Hot Topics in Research Compliance

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Agenda

- Overview of Main Regulatory Bodies
- Defining Clinical Research
- Defining Research Compliance
- Hot Topics in Research Compliance
- Tips for Research Compliance
Objectives

1. Discuss basics of clinical research
2. Identify high risk compliance areas in clinical research.
3. Learn practical strategies to address high risk compliance areas in clinical research.
Why is there Risk in Research?

- Research and related rules are complex
- There is significant pressure on regulators to make things right if public perception is something is wrong
- Training is sometimes sparse
- Physician-investigators are busy and focused on substance and care for their patients
- Administrative support is sometimes lacking
Research Risks

Program income
Time and effort reporting
Direct charging practices
Fraud
Charge allocations
Biosafety
Scientific misconduct
Select agents
Research integrity
Cost transfers
Cost sharing
Informed consent
Award monitoring
Human subject protections
Animal subject protections
Research Compliance Motivators

- Research volume and complexity are increasing
- Broader, multiple and nontraditional collaborations
- Shift from "traditional" funding to alternate funding sources and sponsors
- Numerous areas exist for potential non-compliance risks
- Changes in healthcare regulation/system
- Increasing external access to information
Compliance Program Benefits

- Raises awareness of potential risks
- Can be a mitigating factor if problems are later identified
- May reduce *qui tam* lawsuits through prevention, detection, encouragement of internal reporting
- Recommended by government (see draft OIG Compliance Program Guidance)
Main Regulatory Bodies

❖ National Institutes of Health (NIH)
  ❖ Primary purpose to prevent disease and improve health by engaging in, encouraging, and funding medical research

❖ Food and Drug Administration (FDA)
  ❖ Advance public health by regulating the development of products from clinical trials through manufacturing and distribution into the marketplace.

❖ Office of Human Research Protections (OHRP)
  ❖ Primary oversight responsibility for human subjects protection
Main Regulatory Bodies

- Office for Research Integrity (within HHS)
  - Ensuring scientific integrity of results of research studies

- Office of Management and Budget (OMB)
  - Tracking accounting of federal funds

- States
  - May impose stricter standards

- Institutional Review Boards (IRB)
  - May have different thresholds for risk tolerance due to regional, demographic, or population-related factors
What is Clinical Research?

Clinical research is an activity involving human beings (including specimens or data derived from human beings) that is designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.
4 Phases of Clinical Research - Drugs

Pre-Clinical – Test in animals before humans

Phase 1 – Testing in a small group of people to determine safety, metabolic and pharmacologic actions in humans – identify safe dosage range and side effects

Phase 2 – Study in larger group to determine efficacy and evaluate safety

Phase 3 – Study to determine efficacy in large groups by comparing the intervention to other standard or experimental interventions (placebos)

Phase 4 – After market studies to monitor effectiveness in general population and collect about side effects associated with widespread use
Clinical Trial Agreements

Clinical Trial Agreement (CTA) is a legally binding agreement that manages the relationship between the sponsor and the institution.

- Main body of contract (typical legal clauses)
- Protocol incorporated as an exhibit
- Sponsorship budget incorporated as an exhibit as details of compensation arrangement
Clinical Trial Agreements

A CTA should describe and acknowledge:

- Responsibilities
- Terms of collaboration
- Confidentiality*
- Requirements for payment and reimbursement*
- Publication and intellectual property terms*
- Indemnification* and/or insurance
- Subject injury coverage
- Guidelines for dispute resolution
- Grounds for termination of contract
- Possibility of amending contract terms in the future.

* Hardest terms to negotiate
Hot Topics in Research Compliance
Hot Topics in Research Compliance

- Human Subject Protection
  - Informed Consent
- Clinical Research Billing
- Research Misconduct
- Conflicts of Interest
- Confidentiality
Hot Topics in Research Compliance

Hot Topic #1
Human Subject Protection
Human Subject Protection

Pivotal U.S. event: The Tuskegee Experiment (1932-1972) - U.S. Public Health Service

Purpose: To observe the natural progression of untreated syphilis in rural African-American men in Alabama under the guise of receiving free health care from the United States government

- Study Participants: 600 poor African American sharecroppers from Alabama.
  - 399 had syphilis before the study began; 201 did not have syphilis
  - Free medical care, meals, and free burial insurance for participating in the study
  - After funding for treatment was lost, the study was continued without informing the men they would never be treated
  - None of the men infected were ever told they had the disease, and none were treated with penicillin even after the antibiotic was proven to successfully treat syphilis
Takeaways from the Tuskegee Experiment:

- OHRP
- IRBs
- The Common Rule
Human Subject Protection

The “Common Rule”

- Baseline standard of ethics by which any government-funded research in the US is held
- Nearly all academic institutions hold their researchers to these statements of rights regardless of funding
- No statute, but in regulations at 45 CFR Part 46
- Revised and updated with the new rule published 1-1-7
- Effective date of 1-1-18
Human Subject Protection

- The “Common Rule”
  - Requirements for assuring compliance by research institutions
  - Requirements for researchers’ obtaining and documenting informed consent
  - Requirements for IRB membership, function, operations, review of research, and record keeping.
Human Subject Protection

- The “Common Rule” includes additional protections for certain vulnerable research subjects:
  - Pregnant women, in vitro fertilization, and fetuses
  - Prisoners
  - Children
Informed Consent

Human subjects should:

- be informed (sufficient information)
- clearly understand (comprehension);

and

- voluntarily enroll in studies
Informed Consent

Required parts of informed consent:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed.
5. Identification of any procedures which are experimental.
6. A description of any reasonably foreseeable risks or discomforts to the subject.
7. A description of any benefits to the subject or to others which may reasonably be expected from the research.
Informed Consent

What goes into an informed consent:

1. Informed consent document
2. Subject recruitment materials (advertising/marketing materials)
3. Verbal instructions delivered to subject/family
4. Written materials
5. Question/Answer session
6. Showing of the subject’s agreement and volunteerism, best documented by subject’s signature on written agreement
Informed Consent

Keys to Compliance:

- Clarity of informed consent form
- Obtain informed consent from each research subject prior to participation in the research study
- Provide a copy to the person signing the form
- Document consent process by:
  - The use of a written consent form; and
  - Signed and dated by the human subject
Additional Elements of Human Protection

More Keys to Compliance:

- Document adverse events and serious adverse event management
- Continuing review
- Perform audits
- Have options for anonymous reporting of concerns and issues
Hot Topics in Research Compliance

Hot Topic #2

Clinical Research Billing
Clinical Research Billing

- Medicare Coverage for Clinical Trial Services:
  - Does the study “qualify” for coverage?
  - What items and services are “routine costs”?
  - Do Medicare rules allow coverage of specific “routine costs” within a clinical trial?

- Medicaid – No federal coverage rules
Clinical Research Billing

- Ohio Medicaid:
  - Non-Covered: A service that is performed for purposes of research or clinical trial
  - Nothing in this rule precludes payment for a service that meets all of the following criteria:
    1. The service is medically necessary;
    2. The service is not experimental;
Ohio Medicaid – cont’d

(3) The service is provided to an individual who has received another service that is experimental in nature or that is performed for purposes of research or clinical trial; and

(4) The need for the non-experimental service did not arise solely because the individual received an experimental service or participated in research or a clinical trial.
Clinical Research Billing

Ohio Law: ORC Ann. 1751.01

All health benefit plans including those for public employees must cover costs of any routine patient care administered to an insured participating in any stage of an eligible cancer clinical trial, if that care would be covered under the plan if the insured was not participating in a clinical trial. (See ORC 3923.80 for all the details on coverage)
Clinical Research Billing - Medicare

1. Does the study “qualify” for coverage?
2. What items and services are “routine costs”?
3. Do Medicare rules allow coverage of the specific “routine costs” within a clinical trial?
Clinical Research Billing - Medicare

Additional Considerations:
- What do the funding documents say will be provided?
- What does the informed consent say will be provided at no charge?
Clinical Research Billing - Medicare

Medicare Claims Processing Manual Ch. 32, Section 69.6

1. Z00.6 secondary diagnosis code – examination of patient in clinical trial
2. Use Q0/Q1 modifiers as appropriate
3. Use appropriate condition codes
4. Include clinicaltrials.org number
5. Make sure patient record reflects trial name, sponsor, sponsor-assigned protocol number
Clinical Research
Billing Risks

- Billing for services that are already paid by the sponsor (double billing)
- Billing for services promised free in the informed consent
- Billing for services that are for research-purposes only
- Billing for services that are part of a non-qualifying clinical trial
Clinical Research
Billing Risks

Keys to Compliance:

- Coordination is key
- Make it a team effort
- Address key questions
- Communicate information to the right people managing charges for clinical services
Hot Topics in Research Compliance

Hot Topic #3
Research Misconduct
Research Misconduct: Defining the Legal Standard

Significant departure from the accepted practices of the research community, committed intentionally, knowingly or recklessly and proven by the preponderance of the evidence.
Research Misconduct

- Fabrication, falsification, or plagiarism in proposing, conducting, or reporting on the research
- False statements in federal grant applications
Research Misconduct

- **Fabrication** - Making up data or results and recording or reporting them
- **Falsification** - 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
- **Plagiarism** - The appropriation of another person's ideas, processes, results, or words without giving appropriate credit
- **Research misconduct does not include** honest error or differences of opinion
Research Misconduct

- Non-federal governmental institutions are required to notify ORI of misconduct cases involving PHS-supported research if an institution concludes that an investigation is warranted.
  - Notification of ORI must occur on or before the date on which the investigation begins.
  - The investigation must begin within 30 calendar days of finding that an investigation is warranted (following inquiry).
  - 120 days to investigate.
  - Must provide ORI with investigation report, final action, and findings.
Research Misconduct
Recent Cases

- A former lab analyst in Duke University's pulmonary division filed a complaint against the university under the False Claims Act (FCA).

- Allegation that former colleague, her supervisor and the university had falsified data in research funded by the NIH and the Environmental Protection Agency.

- Manipulated data gathered from machines that researchers use to test lung function of mice to study respiratory ailments.

- That data and accompanying research articles were then used to secure additional $200M in research grants from the federal government.

- Researcher arrested for embezzlement

- 16 of her publications have been retracted

- Case ongoing – potential liability $600M
$10M settlement related to stem cell research fraud
Brigham & Woman’s Hospital self-disclosed to the gov’t that its researchers had
  - failed to follow protocol
  - fabricated data and images
  - submitted misleading data in NIH research grants and in publications.

Launched investigation into the lab run by former Harvard Medical School professors in 2014 after a 2011 paper on the regenerative power of heart stem cells came under scrutiny for alleged scientific misconduct.
Two of the researchers admitted to falsifying data, but sued Harvard and Brigham and Women’s for wrongfully damaging their careers during the investigations.
Research Misconduct

Keys to Compliance:

- Have clear operational policies and procedures for approach to research misconduct and fraud
- Have internal control and review mechanisms for monitoring the ethical and quality aspects of ongoing studies
- Know what your research grants require and monitor risk areas
- Role of IRBs should be strengthened in safeguarding interests of research participants
- Train investigators and other researchers regarding potential harm of misconduct
Hot Topics in Research Compliance

Hot Topic #4
Conflicts of Interest
A conflict of interest (COI) exists when two or more contradictory interests relate to an activity by an individual or an institution.

- The conflict lies in the situation, not in any behavior or lack of behavior of the individual.

OHRP and Congress have pursued investigations, suspended distribution of research funds and issued fines and penalties.

Federal agencies consider COIs a matter affecting integrity.
Types of COIs

- Potential conflicts may be financial or may be a conflict of time, effort and/or commitment.
- Potential conflicts can occur as a result of administrative, scientific, academic, fiduciary or familial situations.
- Situations can be PERCEIVED to be conflicting, whether a “real” conflict exists or not.
Conflicts of Interest

Keys to Compliance:
- Assess existing COI infrastructure
- Develop, vet, and disseminate COI policies
- Require disclosure of all actual or potential COIs
- Create and implement a reporting, evaluation, and management process review by an internal COI committee
- Develop management plan
- Promote culture of disclosure
Hot Topics in Research Compliance

Hot Topic #5
Confidentiality
Confidentiality

- Individually identifiable health information that is collected and used solely for research is not considered Protected Health Information (PHI)

- Access and use of existing PHI from the Covered Entity for research requires prior approval from the IRB even when the investigator is also the research subject’s treatment provider

- Unless research subjects provide investigators with authorization to review their PHI through an informed consent, the Principal Investigator must obtain an IRB approved Waiver of Authorization so the approved access can be accounted for under HIPAA regulations
Certificates of Confidentiality (CoCs) provide protection against compulsory disclosure of highly sensitive research data through means such as subpoenas or court orders.

Adverse consequences for subjects such as damage to their:
- Financial standing
- Employability
- Insurability
- Reputation

Investigators conducting biomedical, social, or behavioral research that includes collection of sensitive identifiable data about illegal behavior, alcohol or drug use, or sexual practices or preferences may be asked to apply for a CoC by the IRB during the review and approval process.

CoCs can be requested from NIH, whether or not the research is sponsored by the NIH.
Compliance Tips

1. Know which IRB has been designated by your organization and what process for IRB review has been established

2. Know what research is going on at your institution
   - Who are the patients enrolled in your studies?
   - Know what is in your CTAs

3. Know what process is in place to educate medical staff on where to send prospective research to be reviewed
   - Is the process adequate, well-publicized, followed?

4. Include research in your compliance program
   - Know what rules apply based on who the sponsor (funding source) is
Questions?
Presenters

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