The History Behind the Regulations

a tale of war crimes, discrimination, and abuse…

World War II

Nazi War Crimes

- Experiments on Twins
- Hypothermia
- Malaria
- Mustard Gas, Sulfonamide, Sea Water, Sterilization Methods, Typhus, High Altitude, and on and on

Result:
The Nuremberg Code 1947

The 10 directives set forth in the Nuremberg Code provided a foundation for the moral, ethical, and legal conduct of human subject research.

The code has served as the basis for many of our modern professional codes of ethics and international, federal, and state regulations.

The Nuremberg Code

1. Voluntary consent of the human subject is absolutely essential
2. The experiment must yield generalizable knowledge that could not be obtained in any other way and is not random and unnecessary in nature
3. Animal experimentation should precede human experimentation
The Nuremberg Code (cont.)

4. All unnecessary physical and mental suffering and injury should be avoided
5. No experiment should be conducted if there is reason to believe that death or disabling injury will occur
6. The degree of risk to subjects should never exceed the humanitarian importance of the problem
7. Risks to the subjects should be minimized through proper preparations

8. Experiments should only be conducted by scientifically qualified investigators
9. Subjects should always be at liberty to withdraw from experiments
10. Investigators must be ready to end the experiment at any stage if there is cause to believe that continuing the experiment is likely to result in injury, disability or death to the subject

Tuskegee: 1932-1972

U.S. Public Health Service funded study to evaluate the natural progression of untreated syphilis with the goal of demonstrating the need for establishing syphilis treatment programs

Study population: black males in rural Macon County, Alabama

And right here in the USA our own sad history of abuse and wrongdoing...

Tuskegee Syphilis Study
Jewish Chronic Disease Hospital
The Willowbrook Hepatitis Studies
Thalidomide
Milgram Obedience Studies
Jesse Gelsinger
and more...

Tuskegee (cont.)

The study continued until 1972 when Jean Heller published the story of Tuskegee in the New York Times and the Washington Star.

Jewish Chronic Disease Hospital: 1963

**Study Purpose:** Explore the relationship between weakened immune systems and the spread of cancer.

**Study Population:** Hospitalized chronically ill, debilitated, immune-compromised patients in New York City’s Jewish Chronic Disease Hospital.

Willowbrook Hepatitis Studies: 1963-1966

**Study Purpose:** to gain an understanding of the transmission of hepatitis and gamma globulin’s potential to prevent or minimize the effects of the disease.

**Study Population:** “mentally defective” child residents of the Willowbrook State School.

Thalidomide: late 1950’s – 1961
The Milgram Obedience
Study: 1961-1962

**Background:** Yale Psychologist Stanley Milgram became interested in the seeming complacency of the German citizenry in regards to the atrocities that occurred during the Holocaust.

Jesse Gelsinger: 1999

**Gene therapy**

Jesse was an 18 year old boy with a genetic enzyme deficiency. Most persons with this deficiency die shortly after birth, Jesse had only a partial mutation and was able to survive with dietary modifications and medication.

Regulatory Milestones

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>The Nuremberg Code</td>
</tr>
<tr>
<td>1964</td>
<td>The Declaration of Helsinki</td>
</tr>
<tr>
<td>1974</td>
<td>The National Research Act</td>
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<tr>
<td>1979</td>
<td>The Belmont Report</td>
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<tr>
<td>1980</td>
<td>Publication of FDA Regulations governing Human Subjects Research</td>
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<tr>
<td>1981</td>
<td>Publication of The Common Rule</td>
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<tr>
<td>2000</td>
<td>OHRP given regulatory authority for all federally funded Human Subjects Research</td>
</tr>
<tr>
<td>2003</td>
<td>HIPAA Privacy Rule</td>
</tr>
</tbody>
</table>

The Belmont Report: 1979

Three Basic Principles:

1. Respect for Persons
2. Beneficence
3. Justice
Respect for Persons

– Individuals should be treated as autonomous agents
– Persons with diminished autonomy are to be afforded increased protections

Beneficence

– Do no harm
– Maximize possible benefits and minimize risks

Justice

– Fairness in the overall distribution of the benefits and risks of participation in research.

Regulations:

- OHRP
- FDA
- HIPAA
- NIH
- CMS
- ICH GCP
- State and Local

OHRP
(Office for Human Research Protections)
Regulations Governing Research Involving Human Subjects

45 CFR 46: Protection of Human Subjects

Scope: All federally conducted or funded human subjects research; and all research conducted at your institution if you have "checked the box" on your FWA.

Federal Wide Assurance (FWA)

The Federal Wide Assurance:
The FWA is a written document submitted by an institution to OHRP committing the institution to compliance with the regulations for the protection of human subjects at 45 CFR part 46.

Terms of the FWA

1. Ethical Conduct of Research (the Belmont Code)
2. Compliance with 45 CFR 46 and Other Applicable Federal, State, Local, or Institutional Laws, Regulations, and Policies
3. Written procedures for the prompt reporting to the institutions, the conducting or funding agency, other applicable regulatory bodies, and the OHRP of unanticipated problems involving risks to subjects or others; serious or continuing noncompliance with the federal regulations or the requirements or determinations of the IRB(s); and suspension or termination of IRB approval.
4. Written procedures for conducting IRB initial and continuing review; determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review; and ensuring prompt reporting to the IRB of proposed changes in a research activity and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subjects.

9. Institutional Support for the IRB(s)
10. Compliance with the Terms of Assurance
11. Assurance Training
12. Educational Training
13. Renewal of Assurance (at a minimum every 3 years)

Food & Drug Administration (FDA)

Regulations governing clinical trials:
- 21 CFR 11: Electronic Records; Electronic Signatures
- 21 CFR 50: Protection of Human Subjects (Informed Consent)
- 21 CFR 54: Financial Disclosure by Clinical Investigators

Food & Drug Administration (FDA)

Regulations governing clinical trials:
- 21 CFR 56: Institutional Review Boards
- 21 CFR 312: Investigational New Drug Application
- 21 CFR 312.120: Foreign Clinical Trials not conducted under an IND
**Regulations** governing clinical trials:
- Forms 1571 (Investigational New Drug Application) and 1572 (Statement of Investigator)
- 21 CFR 314: Applications for FDA Approval to Market a New Drug
- 21 CFR 320: Bioavailability and Bioequivalence Requirements

**Regulations** (cont.)
- 21 CFR 601: Applications for FDA Approval of a Biologic License
- 21 CFR 812: Investigational Device Exemptions
- 21 CFR 814: Premarket Approval of Medical Devices


**21 CFR 50: Protection of Human Subjects**
- **Scope:** All Studies of FDA-regulated Products
- Establishes the required elements of informed consent, the documentation of consent, and specifies additional protections for children and wards of the state.

**21 CFR 50** (cont.)
- Key Differences from OHRP Regs
  - Additional Consent Language: statement noting the possibility that the Food and Drug Administration may inspect the records.
  - Different allowances for waivers or alterations of the consent process (only for emergency research)

**21 CFR 54: Financial Disclosure By Clinical Investigators**

...FDA may consider clinical studies inadequate and the data inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias. One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study...

**21 CFR 56: Institutional Review Boards**
- **Scope:** All Studies of FDA-regulated Products
- Establishes the scope of research subject to IRB review and the organization, function, and operations of Institutional Review Boards that review and approve studies of FDA-regulated products.
- Establishes the regulatory authority of the FDA over IRBs
**Key Differences from OHRP Regs**

- Definition of Research
- Definition of Human Subject
- Exemptions from IRB Requirement: Only for Emergency Uses of Test Articles

**FDA Regulations (cont.)**

21 CFR 312: Investigational New Drug Application

- Scope: All studies of new drugs, some studies of already approved drugs
- Describes clinical trial process for drugs including the responsibilities of Sponsors and Investigators

21 CFR 812: Investigational Device Exemptions

- Scope: All studies of new devices, some studies of already approved devices
- Describes the clinical trial process for devices including the responsibilities of Sponsors and Investigators

**Guidance Documents:**


**Health Insurance Portability and Accountability Act (HIPAA) (45 CFR 160 & 164)**


**HIPAA (cont.)**

- The IRB as the Privacy Board for Research
- Key Functions:
  - Approval of Authorizations, Waivers, and Alterations
Authorization for Research Uses and Disclosures

Core Elements

- Description of PHI to be used or disclosed (identifying the information in a specific and meaningful manner).
- The name(s) or other specific identification of person(s) or class of persons authorized to make the requested use or disclosure.

Core Elements (cont.)

- Authorization expiration date or event that relates to the individual or to the purpose of the use or disclosure (the terms "end of the research study" or "none" may be used for research, including for the creation and maintenance of a research database or repository).
- Signature of the individual and date. If the Authorization is signed by an individual's personal representative, a description of the representative's authority to act for the individual.

Required Statements

- Notice of the covered entity's ability or inability to condition treatment, payment, enrollment, or eligibility for benefits on the Authorization, including research-related treatment, and, if applicable, consequences of refusing to sign the Authorization.

Required Statements (cont.)

- The potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This statement does not require an analysis of risk for re-disclosure but may be a general statement that the Privacy Rule may no longer protect health information.
Authorization for Research Uses and Disclosures

Required Statements (cont.)

➢ The potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This statement does not require an analysis of risk for re-disclosure but may be a general statement that the Privacy Rule may no longer protect health information.

HIPAA Waivers

HIPAA Waivers and Alterations

➢ The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
  – An adequate plan to protect the identifiers from improper use and disclosure.

HIPAA Waivers

HIPAA Waivers and Alterations (cont.)

– An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

HIPAA Waivers

HIPAA Waivers and Alterations (cont.)

– Adequate written assurances that the PHI will not be reused or disclosed except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted by the Privacy Rule.

HIPAA Waivers

HIPAA Waivers and Alterations (cont.)

➢ The research could not practicably be conducted without the waiver or alteration.
  ➢ The research could not practicably be conducted without access to and use of the PHI.

The National Institutes of Health (NIH)
Anyone who becomes aware of the existence (or apparent existence) of fraud, waste, or abuse related to NIH grants or grant funds is encouraged to report this information to the OIG in writing or to the OIG hot line. Examples of fraud, waste, and abuse that should be reported include, but are not limited to, embezzlement, misuse, or misappropriation of grant funds or property, and false statements, whether by organizations or individuals. This includes theft of grant funds for personal use; using funds for non-grant-related purposes; theft of federally owned property or property acquired or leased under a grant; charging the Federal government for the services of “ghost” individuals; charging inflated building rental fees for a building owned by the grantee; submitting false financial reports; and submitting false financial data in bids submitted to the grantee (for eventual payment under the grant).

Part II of the NIHGPS includes administrative and other remedies the Federal government may use if a grantee deliberately withholds information or submits fraudulent information or does not comply with applicable requirements. Even if a grant is not awarded, the applicant may be subject to penalties if the information contained in or submitted as part of an application, including its certifications and assurances, is found to be false, fictitious, or fraudulent. The Federal government may pursue civil or criminal action under a variety of statutes and regulations…

Financial Conflicts of Interest (cont.)

Purpose: This subpart promotes objectivity in research by establishing standards to ensure there is no reasonable expectation that the design, conduct, or reporting of research funded under PHS grants or cooperative agreements will be biased by any conflicting financial interest of an Investigator.

Policies

- NIH Guide Notice 12/21/2007 - Clinical Trials Registration in ClinicalTrials.gov (Public Law 110-85): Competing Applications and Non-Competing Progress Reports
- Inclusion of Children Policy Implementation Page
- NIH Grants Policy Statement (12/03)
- Inclusion of Women and Minorities as Participants in Research Involving Human Subjects Policy Implementation Page
NIH Policies (cont.)

• NIH Policies and IC Guidance for Data and Safety Monitoring of Clinical Trials
• Required Education in the Protection of Human Research Participants Policy
• Revised Policy For IRB Review of Human Subjects Protocols in Grant Applications

NIH Guidelines (cont.)

• NIH HIPAA Privacy Rule Information for Researchers
• NIMH Issues to Consider in Intervention Research with Persons at High Risk for Suicidality
• Research Involving Individuals with Questionable Capacity to Consent: Points to Consider
• Research Involving Private Information or Biological Specimens

NIH

Guidance

• Certificates of Confidentiality
• National Advisory Council on Drug Abuse Guidelines for Administration of Drugs to Human Subjects
• NIAAA Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation
• NIH Guidance on Informed Consent for Gene Transfer Research

Center for Medicare & Medicaid Services (CMS)

Clinical Trial Policies:

http://www.cms.hhs.gov/ClinicalTrialPolicies/

CMS: Policy

Key Points

• Medicare will cover the routine costs incurred by patients participating in qualified clinical trials
• Routine costs in clinical trials include:
  – Items or services that are typically provided absent a clinical trial (e.g., conventional care);
  – Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; &
  – Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service—in particular, for the diagnosis or treatment of complications.
ICH E6: Good Clinical Practice (ICH GCP)


The Principles
• Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
• Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

ICH E6: Good Clinical Practice

Principles (cont.)
• The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
• The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

ICH E6: Good Clinical Practice

The Principles (cont.)
• Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
• A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethic committee (IEC) approval/favorable opinion.

ICH E6: Good Clinical Practice

The Principles (cont.)
• Freely given informed consent should be obtained from every subject prior to clinical trial participation.
• All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
The Principles (cont.)

ICH E6: Good Clinical Practice

• The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
• Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

ICH E6: Good Clinical Practice

The Principles (cont.)

• Systems with procedures that assure the quality of every aspect of the trial should be implemented.

State & Local Regulatory Requirements

Time to take a break!

• Coming up next: Developing and Instituting Your Local Research Compliance Monitoring Program

Structuring your compliance review program

Know Your Research

Tip # 1: Ask your IRB administrator if they can provide you with a breakdown of the types they have reviewed over the past year and amounts of each.

How to Prioritize Your Reviews—Where’s the risk?
Tip #2: Track trends in oversight and warning letters.

- What is everyone else being cited for?
- What are the regulatory agencies focusing their attention on?

OHRP Compliance Oversight Letters

http://www.hhs.gov/ohrp/compliance/letters/index.html

FDA 483 Findings & Warning Letters

Warning Letters:
http://www.fda.gov/foi/warning.htm

Clinical Investigator Inspections:
http://www.fda.gov/cber/compl/clininvlist.htm
http://www.fda.gov/cder/regulatory/investigators/default.htm
http://www.accessdata.fda.gov/scripts/cder/cliil/

Clinical Investigator Inspection List Database

Code Definitions

• 11/01/2005 - 11/01/2007 FDA Inspections of Clinical Investigators (Drug Studies)

NIH: Grants Compliance & Oversight

http://grants1.nih.gov/grants/compliance/compliance.htm
- Table specifying cost principles and audit requirements applicable to various NIH grant types
- Findings and Observations from a series of proactive site visits conducted in 2000 – 2004
- Findings from 2006 Targeted Site Reviews (Financial COIs)
- Several powerpoints and other resources

Helpful List-Servs/e-Newletters:

- http://www.accessdata.fda.gov/scripts/wlcfm/recentfiles.cfm (for e-mail when new FDA warning letters are issued)
- http://www.fda.gov/oc/gcp/ (for e-mail when new information from the FDA on Good Clinical Practices/Human Subjects Protections is posted)
- http://ori.dhhs.gov/ (bottom of page: Stay Informed (for news, newsletter), List-servs)
Start at the top
Interview your research leadership including your Institutional Official. Find out if they have completed the training modules at OHRP. Do they have other training in human subjects protections? Where do they see the strengths and weaknesses in the local research program? What are they concerned about- do they have reviews in mind?

Monitoring the IRB: Full Review
OHRP Self-Assessment Tool:
http://www.hhs.gov/ohrp/qi/

FDA IRB Inspections Manual:

Targeting Your Reviews: Studies
– By Department
– By Funding Source
– By Volume
– By Phase
– By Initiator
– Based on Advice

Monitoring the IRB: Targeted Review
• Single Study
  – Agenda, minutes, study file- complete, well-organized, all required determinations documented with basis
• Single Subject
  – For example: waivers of consent, research involving children or other vulnerable population, minutes (all regulatory component?), communication with investigators (written determinations with basis)

Don’t Forget to Monitor the IRB
If the IRB isn’t applying the regulations properly, your entire research program is at risk.
– Look at the trends in the OHRP & FDA warning letters and review your IRB for one or more of the common findings.
– Conduct side-by-side reviews- when you monitor a study- review the IRB file in addition to the investigator files.

Before you start visiting investigators:
Make sure your program is defined-
– purpose of the program
– who your reports go to
– possible outcomes
– repercussions
### Flexibility in Monitoring:
- Full Regulatory Review – Subject files and Regulatory Binder
- Informed Consent Review
- Drug Accountability Review
- Preparation for Sponsor or FDA Audit

### Program Descriptions
- University of Kentucky: [http://www.research.uky.edu/ori/QIP/QIP%20Main.htm](http://www.research.uky.edu/ori/QIP/QIP%20Main.htm)
- Partners Healthcare: [http://www.partners.org/phsqi/](http://www.partners.org/phsqi/)
- Children’s Hospital Boston: [http://www.childrenshospital.org/cfapps/research/data_admin/Site2207/mainpageS2207P0.html](http://www.childrenshospital.org/cfapps/research/data_admin/Site2207/mainpageS2207P0.html)

### Announcing your Visit:
- Set the tone- QA & QI
- Brief program description
- Describe the materials that you will need (Informed Consents, Subject Research Records, Subject Medical Records, Case Report Forms, Regulatory Binders, Study Correspondence)
- Time frame

### TIP #3: Monitoring & Audit Reports
Industry sponsored clinical trials are subject to routine monitoring by the sponsor or their agent. Stage your review, request the monitoring reports & audit reports going back 6 months to 1 year. Use this information either to screen out the need to do a review or to target what you will review.

### Conducting the Review:
- Checklists, checklists, & more checklists
- Handouts- Regulatory Binder, Subject File., Informed Consent Checklists
- Handouts: Sample Letters

### Tip #4: FDA’s documentation principles
- **A**- Attributable
- **C**- Credible
- **L**- Legible
- **C**- Consistent
- **C**- Contemporaneous
- **C**- Corroborated
- **O**- Original
- **A**- Accurate
Common Findings
Consent Issues:
1. Wrong consent version
2. Incomplete (missing dates, initials, optional sections)
3. No documentation of time consent obtained
4. No documentation of process
5. Failure to use impartial witness when required
6. Dated by study personnel, not subject

Documentation Issues:
6. Staff doing study activities who have not been identified with the IRB or on the Delegation of Responsibility Log
7. No documentation of training for persons doing key study activities (study assessments, study med administration)
8. Failure to report changes in study activity to IRB (protocol deviations/violations)- approval prior to change almost always required

Resources
• Virtual Regulatory Binder: http://www.partners.org/phsqi/vrb/files/index.htm
• Self-Assessment Tool: https://www.research.uky.edu/cfdocs/ORI/IRB_QA/
• Good Clinical Practice: A Guide To Good Clinical Practice, 3rd Edition; Kanarek, Alex; D&M Publications

Fabrication & Falsification
Fabrication is making up data or results and recording or reporting them.
Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

Source: Office of Research Integrity (http://ori.dhhs.gov/)
Structuring your compliance review program

Falsification (cont.):
• failing to update the patients’ status and representing data from prior contacts as being current;
• altering the results of particular tests on blood samples to show that the test accurately predicted a disease or relapse;
• backdating follow-up interviews to fit the time window determined by the study protocol; and
• falsifying the times that blood samples were drawn from human subjects.

Fabrication:
• creating records of interviews of subjects that were never performed;
• making up progress notes for patient visits that never took place and inserting them into the medical record to support published and unpublished research reports; and
• preparing records for calls and follow-up contacts to subjects who had already died.

General Warning Signs of Fraud
• High staff turnover
• Disgruntled, fearful, anxious, depressed, or defensive staff
• High-pressure work environment
• Obsession with study payments
• Absent investigators
• Lack of Good Clinical Practice training
• Unusually fast recruitment

Data Identifiers of Fraud
• Implausible trends/patterns (100% drug compliance, identical laboratory/ECG results, no serious adverse events reported, subjects adhering perfectly to a visit schedule, perfect efficacy responses)
• Source records lack an audit trail (no signatures and dates of persons completing documentation)

Data Identifiers of Fraud (cont.)
• Questionable subject visit dates (Sundays, holidays, staff vacations)
• Impossible events (subject randomized before investigational product is even available at the site)
• Subject visits cannot be verified in the medical chart or appointment schedule

Source: SoCRA Source: February 2008
Structuring your compliance review program

Data Identifiers of Fraud (cont.)

- Data contains “digit preference”: some digits are used more frequently than others (0,5, and even digits)
- “Halo” around the date or test value indicating the original was obliterated with correction fluid

Source: SoCRA Source: February 2008

Who to tell?
- Research Integrity Officer
- Institutional Official
- IRB Chair or Director

Financial Management

Financial Management Reviews
- Grants Management
  - Inappropriate Use of Grants Funds
- Clinical Trial Billing
  - Inappropriate or Double Billing

Grants Management

NIH Compliance Oversight: Common Mistakes:
- Unallowable costs
- Misallocation of costs
- Excessive cost transfers
- Inaccurate effort reporting
- Incomplete other support

Common Mistakes (cont.)
- Inadequate subrecipient monitoring
- Administrative & Clerical costs
- Noncompliance with Assurances and special terms and conditions of award
- Delinquent closeout reporting

Source: NIH Common Compliance Pitfalls and Strategies for Success
Keys to Compliance
- All charges to grants must be reasonable, allowable, allocable, and consistent.
- Primary grantees are responsible and accountable for the proper use of grant funds by subcontract participants – actively monitor.
- Pay attention to food and other such expenditures: entertainment costs are not allowed; but some meal costs are.
- Pay attention to special terms of award.

Structuring your compliance review program

Clinical Trial Billing
- How is it determined which costs are standard of care versus research costs?
  - If an item is questionable, use the 80% rule
  - Who makes this determination- PI? Study Coordinator? Disinterested party?

Grants and Clinical Trials Billing

Resources
NIH Office of Extramural Research Grants Compliance & Oversight:
http://grants.nih.gov/grants/compliance/compliance.html#activities

Thank You!

Monitoring
- Actual expenses are periodically compared with budget (monthly)
- Actual expenses are accurate, i.e., reasonable, allocable, allowable and consistently charged
- Mis-charges are corrected in a timely manner (within 90 days of finding)
- Prior approvals are obtained when required
- Subrecipient expenses
- Approval of post-award changes

Source: NIH Grants Compliance: All About Costs
# Clinical Investigator Inspection List

## For Investigational New Drug Studies

<table>
<thead>
<tr>
<th>Investigator ID No.</th>
<th>Name</th>
<th>Location</th>
<th>Address</th>
<th>City</th>
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<th>Inspection Date</th>
<th>Type</th>
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<td>140205</td>
<td>alian, j d JR MD</td>
<td>new england deaconess hosp</td>
<td>185 pilgrim rd</td>
<td>boston</td>
<td>MA</td>
<td>US</td>
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<td>avery, edwin g MD</td>
<td>mgh dept anesthesia &amp; critical care clins 3</td>
<td>55 fruit st</td>
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<td>421591</td>
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<td>243 charles st</td>
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<td>baden, lindsey r MD</td>
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<td>330 brookline ave</td>
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<td>23529</td>
<td>ball, harrison g III MD</td>
<td>univ massachusetts mem med ctr</td>
<td>119 belmont st</td>
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<tr>
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<td>29 mt hooood rd</td>
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<td>08-Sep-2003</td>
<td>DA</td>
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</tr>
</tbody>
</table>
Clinical Investigator Inspection List  
Database Code Definitions

The following codes occur in the CLIIL database: Classification, Deficiency, and Inspection Type. Some codes are no longer being used, but they still appear in the database.

Classification Codes

- **MTF** - Case closed with a Memo to File
- **NAI** - No Action Indicated. No objectionable conditions or practices were found during the inspection.
- **VAI** - Voluntary Action Indicated. Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntarily.
  - **VAI1** - Correction made on site
  - **VAI2** - No response requested
  - **VAI2C** - Consent problems found
  - **VAI3** - Response requested
  - **VAI3C** - Case closed
  - **VAI3F** - Follow-up for cause inspection issued
  - **VAI3R** - Response received and accepted
  - **VAIRC** - 30-day response requested and case closed
  - **VAIRR** - 30-day response requested, received and accepted
  - **VAIR** - 30-day response requested
- **OAI** - Official Action Indicated. Objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated.
  - **OAIC** - Completed
  - **OAIR** - Response requested
  - **OAIRR** - Response requested and accepted
  - **OAIW** - Warning letter issued
- **CANC** - Cancelled. The inspection assignment was canceled before the inspection was started.
- **WASH** - Washout. An inspection was initiated but no meaningful information could be obtained.
- **REF** - Reference

Deficiency Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Deficiency</th>
<th>Code of Federal Regulations (CFR) Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>No deficiencies noted</td>
<td>n/a</td>
</tr>
<tr>
<td>01</td>
<td>Records availability</td>
<td>21 CFR 312.62</td>
</tr>
<tr>
<td>02</td>
<td>Failure to obtain and/or document subject consent</td>
<td>21 CFR 312.60, 50.20, 50.27</td>
</tr>
<tr>
<td>03</td>
<td>Inadequate informed consent form</td>
<td>21 CFR 50.25</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td>CFR References</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
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<tr>
<td>04</td>
<td>Inadequate drug accountability</td>
<td>21 CFR 312.60, 312.62</td>
</tr>
<tr>
<td>05</td>
<td>Failure to follow investigational plan</td>
<td>21 CFR 312.60</td>
</tr>
<tr>
<td>06</td>
<td>Inadequate and inaccurate records</td>
<td>21 CFR 312.62</td>
</tr>
<tr>
<td>07</td>
<td>Unapproved concomitant therapy</td>
<td>21 CFR 312.60</td>
</tr>
<tr>
<td>08</td>
<td>Inappropriate payment to volunteers</td>
<td>21 CFR 50.20</td>
</tr>
<tr>
<td>09</td>
<td>Unapproved use of drug before IND submission</td>
<td>21 CFR 312.40(d)</td>
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<tr>
<td>10</td>
<td>Inappropriate delegation of authority</td>
<td>21 CFR 312.7, 312.61</td>
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<tr>
<td>11</td>
<td>Inappropriate use/commercialization of IND</td>
<td>21 CFR 312.7, 312.61</td>
</tr>
<tr>
<td>12</td>
<td>Failure to list additional investigators on 1572</td>
<td>21 CFR 312.60</td>
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<tr>
<td>13</td>
<td>Subjects receiving simultaneous investigational drugs</td>
<td>21 CFR 312.60</td>
</tr>
<tr>
<td>14</td>
<td>Failure to obtain or document IRB approval</td>
<td>21 CFR 312.60, 62, 66; 56.103</td>
</tr>
<tr>
<td>15</td>
<td>Failure to notify IRB of changes, failure to submit progress reports</td>
<td>21 CFR 312.66</td>
</tr>
<tr>
<td>16</td>
<td>Failure to report adverse drug reactions</td>
<td>21 CFR 312.64, 312.66</td>
</tr>
<tr>
<td>17</td>
<td>Submission of false information</td>
<td>21 CFR 312.70</td>
</tr>
<tr>
<td>18</td>
<td>Other</td>
<td>n/a</td>
</tr>
<tr>
<td>19*</td>
<td>Failure to supervise or personally conduct the clinical investigation</td>
<td>21 CFR 312.60</td>
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<tr>
<td>20*</td>
<td>Failure to protect the rights, safety, and welfare of subjects</td>
<td>21 CFR 312.60</td>
</tr>
<tr>
<td>21*</td>
<td>Failure to permit FDA access to records</td>
<td>21 CFR 312.68</td>
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</table>

* Codes 19, 20, and 21 became effective October 1, 2005.

**Inspection Type Codes**

- **DA - Data Audit**: An inspection in which the focus is on verification of study data.
- **FC - For Cause**: An inspection in which the focus is on the conduct of the study by the Clinical Investigator.
- **IG - Information Gathering**
11/01/2005 - 11/01/2007 FDA Inspections of Clinical Investigators (Drug Studies)

455 Inspections

411 Drug Application Inspections (90.33%)
44 For Cause Inspections (9.67%)

Classification:

251 No Action Indicated (55.16%)
191 Voluntary Action Indicated (41.98%)
13 Official Action Indicated (2.86%)

Deficiencies Cited (from Most Common to Least Common): 355 total citations

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Regulatory Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to follow investigational plan (136 citations)</td>
<td>21 CFR 312.60</td>
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<tr>
<td>Inadequate and inaccurate records (98 citations)</td>
<td>21 CFR 312.62</td>
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<tr>
<td>Inadequate drug accountability (31 citations)</td>
<td>21 CFR 312.60, 312.62</td>
</tr>
<tr>
<td>Failure to obtain and/or document subject consent (24 citations)</td>
<td>21 CFR 312.60, 50.20, 50.27</td>
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<tr>
<td>Failure to report adverse drug reactions (17 citations)</td>
<td>21 CFR 312.64, 312.66</td>
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<tr>
<td>Inadequate informed consent form (14 citations)</td>
<td>21 CFR 50.25</td>
</tr>
<tr>
<td>Failure to notify IRB of changes, failure to submit progress reports</td>
<td>21 CFR 312.66</td>
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<tr>
<td>(12 citations)</td>
<td></td>
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<tr>
<td>Other (10 citations)</td>
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<td>Records availability (5 citations)</td>
<td>21 CFR 312.62</td>
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<tr>
<td>Failure to obtain or document IRB approval (4 citations)</td>
<td>21 CFR 312.60, 62, 66; 56.103</td>
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<td>Failure to list additional investigators on 1572 (2 citations)</td>
<td>21 CFR 312.60</td>
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<tr>
<td>Inappropriate delegation of authority (1 citation)</td>
<td>21 CFR 312.7, 312.61</td>
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<tr>
<td>Unapproved concomitant therapy (1 citation)</td>
<td>21 CFR 312.60</td>
</tr>
<tr>
<td>QUESTION</td>
<td>Y/N/NA</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Is Regulatory Binder well-organized?</td>
<td></td>
</tr>
<tr>
<td>Does the binder contain copies of all IRB approved protocols?</td>
<td></td>
</tr>
<tr>
<td>Does the binder contain copies of all IRB approved consent forms?</td>
<td></td>
</tr>
<tr>
<td>Does the binder contain copies of all submissions to IRB?</td>
<td></td>
</tr>
<tr>
<td>o Initial</td>
<td></td>
</tr>
<tr>
<td>o Continuing Reviews</td>
<td></td>
</tr>
<tr>
<td>o Amendments</td>
<td></td>
</tr>
<tr>
<td>o Local Adverse Events</td>
<td></td>
</tr>
<tr>
<td>o Informational Items</td>
<td></td>
</tr>
<tr>
<td>Does the binder contain copies of all IRB acknowledgements/approvals?</td>
<td></td>
</tr>
<tr>
<td>Does the binder contain copies of all other study-related correspondence with the IRB?</td>
<td></td>
</tr>
<tr>
<td>Does the binder contain correspondence with Sponsor?</td>
<td></td>
</tr>
<tr>
<td>Have all recruiting materials including advertisements been submitted to and approved by the IRB?</td>
<td></td>
</tr>
<tr>
<td>Have all subject materials such as questionnaires been submitted to and approved by the IRB?</td>
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</tr>
<tr>
<td>Are there other items present in the binder which require submission to the IRB but have not yet been submitted?</td>
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<tr>
<td>Is the number of subjects enrolled (signed consent) less than the target enrollment goal approved by the IRB?</td>
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<tr>
<td>Does the binder contain a Delegation of Responsibility Log?</td>
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<tr>
<td>Are all study personnel listed on the Delegation of Responsibility Log listed with the IRB?</td>
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<tr>
<td>Is there documentation of human subjects protections training for all study personnel?</td>
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<td>Question</td>
<td>Answer</td>
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<tr>
<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Is there documentation of training for key responsibilities (ex. drug administration, side effects, study-specific assessments, etc.)</td>
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</tr>
<tr>
<td>Is the subject screening log present and up to date?</td>
<td></td>
</tr>
<tr>
<td>Is the subject enrollment log present and up to date?</td>
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<tr>
<td><strong>For Trials Subject to FDA Regulations:</strong></td>
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<tr>
<td>Is up to date 1572 on file?</td>
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<tr>
<td>Are all Investigators listed on the 1572 also listed with the IRB?</td>
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</tr>
<tr>
<td>Are there current CVs (within 2 years) on file for all investigators and key personnel?</td>
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<tr>
<td>Are there up to date licenses on file for all investigators and other licensed personnel (research nurses, etc.)?</td>
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<tr>
<td>Does the binder contain copies of all IRB approved Investigator Brochures and/or drug/device labeling?</td>
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<tr>
<td>Who is responsible for drug/device accountability?</td>
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<tr>
<td>o Investigational Pharmacy</td>
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<tr>
<td>o Investigator</td>
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<tr>
<td>Is there adequate documentation? (shipments, storage, dispensing, returns, etc.)</td>
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**Responsible Party:** ______________________

**Review Date:** ________________

**BMC IRB #:** ________________

**Principal Investigator:** _____________________________________________

**Reviewer (Print Name):** ______________________________________________

**Reviewer Signature:** _________________________________________________
<table>
<thead>
<tr>
<th>Question</th>
<th>Y/N/NA</th>
<th>Notes</th>
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<tr>
<td>Did subject meet all criteria for enrollment into study?</td>
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<tr>
<td>Is eligibility clearly documented?</td>
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<tr>
<td>Did all study visits occur within protocol defined time frame?</td>
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<tr>
<td>Did all study procedures take place as defined in the protocol?</td>
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<tr>
<td>Does source documentation verify reported study data?</td>
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<td>Are source documents:</td>
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<tr>
<td>o Attributable</td>
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<td>o Legible</td>
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<td>o Contemporaneous</td>
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<td>o Original</td>
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<tr>
<td>o Accurate</td>
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<tr>
<td>Have changes to documentation been properly executed (single-line cross through, dated, initialed, explanation if necessary, no scribbles, no white-out, etc)?</td>
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<tr>
<td>Are study documents complete and up to date?</td>
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<tr>
<td>Have all adverse events and unanticipated problems been assessed by the investigator and, if required, been reported to the IRB and sponsor?</td>
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<tr>
<td>Is there adequate documentation of all study related communication with the subject?</td>
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<td>o Phone log</td>
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<td>o Correspondence</td>
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<td></td>
</tr>
<tr>
<td>o Visit notes</td>
<td></td>
<td></td>
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<tr>
<td>Are all personnel taking part in research activities (consent, assessments, etc.) listed with the IRB?</td>
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Subject ID: __________________________

Review Date: _________________       BMC IRB #: _________________

Principal Investigator: __________________________

Reviewer (Print Name): __________________________

Reviewer Signature: __________________________

v. 07/26/2008
## INFORMED CONSENT COMPLIANCE CHECKLIST

**Subject ID:** ____________  
**Date Consent Obtained:** ____________  
**Consent Version:** ____________

<table>
<thead>
<tr>
<th>ITEM</th>
<th>Y/N/NA</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was an IRB approved consent form used to consent subject?</td>
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<tr>
<td>Was the consent form used the <em>most recently approved</em> version (check valid dates)?</td>
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</tr>
<tr>
<td>Is the consent form in the research file the <em>original</em> signed and dated version (not a photocopy)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are all pages of the consent form present?</td>
<td></td>
<td></td>
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<tr>
<td>Did subject initial each page of the consent form (excluding signature page)?</td>
<td></td>
<td></td>
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<tr>
<td>Are all yes/no or similar options on the consent form complete (e.g. initialed)?</td>
<td></td>
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</tr>
<tr>
<td>Did subject sign and date the consent form for him/herself? (excluding IRB approved surrogate/parental consent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did an IRB approved study representative obtain consent?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the IRB approved study representative obtaining consent sign and date for him/herself?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the subject and study representative enter the same date on the consent form?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a witness required (subject not able to read or sign consent form)? If so did witness sign? Was witness independent of the study?</td>
<td></td>
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<tr>
<td>Is the consent form free of any handwritten changes/corrections (e.g. updated physician contact telephone number)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Was informed consent obtained prior to the start of any study procedure(s)? (including screening procedures to determine eligibility)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there documentation of the consent process? (adequate time, asking &amp; answering of questions, etc.)</td>
<td></td>
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</tr>
<tr>
<td>Is there documentation to support that the subject received a copy of their signed and dated consent form?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a copy of each subject’s signed consent form sent to/placed in subject’s medical record?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments/Notes: ____________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Review Date: _________________
BMC IRB #: _________________
Principal Investigator: ________________________________________________
Reviewer (Print Name): ________________________________________________
Reviewer Signature: _______________________________________________
Sample Letter 1: FDA Audit Preparation

This is a preliminary high level overview of weaknesses identified in the XXXX study documentation. This is a quality assurance activity designed to assist in preparation for next week’s FDA inspection. This is not inclusive of all deficiencies and does not speak to study strengths. Be prepared to speak to these weaknesses and discuss the changes in study staff, in training, and in practice that have occurred/been instituted since this study was completed.

Source Document Weaknesses:

Source documents created by XXXX: consistently fail one or more of the following principles.

- A- Attributable
- L- Legible
- C- Contemporaneous
- O- Original
- A- Accurate
- C- Credible
- C- Consistent
- C- Corroborated

(examples: Vital signs and other study measurements on torn off slips of paper without dates, patient ID, signatures; physical exam work sheets without patient ID or signature)

Medical Records as Source Docs: consistently do not cover all of the data points needed for the study. (example: in describing a surgical wound site- some of the characteristics are described but not all that are needed for the study).

Significance: FDA inspectors may choose to not allow the use of source documentation that does not meet the above standards. If they make this decision then the data must be able to be corroborated by another source such as the medical record. If the medical record does not capture all of the data points then the data may be discarded.

Citations that may occur: Inadequate and inaccurate records.

Case Report Forms as Compared to Source Documents:

Several inconsistencies noted. (example: the study requires the recording of the highest temperature of the day, the temperature recorded was not the highest temperature of the day, this error is repeated over several days)

Significance: The data may be discarded.

Citations that may occur: Inadequate and inaccurate records.

Informed Consents:

5 out of 30 (see tagged forms) have issues ranging from not missing initials and dates for optional blood collection for genetic testing to not having a witness signature when one is required (ex. Spanish speaking patient, documented as illiterate in both English and Spanish).

Significance: Consent may be considered invalid.

Citations that may occur: Failure to obtain and/or document subject consent.

Regulatory:

Delegation of Authority Log: Assessment of adverse events and serious adverse events assigned to nurses on study staff but not to physician investigators. No delegation of authority to administer study med to either floor nurses or home health agencies. No SOP describing this as standard delegation.

Training: No documentation of training of floor nurses or home health care agency on protocol or administration of study medication.

Significance: Assessment of adverse events particularly for causality and relatedness is a study activity that should be conducted by physicians. Nurses and other study staff can identify events, dates, treatments, etc. but the actual assessment of the event should be by a physician. All personnel who conduct tasks or assessments specifically for a research protocol must be appropriately trained and qualified.

Citations that may occur: Inappropriate delegation of authority.
January 15, 2008

Dear Dr. XXX,

Thank you for accommodating the HRPP QA/QI review of the above cited study on 01/13/2008. The BMC Human Research Protection Program (HRPP) conducts study reviews for the purposes of (1) assessing the accuracy and completeness of IRB and investigator files, (2) assessing adherence to Federal and State regulations and IRB policies and requirements, and (3) providing education to investigators and study staff.

In general, if the findings of a review include significant regulatory concerns, corrective action plans are requested. Once received, the study review report and the corrective action plan are brought to the Research Compliance Committee for their review and consideration. The Research Compliance Committee meets as needed to consider instances of possible noncompliance, with or without intent, in the conduct of research and makes recommendations to the Institutional Review Board (IRB), the Institutional Animal Care and Use Committee (IACUC), the Institutional Biosafety Committee (IBC) and/or the Institutional Official on the management of findings of noncompliance.

As we discussed, failure to obtain consent prior to the submission of patient data to a research registry is a significant regulatory violation. The patients whose information was provided to this registry without their consent must be contacted and consented as soon as possible. If you are unable to obtain consent, the sponsor must be contacted and the patient’s information stricken from the database. I will be following up with your research coordinator to verify.

A corrective action plan designed to minimize the risk of recurrence of this type of violation must be developed and filed with this office by January 22, 2008. Once received, I will be submitting this report and the corrective action plan to the Research Compliance Committee for their review and consideration.

I am available to you for review of this report and to provide assistance in developing corrective actions. I can be contacted by phone at 999-9999 or via e-mail at karen.christianson@bhs.org.

The following pages contain the details of my review.

Sincerely,

Karen Christianson, RN, BSN, CCRP
HRPP Integrity/Education Manager

Cc: (Institutional Official)
(Department Chair)
(IRB Chair)
(Research Integrity Officer)
Findings and Associated Regulatory Risks:

This study review was limited to review and verification of informed consent. A total of 56 patients have been enrolled into “The XXXX Registry” locally. Consent was verified for 49 of these 56 patients. To summarize our discussion regarding the absence of consent for 7 patients: your research nurse coordinator resigned in December; in the time since she left until the start of your new research nurse coordinator, the administrative assistant who has been responsible for data entry for this registry continued to gather and submit data on patients receiving XXXX without verifying consent and without your knowledge. Ms. X did have CITI training but was not listed as study staff with the IRB for this study or any others. Ms. X has recently left her position at this institution and as such will no longer be doing any research work on this or other BMC research studies.

Review of the existing consents included a few less significant findings such as occasional discrepancies between the date of subject signature and the date of study representative signature, no notation documenting the provision of a copy of the signed consent form to each subject, and occasional missing initials at the bottom of each page of the consent. 3 patients who were minors at the time of enrollment (Subject IDs: 1111, 2222, AND 3333) have now reached the age of consent. Consent for continued participation should be obtained and documented at the next opportunity; new information on these patients can not be submitted to the database until this occurs.

Based on the findings described above, if subjected to a FDA inspection you would be at risk for the following citations:

1. Failure to obtain and/or document subject consent (21 CFR 312.60, 50.20, 50.27).
2. Failure to supervise or personally conduct the clinical investigation (21 CFR 312.60).
3. Inappropriate delegation of authority (21 CFR 312.7, 312.61).

In addition, since the submitted information is considered identifiable under HIPAA, the disclosure of this information without authorization would be considered a violation of HIPAA.

Opportunities for Improvement:

In order to minimize your risk, I recommend the following:

1. Either obtain and document consent/assent and HIPAA authorization for the 7 patients from whom consent and authorization has not yet been obtained or instruct sponsor to remove all data submitted on these patients.
2. Develop and implement a corrective action plan to prevent recurrence.
3. Document in a note–to-file your understanding of the circumstances that resulted in the failure to obtain consent and authorization and your subsequent corrective actions.
4. Track improved compliance by conducting interim reviews of study documentation, etc.

Your corrective action plan must be provided to this office by January 22nd. Please contact me if you have questions or if I can be of assistance in corrective action plan development.