

MEDICAL DEVICE SUBJECT RECRUITMENT AND RETENTION

HUMAN SUBJECT PROTECTION CONCERNS IN DEVICE TRIALS

May 12, 2008

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SPEAKER AS INVESTIGATOR

- PHARMACEUTICAL PACKAGING SYSTEM
- INTRAVENOUS FILTERS
- PATIENT CONTROLLED ANALGESIA PUMPS
- SYRINGE INFUSION PUMPS
- PHARMACOEPIDEMIOLOGY
- TOXICOKINETICS/PHARMACOKINETICS OF INTRAVENTRICULAR DRUG IMPLANTED CATHETER

SPEAKER AS AUTHOR / EDITOR

- Lass and O'Donnell. Clinical Research Risks and the Importance of Life-Cycle Safety Assessments, *Update*. *FDLI* September/October 2006
- Smith and O'Donnell: *The Process of New Drug Discovery and Development*, second Edition, 2006 (Nesbitt L: *The Front Lines of Clinical Research: The Industry*).
- O'Donnell J. *Drug Injury: Liability, Analysis and Prevention*. 2005 (Ahuja and Clark. *The Protection of Subjects in Clinical Research*).

IRB REVIEW MAY 7, 2008

- LASER PHOTOCOAGULATION
- CARBOPLATIN/PACLITAXEL AND bsi-201 IN RECURRENT UTERINE CARINOSARCOMA
- ANTI-INTERLEUKIN 1 MONOCLONAL ANTIBODY IN PATIENTS WITH MUCKLE-WELLS SYNDROME
- AMENDMENT – RESPONSIVE NEUROSTIMULATORS
- PHARMACOEPIDEMIOLOGY-DEVELOPMENTAL EFFECTS OF ANTIEPILEPTIC DRUGS
- SAE's Drug Eluting Coronary Stent System in the Treatment of Subjects with Coronary Artery Lesions
- EMERGENCY USE PULMONARY VALVED CONDUIT

DEVICE COMPLEXITY

- BAND-AID TO AN ARTIFICIAL HEART
- EXTREMELY BROAD SPECTRUM
- MATERIALS ENGINEERING
- COMPUTER SOFTWARE
- ELECTRONICS
- COMMONALITY – HUMAN SUBJECT
- OVERLAP WITH DRUG DEVELOPMENT

Milestones in U.S. Drug Research Regulation

- 1962: The Thalidomide Experience
- 1964: NIH Ethics Committee
- 1964: The World Medical Association Declaration of Helsinki
- 1966: The Ethics of Clinical Research and the New England Journal of Medicine
- 1973: Congressional Hearings on the Quality of Health Care and Human Experimentation

Milestones in U.S. Drug Research Regulation

- Willowbrook Hepatitis Studies
- Jewish Chronic Disease Hospital Studies
- Milgram Studies of Obedience to Authority
- San Antonio Contraception Study
- Tearoom Trade Study
- Tuskegee Syphilis Study
- 1974: The National Research Act and the IRB System

The Belmont Report

- Principle 1: Respect for Persons
 - o Treat individuals as autonomous agents
 - o Protect persons with diminished capacity
 - o Use consent monitors if indicated
- IRB Approval
 - o Participants must voluntary consent
 - o Informed consent must be obtained
 - o Privacy and confidentiality protected

The Belmont Report

- Principle 2: Beneficence
 - Golden Rule: Do unto others as you would have them do unto you
- IRB must make ethical choice of trade-off between societal and personal benefit
 - Risks must be justified by potential societal gain
 - Study design should minimize risk
 - Conflicts of interest are managed adequately

The Belmont Report

- Principle 3: Justice
 - Distribute risks and potential benefits of research equally among those who may benefit from the research
 - IRB Approval Requirements
 - Vulnerable subjects not picked for convenience
 - People who are unlikely to benefit from the research are not systematically excluded

Institutional Review Board (IRB)

- The IRB is intended to provide patient protection and ensure proper conduct of clinical trials under:
 - o 21 CFR § 50, Protection of Human Subjects
 - o 21 CFR § 56, Institutional Review Boards

IRB Defined

- The IRB is a committee
 - Primary responsibility is to protect the rights and welfare of research subjects
- The IRB is a kind of ethics committee
 - IRB must consider:
 - What is right and wrong
 - What is desirable or undesirable

The Role of IRB Members

The Mission of the IRB is to protect the rights and welfare of research subjects

IRB members must guard against being distracted from evaluating the ethics of a research study

IRB Responsibilities

- Approve and monitor study with PI:
 - o Protocols
 - o Informed consent documents
 - o Ongoing review of serious AE reported by patients

Informed Consent

- Ethical Research is based on informed consent
 - o Subjects must understand the important implications of their choice to participate
 - o Subjects must actively agree to such participation
 - o Informed consent follows from the principle of respect for persons

IRB Authority and Responsibilities

- IRBs have the authority and responsibility to stop a clinical trial when necessary for safety concerns

Changes to the Research Protocol

- Is a proposed change likely to improve the welfare of research subjects? If the answer is **no** then the IRB should approve the research protocol without change
- If the answer is **yes** then the research protocol must not be approved as proposed

IRB Deficiencies

- Any deficiency places patients at risk
- Short and Long term impact on patient safety:
 - o Improper study conduct
 - o Inadequate review of AE

IRB Deficiencies

- Patient protection through informed consent is critical
- FDA Warning Letter was issued to the IRB for the Baltimore City Health Department on December 15, 2005:
 - o Failure to follow IRB procedures
 - o Informed consent issues
 - o Failing to conduct continuing review

Clinical Pitfalls

- Protocol Design Goals
 - Capture anticipated AE
 - Capture unanticipated AE

Clinical Principal Investigator (PI)

- PI responsibilities
 - Oversight of conduct of study
 - Provides for patient safety as described in 21 CFR §312.60, Subpart D

Example of PI and IRB Failure

- FDA issued a Warning Letter to Dr. Alkis Togias of Johns Hopkins Asthma and Allergy Center, March 31, 2003
 - Death of a healthy, normal volunteer
 - Experienced PI failed to submit IND application
 - Omitted elements of informed consent, e.g. risk of lung toxicity and death
 - IRB failed to provide oversight

FDA Scrutiny

- FDA examines numerous aspects of the role the PI plays in the study
 - o Delegation of authority
 - o Investigator supervision
 - o Research site
 - o Data collection methods
 - o Other aspects as needed

PI Responsibilities

- Subject eligibility for enrollment
- Reviews AE for each subject
- Interventions
 - Drug dosing adjustment
 - Termination
 - Suggestions for Protocol revisions

Regulatory Scrutiny of PI

- FDA Warning Letters
 - FDA letters have increased over the ten year period for 1977-2006
 - The peak year for most warning letters was 32 during 2004

Regulatory Compliance

- Increased enforcement of regulatory compliance has required increased
 - o Focus on risk assessment
 - o Focus on risk management
- Regulations provide a review and assessment of safety data
- Legal compliance is not a guarantee of the safety of a drug or device

Benefit-Risk Profile

An ongoing life-cycle process

- Discovery phase
- Preclinical phase
- Clinical phase
- Post marketing phase

Protocol Design Goals

- Incorporate into Study Goals
 - o Specific safety objectives
 - o Use directed data collection
 - o Sufficient safety surveillance measures must be maintained during clinical development

FDA Inspector Tasks

- Compare received data with PI study records
- Common Deficiencies
 - o Inadequate or inaccurate records
 - o Inadequate Drug Accountability
 - o Protocol violations
 - o Informed consent noncompliance
 - o Poor AE reporting

FDA Review Actions

- No action taken
- Voluntary response
- Official Response
- Warning Letter
- Examples
 - o Drs. Robert Hostoffer and Clark Bishop were issued Warning Letters in June 2005 for:
 - Protocol Violation
 - Informed Consent issues
 - Improper reporting of serious AE

Role of Risk Management

- Regulatory compliance reduces but does not eliminate risk
 - FDA requires long-standing safety reporting
 - Global regulatory agencies have created guidelines for ongoing risk assessment
 - FDA, CDER, & CBER, Guidance for Industry: Premarketing Risk Assessment, available at <http://www.fda.gov/cder/guidance/6357fnl.pdf> (issued Mar, 2005)

Safety Surveillance

- Throughout Clinical Development
 - o Trend Analysis
 - o Signal detection

Severe Inflammatory Response to Investigational New Drug (IND)

- TeGenero's IND TGN1412
 - o 6 patients received the drug at Northwick Park Hospital, London, England
 - o All subjects had a severe inflammatory response with multi-organ system involvement and were taken to Critical Care

Severe Inflammatory Response to Investigational New Drug (IND)

- UK's Regulatory Agency (MHRA)
 - Did not identify concerns during preclinical testing and the adverse events (AE) were not foreseeable
 - One volunteer complained of being rushed to sign informed consent
- TeGenero filed for bankruptcy protection
 - All six subjects recovered
 - TGN1412 was legally compliant but not safe

SPEAKER AS CONSULTANT

- ETHYL CHLORIDE SPRAY CAN DEATH
- GLIATECH RESEARCH AND MARKETING FRAUD LITIGATION
- IMPLANT TOXICOLOGY INVESTIGATION
- DEVICE MARKETING AND WARNING CONSULTANT – OVERPROMOTION GYNECOLOGICAL SURGERY

The Fugitive

- All the liver samples were from the same patient
- Big money drives fraud
- Killing investigators who asked questions
- This is the stuff they make movies about

Fraud in clinical research

Chicago Center for Clinical Studies

H2 Antagonists ulcer research

Criticized for not recruiting subjects

- Dallas office successful

- Dallas office “creating patients” – same endoscopy photos used for 20 patients

gliatech

- The company's biosurgery products included ADCON-L, ADCON-T/N, and ADCON Solution, which were proprietary, resorbable, carbohydrate polymer medical devices to inhibit scarring and adhesions following spinal surgery.

GLIATECH ADCON GEL

- INADEQUATE RESEARCH /DEVELOPMENT
 - LIMITED ANIMALS
 - QUADRIPED V. BIPEDAL
 - INCOMPETENT RESEARCH MONITOR
 - LIED TO INVESTIGATORS /HID DATA FROM INSPECTORS
 - IGNORED SIGNALS
 - MORE INTERESTED IN BONUSES
 - FAILED TO REPORT TO FDA
 - CRIMINAL CHARGES AND PENALTIES

Gliatech

- ?faulty science
- Scar inhibitor
- Pmn inhibitor
- Predictable decreased healing
- Explanation for CNS leaks/headaches
- Patients worse off after surgeries

GLIATECH CRIMINAL PROSECUTION

- FDA concerned with clinical testing
- defective packaging and sterility problems associated with Adcon-L, and patient complaints of cerebral spinal fluid leaks.
- Aluminum flecks in spinal cord gel
- Quality control problems

Gliatech Research Fraud motivation?

- **Guilford Pharmaceuticals to purchase Gliatech Inc. for 7.39 times revenue**
- **Weekly Corporate Growth Report, Jun 12, 2000**
- **\$207,000,000 purchase**

VP/Med Director Criminal

- Gregory A. White, United States Attorney for the Northern District of Ohio, today announced that Derrick S. McKinley was sentenced to 24 months imprisonment and 3 years supervised release following his conviction by guilty plea to one count of insider trading, a form of securities fraud.

Preclinical Safety Clues

- Preclinical studies should anticipate clinical use
 - o Chymopapain, a proteolytic enzyme derived from papaya introduced in the 80s
 - o Allergic reactions were anticipated
 - o Neurological AE were not

Preclinical Studies for Chymopapain

- Anticipated allergic reactions were observed including anaphylaxis
- Unanticipated neurological reactions were also observed
 - o Transverse myelitis
 - o Seizures
 - o X-Rays during procedures showed migration of dye into the spinal canal
 - o The dye used, Renografin, later demonstrated neurotoxicity when used intrathecally

Post Marketing Studies for Chymopapain and Renografin

- After dozens of neurological events
 - o Primate studies were done with both Chymopapain and the dye
 - o Primates had a 75% complication rate when studied with both agents
 - o If this had been done in pre-clinical studies the drug would not have proceeded to clinical use in humans

Toxicology research/drug development

- o WALK ON THE BEACH
- o IF IT MOVES, METABOLIZES, AND CHANGES THE BODY, IS IT A DRUG OR A DEVICE?
- o Mentor research – hand cream tox studies demonstrated reduction in testicular size in male monkeys
- o Estrogen replacement drug development demonstrated metabolism by the body of the chemical constituent of the cream/device

Gynecological surgery device

- Inhibit post surgical abdominal adhesions
- Indicated for open laparotomy
- Promoted for laparoscopy - 70% of market laparoscopy
- Promoted to surgical centers – no laparotomy
- Reports of laparoscopy complications
- Serious reactions to patients

Closing remarks/advice

- Do the right thing
- Doctor, patient, PI, IRB, FDA look to the industry as the expert
- Be transparent
- Be pro-active – look for trouble
- Hire/consult with the right experts