en route to the liver or the kidney, not the right ventricle, which can lead to serious cardiac irregularities. There is always the possibility, however, that the ventricle will be entered inadvertently. This occurs in at least half the cases, according to 1 expert — "but if properly done is too transient to be of importance."

**Liver biopsy:** the death rate here is estimated at 2 to 3 per 1000, depending in considerable part on the condition of the subject.

**Anesthesia:** the anesthesia death rate can be placed in general at about 1 death per 2000 cases. The hazard is doubtless higher when certain practices such as deliberate evocation of ventricular extrasystoles under cyclopropane are involved.

**Publication**

In the view of the British Medical Research Council it is not enough to ensure that all investigation is carried out in an ethical manner: it must be made unmistakably clear in the publications that the properties have been observed. This implies editorial responsibility in addition to the investigation.

*As far as principle goes, a parallel can be seen in the recent Mapp decision by the United States Supreme Court. It was stated there that evidence unconstitutionally obtained cannot be used in any judicial decision, no matter how important the evidence is to the ends of justice.

**Summary and Conclusions**

The ethical approach to experimentation in man has several components; two are more important than the others, the first being informed consent. The difficulty of obtaining this is discussed in detail. But it is absolutely essential to *strive* for it for moral, sociologic and legal reasons. The statement that consent has been obtained has little meaning unless the subject or his guardian is capable of understanding what is to be undertaken and unless all hazards are made clear. If these are not known this, too, should be stated. In such a situation the subject at least knows that he is to be a participant in an experiment. Secondly, there is the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator.

Ordinary patients will not knowingly risk their health or their life for the sake of "science." Every experienced clinician investigator knows this. When such risks are taken and a considerable number of patients are involved, it may be assumed that informed consent has not been obtained in all cases. The gain anticipated from an experiment must be commensurate with the risk involved.

An experiment is ethical or not at its inception; it does not become ethical *post hoc* — ends do not justify means. There is no ethical distinction between ends and means.

In the publication of experimental results it must be made unmistakably clear that the proprieties have been observed. It is debatable whether data obtained unethically should be published even with stern editorial comment.

**References**

3. Pappworth, M. H. Personal communication.