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Good Clinical Research Practice

Working in the World of Regulated Research

Marta Haley Fields

Compliance Director, Global Clinical Quality Assurance

Amgen Inc.

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Good Clinical Practice

Research is the act of going up alleys to see if they are blind - Plutarch

Why Good Clinical Practice (GCP)?

- **“In yesterday's letter, the FDA said visits from an Aventis contractor and the drug maker's own audits documented "serious protocol violations and regulatory noncompliance by multiple clinical investigators." The agency said it was "unable to find evidence" that the company either fixed the problems or threw the problematic doctors out of the study and told the FDA. The FDA also faulted Aventis for failing to make sure the study was properly conducted and for allowing unqualified investigators to participate in the trial.” - *Wall Street Journal* October 25, 2007 article on issues surrounding the antibiotic Ketek**

How to avoid this outcome?

- **Understand the differences between private practice and regulated registrational research**
 - Protocol driven treatment
 - Coordinated across many centers
 - Governed by regulation
 - Personal accountability
 - Extensive documentation
 - 3rd party oversight, including sponsor, IRB, and FDA
- **Adhere to the principles of GCP**
 - Good Clinical Practice

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Investigator Responsibilities

For Studies Conducted Under a US – IND

**You can delegate a task,
but you cannot delegate responsibility.**

*Regardless of who performs a study
related activity, the investigator is
accountable for how the study is
conducted*

FDA Form 1572 – under a US-IND

<p>8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:</p> <p><input type="checkbox"/> FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.</p> <p><input type="checkbox"/> FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.</p>		
<p>9. COMMITMENTS:</p> <p>I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.</p> <p>I agree to personally conduct or supervise the described investigation(s).</p> <p>I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.</p> <p>I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.</p> <p>I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.</p> <p>I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.</p> <p>I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.</p> <p>I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.</p> <p>I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.</p>		
<p>INSTRUCTIONS FOR COMPLETING FORM FDA 1572 STATEMENT OF INVESTIGATOR:</p> <ol style="list-style-type: none"> 1. Complete all sections. Attach a separate page if additional space is needed. 2. Attach curriculum vitae or other statement of qualifications as described in Section 2. 3. Attach protocol outline as described in Section 8. 4. Sign and date below. 5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). 		
<p>10. SIGNATURE OF INVESTIGATOR</p>	<p>11. DATE</p>	
<p>(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)</p> <p>Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p>		
<p>Food and Drug Administration CDER (HFD-99) 1401 Rockville Pike Rockville, MD 20852-1448</p>	<p>Food and Drug Administration CDER (HFD-94) 5516 Nicholson Lane Kensington, MD 20895</p>	<p>*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*</p>
<p>Please DO NOT RETURN this application to this address.</p>		

Good Clinical Research Practice

Investigator Responsibilities

- **Personally** conduct or supervise the study
- Ensure staff **is informed** of their obligations
- Conduct the study **according to protocol**
- Maintain adequate & **accurate records**
- Ensure **informed consent process** meets requirements
- Ensure **IRB/IEC complies** with requirements
- **Report adverse events**

Is there documentation to show that these responsibilities were met ?

Delegation of Authority

Staffing

- **Ensure adequate resource to handle volume of work**
- **Make sure all site staff are appropriately trained and understand**
 - **Protocol (inclusion/exclusion criteria)**
 - **Electronic systems (e.g., IVRS, EDC, e-diary)**
 - **Investigational Product (IP) Administration**
 - **Adverse event recording/reporting**
 - **Procedures and measurements**
 - **Source documentation**

Protocol Compliance

- **Read the protocol – all of it**
- **Attend protocol training – investigator meetings**
- **Enroll eligible subjects**
- **Understand the dosing rules**
- **Ensure that protocol required tests/activities occur**
- **Be mindful of the sequence of events**
- **Review safety reporting requirements**

Maintain Adequate & Accurate Records

Source Data

- **Ensure medical records “tell the whole story”**
 - Who **did** what to whom; when and why
 - **Rationale** for decisions
 - **Audit trail** for data corrections
- **Complete Case Report Forms (CRFs) as soon as possible**
- **Remember if it is not documented, it did not happen**

Maintain Adequate & Accurate Records

Elements of data quality

- **A**ccurate – verify accuracy of transcription
- **L**egible - comprehensible
- **C**ontemporaneous – document in real time
- **O**riginal documents – no photocopies or “shadow” charts
- **A**tributable – entries signed or initialed

Elements of data integrity

- **C**redible
- **C**onsistent

Informed Consent Process

Informed Consent

- **Consented before any study specific procedures occur**
- **Dated and signed by subject and individual consenting subject at the time of consent**
- **Noted in subject medical record**
 - Time of consent
 - Any special circumstances
- **Consented in a language that subject understands with translated copy of consent**

IRB/IECs

Institutional Review Board / Independent Ethics Committee Interactions

- **Ensure IRB/IEC is duly constituted – no conflict of interest**
- **Ensure SAEs and IND Safety reports are submitted to the IRB/IEC in a timely manner**
- **Ensure documentation exists of all submissions to and approvals received from the IRB/IEC**
- **Ensure Annual Review and renewals occur**

Safety Reporting

Adverse Events

- **Immediately report Serious Adverse Events (SAEs) upon discovery or notification**
- **Personally assign causality/severity or delegate to medically qualified individual**
- **All adverse events – Follow medically significant AEs considered to be related to the Investigational Product (IP) until resolution or at least considered stable**

Study Oversight

- **You will be monitored**
 - Frequency will depend upon complexity of study and number of subjects enrolled
 - Source data verification
 - Drug accountability
- **The monitor is your friend**
 - Answers questions about the protocol/study
 - Identifies issues with the data, protocol and GCP compliance, and potential logistics problems
- **Maintain open communication with the monitor**
 - Quickly resolve identified issues
- **You may be audited**
 - Audits look at both site and sponsor compliance

Health Authority Inspections

Some examples include:

- **FDA (United States Food & Drug Administration)**
- **Local Regulatory Agency (eg, Health Canada)**
- **EMA (European Medicine Agency)**
- **Japanese MHLW (Ministry of Health, Labor and Welfare)**

Health Authority Inspections

Reasons for Health Authority inspections

- **Pre-approval inspections**
- **High recruitment rate in “pivotal studies”**
- **Sites involved with multiple studies**
- **Statistical outliers**
 - **Data inconsistent with other sites in study**
- **“Directed”**
 - **Complaints, informants, media spotlight**
- **Routine Inspection Programmes**

Always do right; this will gratify some people and astonish the rest – Mark Twain