Good Clinical Practice Overview

Presented by

Jennifer Sharpe Potter, Ph.D., M.P.H

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Learning Objectives

Outline

- Section 1: Institutional Review Boards (IRBs)
- Section 2: Confidentiality and privacy regulations
- Section 3: Performing quality assurance
- Section 4: The research protocol
- Section 5: Documentation and record–keeping
- Section 6: Define research misconduct

Introduction

- Why do we have GCP training again...and again?
  - Protect human participants in research
  - Protect our research staff
  - Protect the public interest
  - Ensure the continued support for clinical trials by maintaining high standards
- State how presentation will benefit audience.
  - Booster training
  - Prevent drift

What Doctors Don't Know (Almost Everything)
Kevin Patterson
New York Times 1857-Current; May 5, 2002; ProQuest Historical Newspapers The New York Times (1851 - 2005)
pg. E74

What Doctors Don't Know (Almost Everything)

Until recently, medicine was governed by the educated guess. But a new emphasis on data is challenging that tradition — with profound implications for both doctors and patients.

By Kevin Patterson Photographs by JOCELYN LEE

Panel Seeks Better Monitoring Of Experiments Using People
PHILLIP J. HILTS
New York Times (1857-Current file); Mar 2, 2000; ProQuest Historical Newspapers The New York Times (1851 - 2005)
pg. A20

Panel Seeks Better Monitoring Of Experiments Using People

By PHILLIP J. HILTS

Citing failures of scientists to report problems, federal health officials and members of the National Bioethics Advisory Commission said yesterday that changes were needed in the monitoring of research on people

thing that happens to a subject while an experiment is under way, even things seemingly unrelated to the research. (Sometimes a serious event may not appear to be related to an experiment, but is later found to be related For example, if a patient falls down the stairs and is injured,

Gene Therapy Ordered Halted At Universi
SHERYL GAY STOLBERG.
New York Times (1857-Current file); Jan 22, 2000; Pr
pg. A1

Gene Therapy Ordered Halted At University

By SHERYL GAY STOLBERG

WASHINGTON, Jan. 21 — The Food and Drug Administration temporarily shut down human gene therapy experiments at the University of Pennsylvania today after an inspection uncovered "numerous serious deficiencies" in ensuring patient safety during a clinical trial that cost an 18-year-old Arizona man his life.

DRUG TRIALS FOR PAINKILLER ADDICTS

NEW YORK POST
24 HOURS A DAY

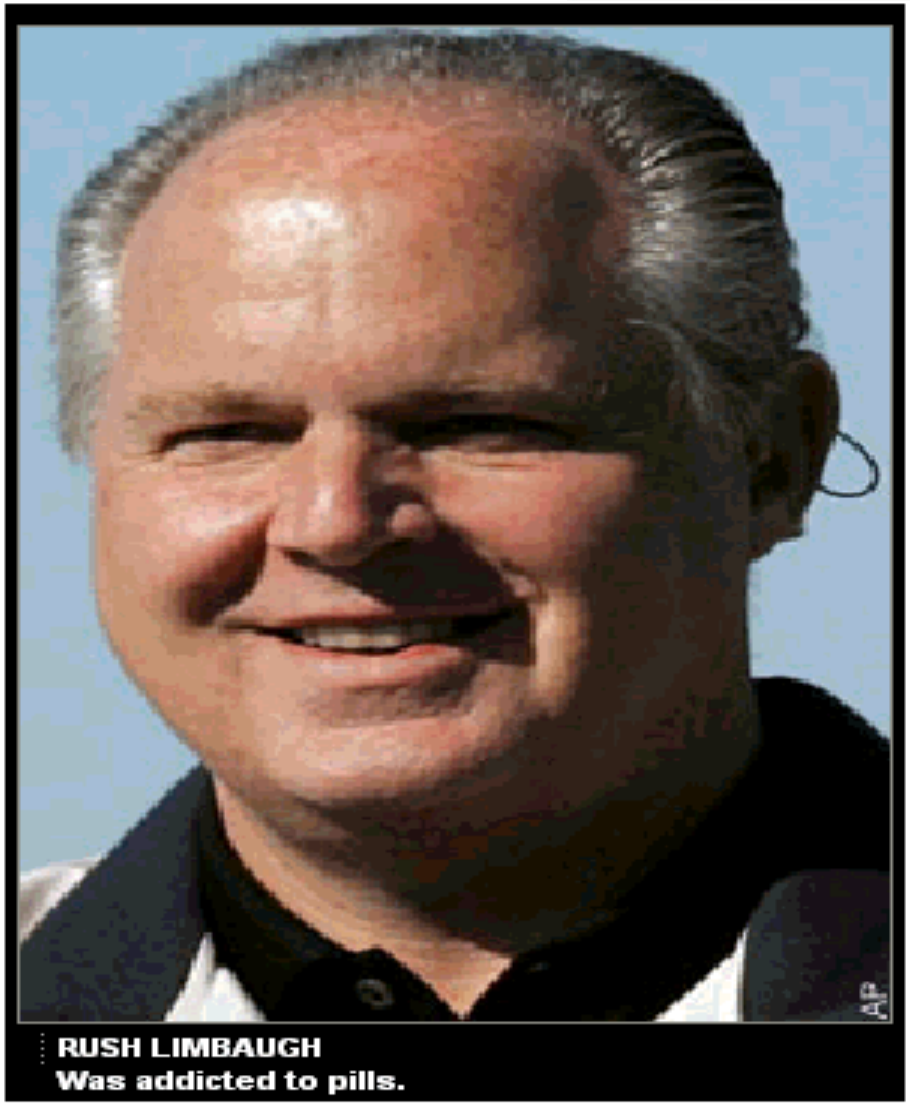
By CARL CAMPANILE

April 2, 2007

Pill-popping addicts could get dope through NYU Medical Center and Bellevue Hospital - just like heroin junkies receive methadone - to wean them off the prescription pain killers that have bedeviled celebrities such as Anna Nicole Smith and Rush Limbaugh, The Post has learned.

The National Institute on Drug Abuse is launching its first large scale Prescription Opiate Addiction Treatment Study at 12 sites across the country, including the NYU/Bellevue primary-care clinic. The drug trials will test the effectiveness of buprenorphone/naloxone tablets - marketed as Suboxone - to break patients' addictions to painkillers such as Vicodin and OxyContin. The tablets will be accompanied by different levels of drug-abuse counseling, a key aspect of the study.

While methadone must be administered through a licensed clinic, Suboxone can be prescribed in a doctor's office for home use.



RUSH LIMBAUGH
Was addicted to pills.

Health experts said addiction to prescription pills has mushroomed into an epidemic. A 2005 federal study found 2.2 million Americans aged 12 and older became "non-medical" users of pain relievers that year - surpassing new marijuana users.

The trial seeks to enroll 648 patients at 12 sites - including 55 at the NYU/Bellevue site - over an 18 month period.

Scientific Misconduct: Rare but Occurs

Findings of Scientific Misconduct

Notice Number: NOT-OD-08-096

Key Dates
Release Date: July 23, 2008

Issued by
Department of Health and Human Services

Notice is hereby given that the Office of Research Integrity (ORI) and the Assistant Secretary for Health have taken final action in the following case:

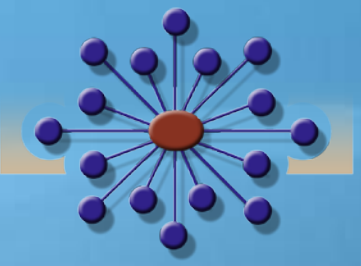
Mr. Doe knowingly and intentionally falsified and fabricated multiple follow-up interviews, urine samples, and urine sample records of human subject study participants and entered such false and fabricated data into the study's data base. Mr. Doe was assigned to interview 53 subjects located for the follow-up study. Over a six-month period, Mr. Doe falsely claimed to have conducted face-to-face interviews for the study while subsequent contacts with the subjects revealed that they had not been interviewed for the study. A review by the institution determined that the respondent fabricated interviews for 20 interviews assigned to him. In addition, he falsified the urine specimens for those 20 subjects and caused the entry of false information into the study tracking and locating data base for 11 subjects. Aggravating factors included the theft of $5180 for incentive payments to subjects and travel expenses.

Inquiries

For Further Information Contact:

Director
Division of Investigative Oversight
Office of Research Integrity,
1101 Wootton Parkway, Suite 750
Rockville, MD 20852
(240) 453-8800

Questions and comments are welcome!
Simply press *1 on your telephone.



Institutional Review Boards (IRBs)

Section 1: Institutional Review Board

- Types of Submissions
  - Initial Review
  - Continuing Review
  - Amendments or Modifications
  - Reports
  - When in doubt about whether to submit information, ask your IRB

Section 1: Institutional Review Board

- Responsibilities of Principal Investigator
  - Provide complete description of the proposed research (protocol)
  - Supply samples of the Informed Consent documents must be included with protocol
  - Provide all research recruitment materials (brochures, radio and/or television advertisements)

Section 1: Institutional Review Board

- Responsibilities of Principal Investigator (2)
  - Submit study safety information
  - Report research progress
  - Obtain informed consent before human subjects are involved in research
  - Comply with all IRB decisions, conditions, and requirements

Section 1: Institutional Review Board

- Some final thoughts to consider…
  - IRBs are required to have representation from a scientist, but no scientist understands all types of science
  - Some studies may be reviewed by non-scientists, or by scientists from different fields than the investigator
  - In cutting-edge research the IRB will always be at a disadvantage in understanding the research they are reviewing

Section 1: Institutional Review Board

- Strategies for IRB Submissions (1)
  - If the nature of the research is known to be complex, talk with the IRB BEFORE initial submission…in fact, always talk with your IRB first
    - If you are new, call/email to introduce yourself
    - Identify internal resources and use the instructions!
  - If, after initial review more questions are raised or the IRB defers action, talk with the IRB before the subsequent submission
  - Always follow the instructions
  - Beware of old submissions unless they are in compliance with current review guidelines

Section 1: Institutional Review Board

- Strategies for IRB Submissions (2)
  - The information that the IRB is approving should be clear and concise
    - USE LAY LANGUAGE
    - Clearly describe how procedures will work
  - Submit all documents requiring approval <u>together</u> in one packet
    - Keep similar research elements together

Section 1: Institutional Review Board

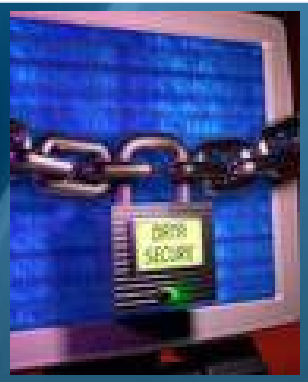
- Lead node efforts to facilitate IRB review
  - Start early in obtaining IRB approval
  - Determine the level or review burden participating sites will have during the site selection process
  - Work with NIDA and make them aware of progress in seeking IRB approval

Confidentiality and Privacy

Section 2: Confidentiality and Privacy

- All records of the identity, diagnosis, prognosis, or treatment of any person that are maintained in connection with alcohol or drug abuse prevention, education, training, treatment, rehabilitation, or research must be kept confidential.
- Do not disclose any information that identifies a person
  - The person consents to the disclosure in writing, or
  - The disclosure is allowed by a court order

Section 2: Confidentiality and Privacy



- The privacy regulations cover any info at the site that is “identifiable”
  - Names
  - Addresses
  - Employers’ names/addresses
  - Relatives’ names or addresses
  - Dates
  - Telephone and fax numbers
  - E-mail addresses
  - S.S. numbers
  - Medical record numbers

Section 2: Confidentiality and Privacy

- Use
  - Happens within a covered entity
  - Under direct control of that organization
    - e.g. A nurse in a clinical care setting is using PHI
- Disclosure
  - Information is given to someone outside the covered entity's work force
    - e.g., A site shows source documents to a monitor
      - You are disclosing that info, even if the monitor does not physically remove any PHI from the site

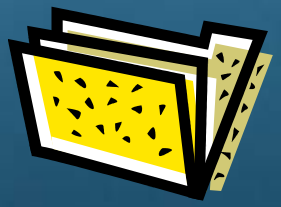
Section 2: Confidentiality and Privacy

- A covered entity is required to issue a written Notice of Privacy Practices to patients that includes
  - Inform patients of their rights and how to exercise them
  - Explain the organization's list all the uses and disclosures of PHI required or allowed by law
  - Explain process to gain access to medical records

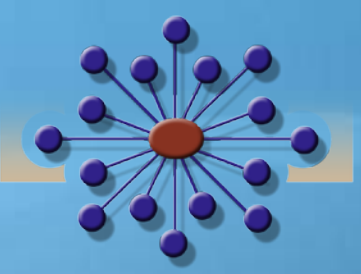
Section 2: Confidentiality and Privacy

- Use and Disclosure outlined in section 45 CFR 164.502(b)
- Staff can look at their patient's entire medical record and share information freely with other clinicians directly caring for that patient
- The minimum necessary standard does not need to be followed if subjects sign an authorization

Section 2: Confidentiality and Privacy



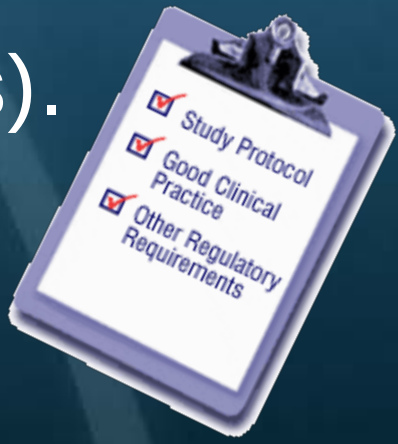
- Best practices
  - Don’t discuss subject information in a public place
  - Don’t leave medical records unattended
  - Don’t use easily guessed passwords for computer accounts
  - Know your own institutions interpretation of regulations and how the regulations have been operationalized



Performing Quality Assurance (QA)

Section 3: Performing Quality Assurance (QA)

- Planned, systematic activities conducted to ensure that a trial is performed and that trial data are generated, documented, and reported in compliance with the protocol and with GCP and all other applicable regulatory requirement(s).



Section 3: Performing Quality Assurance (QA)

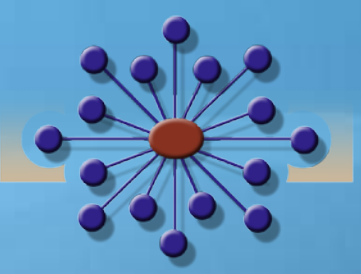
- QA is the responsibility of every member of the research team. The role of QA staff is to support and assist members of the research team in adhering to high quality standards.

Section 3: Performing Quality Assurance (QA)

- Monitoring verifies
  - Rights and well-being of human participants are protected
  - Reported trial data are accurate, complete, and verifiable
  - The trial is conducted in compliance with the currently approved protocol (including any amendments), as well as with GCP and all other applicable regulatory requirement(s).
- In general, on-site monitoring is required before, during, and after completion of a trial.

Section 3: Performing Quality Assurance (QA)

- All CTN studies undergo QA monitoring by the CCC
  - Initiation, Interim, and Close-out visits
  - File reports with the CTP, the local Node, NIDA and the Lead Investigator as required
  - Detailed Monitors' responsibilities
    - ICH GCP 5.18.4
- Good monitoring is not the enemy of good research; it protects our participants and research



Section 4

The Research Protocol

Section 4: The Research Protocol

- Provides a plan for the essential aspects of the proposed research
- Must be approved by a designated IRB
- Clearly and succinctly describe
  - Why the study is being done
  - What will be done in the study
  - Where the study will be done
  - Who is involved in the research study
  - When study interventions will take place

Section 4: The Research Protocol

- A protocol amendment is a change to some aspect of the study
  - Must be approved by the IRB before implementation
  - IND Studies must be submitted to the FDA & IRB
- A protocol violation is an action not adhering to the research protocol
  - Each must be documented and action must be taken to correct the situation that led to the violation
  - Repeated protocol violations may indicate the need for additional staff training or a protocol amendment

Section 4: The Research Protocol

- When a protocol violation occurs
  - Participant safety concerns must be addressed immediately
  - Document the violation and correction plan
  - Report to the protocol principal investigator, the lead investigator, Node staff, and the sponsor
  - Notify local IRB according to the IRB's documented procedures

Documentation and Record-keeping

Section 5: Documentation and Record-keeping

- Every aspect of a clinical study must be documented to
  - Obtain useful data
  - Demonstrate compliance with
    - GCP and Regulations

Section 5: Documentation and Record-keeping

- Essential documents defined *(ICH GCP 8.1)*

  … those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements."

- May be audited or inspected by monitors or by regulatory authorities to confirm the validity of the study and the integrity of the data collected

Section 5: Documentation and Record-keeping

- 21CFR312.62 - Documentation requirements in federal regulations
  - Disposition of drug
  - Case histories
  - Record retention for two years
- ICH Guidelines for GCP E6 - Essential documents for every clinical study
  - Before study begins
  - While study is in progress
  - After study is complete/terminated

Section 5: Documentation and Record-keeping

- Source documents
  - original documents, data, or records that are created during a clinical study, that relates to the medical treatment and the history of the participant, and from which study data are obtained
- Required by GCP guidelines
- Purpose
  - Document the existence of study participants
  - Substantiate the integrity of data collected
- Documentation protects us and ensures the quality of our research

Section 5: Documentation and Record-keeping

- Progress notes document participants' involvement in the study and the study–related care they receive. Progress notes are used to monitor the progress of the study and substantiate the data recorded in the case report forms (CRFs).

Section 5: Documentation and Record-keeping

- Site Binder & Submitted to the CCC
  - Investigator Agreement
    - CV's for each investigator listed on the Investigator's Agreement
    - Appropriate licenses for everyone listed on the Investigator Agreement per local regulations
  - Financial disclosure certifications
    - For everyone listed on the Investigator Agreement
  - IRB Protocol Approval
  - IRB Consent Approval
  - Other IRB Approvals (e.g. Advertising materials)
  - Federal Wide Assurance Number and Expiration Date
  - Signature Sheet and Delegation of Responsibility Log
    - Updated when staff changes occur
  - Protocol Signature Page
  - Certifications for Human Subject Protection Training
  - Clinical laboratory certification and normal ranges

Section 5: Documentation and Record-keeping

- Source documents
  - Adverse event and concomitant medication logs
  - Reports of diagnostic test results
  - Signed and dated Informed consent forms
  - Participant diaries
  - Appointment calendars
  - Progress notes
  - Paper Case report forms (CRFs)
- Available and retrievable for quality assurance monitoring and for audit or inspection

Section 5: Documentation and Record-keeping

- Case Report Form purpose
  - Gather study data in a standardized format so that the data can be entered into a computerized database and analyzed
- Record of all information needed to
  - Complete data analyses
  - Assess study outcomes

Section 5: Documentation and Record-keeping

- Required regulatory documents
- Copy to EMMES to maintain the CCC regulatory files
- Copy in the site regulatory binder
  - Some documents are only in the site binder

Section 5: Documentation and Record-keeping

- What do monitors look for?
  - Expiration dates
  - Updated FWA
    - Sometimes renewed prior to expiration
  - Human Subject Protection training certificates
    - Current and past staff
  - Regulatory binder organization

Research Misconduct

Section 6: Research Misconduct

- The U.S. Public Health Service created regulations for dealing with research misconduct (42 CFR 50 Subpart A)
- These policies generally have three goals:
  - To define research misconduct
  - To establish procedures for reporting and investigating research misconduct
  - To protect both those who report alleged research misconduct and those accused of research misconduct

Section 6: Research Misconduct

- Fabrication
  - making up data or results and recording or reporting them.
- Falsification
  - changing research materials, equipment, or processes or altering or omitting data or results so that the research record does not accurately reflect the research findings.
- Plagiarism
  - using another person's ideas, processes, results, or words without giving appropriate credit.
- Research misconduct does not include honest error or differences of opinion
- Applies to all CTN member institutions

Section 6: Research Misconduct

- All three of these elements must be present for a finding of research misconduct to be made
- Significant departure from accepted practices of the relevant research community
- Misconduct committed intentionally, or knowingly, or recklessly
- Allegation be proven by a preponderance of the evidence
- Research institutions' expected tasks in dealing with such allegations are specified in 42 CFR Part 50 Subpart A

Section 6: Research Misconduct

- Three stages to an allegation response
  - Inquiry (to assess the facts of the allegation)
  - Investigation (if the inquiry provides adequate basis for one)
  - Adjudication (imposing of suitable penalties if the allegation is found to have merit)
- Penalties for research misconduct may include termination of employment, suspension or termination of a research grant, and suspension or debarment from receiving federal funds

Polling Questions

Questions and comments are welcome!
Simply press *1 on your telephone.

Resources

- List of essential documents
  - Guidance for Industry E6 GCP Consolidated Guidance
  - Journal of Medical Ethics Article
    - The hexamethonium asthma study and the death of a normal volunteer in research