

# Legal Issues in Clinical Research: What You Need to Know

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# Agenda

- Sources of Regulation
- Focus on Reimbursement of Clinical Trial Costs
  - Update on Medicare Coverage
  - Emerging Issues in Medicaid Coverage
- Other Legal Issues and Practical Approaches

# Sources of Research Rules and Enforcement Authorities



# Why is There Risk in Research?

- Research and related rules are complex
- There is significant pressure on regulators to make things right where public perception is that they have gone very wrong
- Education is non-mandatory and sometimes sparse
- Physician-investigators are busy and focused on substance and care for their patients
- Administrative support is sometimes lacking (but the PI is always ultimately accountable)
- Consequences of non-compliance are not well-known or understood
- Priorities



# About Those Rules

*It's easy to trip . . .*

- Whatever we may think, the agencies who impose those complex rules believe they're important:
  - To protect the rights and welfare of subjects
  - To assure sound, reliable research
- The physicians, hospitals, and AMCs that conduct research are required to assure compliance . . . when they fail, they face:
  - Fines, civil penalties
  - Cessation of all human research activities (*e.g.*, Hopkins)
  - Bad PR (and loss of future research volunteers)
- The Principal Investigator is:
  - Presumed to **know**, **understand**, and **comply** with all of the rules, regardless of educational opportunities or available administrative support
  - Held ultimately accountable for everything he/she does and everything anyone else on the study team does . . . to the extent the PI delegates tasks, it's the PI's responsibility to educate those performing them and the PI is *still* accountable for their acts or omissions

# Traditional Sources of Research Rules and Enforcement Authorities

- Common Rule – 45 C.F.R. part 46
- General rule adopted by 17 federal agencies, including OHRP (Office for Human Research Protections); OHRP adds special protections for prisoners, pregnant women and fetuses, and minors
- Applies to human research conducted or supported by any of the adopting federal agencies



# Traditional Sources (cont'd)

- Drugs, Devices and Biologics – 21 C.F.R.
  - 21 C.F.R. part 11 (electronic records)
  - 21 C.F.R. part 50 (protection of human subjects)
  - 21 C.F.R. part 54 (financial disclosures)
  - 21 C.F.R. part 56 (IRBs)
  - 21 C.F.R. part 312 (drugs, biologics) and 812 (devices)
- Adopted and enforced (civilly and criminally) by FDA under the Food, Drug and Cosmetic Act
- Applies to human research involving drugs, devices, and biologics (without proper approvals – INDs and IDEs where required – investigator and research team members may be guilty of adulteration or misbranding)



# Traditional Sources (cont'd)

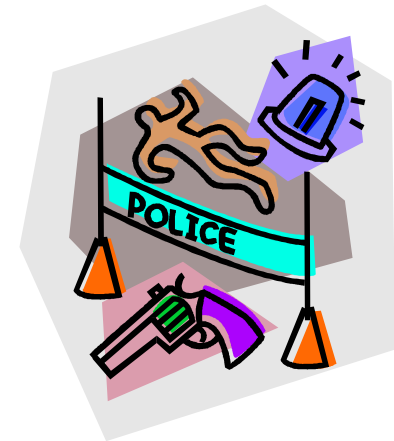
- Studies Funded by NIH
  - Grants Policy Statement, etc.
- Research Misconduct – Office of Research Integrity
  - Fabrication, falsification, plagiarism
- Health Fraud and Other Violations and Crimes – OIG and DOJ
- Plus: formal and informal guidance, reports of enforcement activities, advisory opinions, etc.





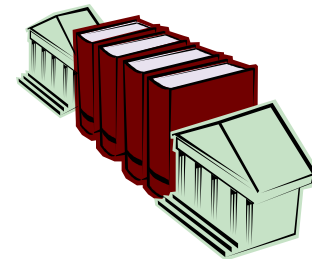
# Other Sources of Rules and Enforcement Authorities

- The Usual Suspects, *e.g.*:
  - Professional negligence/malpractice exposure
  - Privacy/HIPAA
  - Billing/reimbursement compliance
- Fraud and Misrepresentation
  - “Common Law” (private citizens, government prosecutors)
  - Mail Fraud, Wire Fraud, Health Fraud Statutes (Department of Justice)
- False Statements (DOJ)
- False Claims (DOJ and *qui tam* relators)
- Anti-Kickback Law (HHS OIG and DOJ)
- Anti-Self Referral Law (HHS OIG and DOJ)



# Investigator/Institutional Commitments

- PHS Grant Applications
- Clinical Research Agreements
- FDA 1571, 1572, IDE applications
- IRB Applications, SOPs, etc.
- Conflict of Interest Policies
- Federal Wide Assurance (FWA)
- Other Institutional Policies



# Ethics, Policy, Best Practice Sources

- Nuremberg Code <http://ohsr.od.nih.gov/nuremberg.php3>
- Declaration of Helsinki <http://ohsr.od.nih.gov/helsinki.php3>
- Belmont Report  
<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>
- National Bioethics Advisory Commission  
<http://www.georgetown.edu/research/nrcbl/nbac/>
- President's Council on Bioethics <http://bioethics.gov/>
- Institute of Medicine (10/02) *Responsible Research: A Systems Approach to Protecting Research Participants*  
<http://www.iom.edu/report.asp?id=4459>

*Some plaintiffs' lawyers have sought to enforce these through litigation.*

# Clinical Trials Reimbursement

Medicare Developments

# What is Clinical Research Billing Compliance All About?

- **Clinical research billing compliance involves:**
  - Identifying clinical research services that can or cannot be billed to third-party payors
  - Ensuring processes are in place to bill to third-party payors only services that billing rules allow to be billed
  - Harmonizing relevant portions of study documents in accordance with billing rules

# Clinical Research Services Billing

## Coordination is Key to Compliance

1. **The protocol's schedule of events**
2. **The compensation arrangement in the sponsorship contract or grant (the "budget")**
3. **The financial disclosure language of the study's informed consent**

# Compliance Risks

- Ignoring clinical research billing rules can lead to:
  - 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

## Medicare Clinical Research Services Coverage – A Year of Suspense

- The Clinical Trials NCD (310.1) has been under reconsideration by CMS since July 2006.
- Final revisions to the policy are expected October 17, 2007
- The new coverage policy will be called as the Clinical Research Policy (CRP).
- The current coverage policy is now called the Clinical Trial Policy (CTP).
- CMS has proposed that the CRP will be the coverage rule for any study that has not begun enrollment by October 17 and the CTP will remain the coverage rule for any study that has begun enrollment by October 17.
- As a practical matter, 2 coverage rules will exist for several years.



# Medicare Clinical Research Services Coverage – the CTP & CRP

- The CRP maintains most of the same concepts as the CTP, but offers better language and different mechanisms for compliance within the concepts.
- Keys concepts in both CTP & CRP:
  1. Does the research study meet certain requirements to qualify for coverage?
  2. What items and services required by the protocol are for the clinical management of the enrolled patient?
  3. Does Medicare normally cover the patient care services outside the study?
  4. Providers must not bill Medicare for items and services paid for by the sponsor
  5. Providers must not bill Medicare for items and services promised free in the informed consent document.

# Qualifying Status of a Research Study

- CTP requires that a research study be a “Qualifying Clinical Trial” in order to bill Medicare for any study required items and services – there are 10 criteria.
- CRP requires that a research study be a “Qualifying Research Study” in order to bill Medicare for any study-required items and services – there are 13 standards.
- If a study is not a QCT or QRS, then no items or services are billable to Medicare that are required by the research study.
- Exception: Medicare covers treatment of complications for non-QCTs and non-QRSs.

# Qualifying Clinical Trial Under CTP

- In order to be a QCT, a study must be:
  - Part 1: One of 4 types of studies that are “deemed” to have 7 desirable characteristics; and
  - Part 2: Have all 3 “necessary requirements”:
    - The investigational item or service must fall within a Medicare benefit category
    - The study must enroll patients with diagnosed disease
    - The study must have therapeutic intent

# Qualifying Clinical Trial Under CTP

- Studies “deemed” to have the 7 desirable characteristics:
  1. Studies funded by NIH, CDC, AHRQ, CMS, DOD, and VA;
  2. Studies supported by centers or cooperative groups funded by NIH, CDC, AHRQ, CMS, DOD, and VA;
  3. Studies being conducted under an IND application; or
  4. IND exempt studies

# Qualifying Clinical Trial Under CTP

- What is sufficient therapeutic intent?
  - “The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.”
  - Note the 1<sup>st</sup> desirable characteristic: “The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes.”
- CMS oral interpretations have suggested that one of the primary objectives of the study should evidence therapeutic intent.
- Controversy: Phase 1 cancer drugtrials

# Routine Costs During a QCT

- Medicare covers “routine costs” during qualifying clinical trials
  - Conventional care
  - Detection & prevention of complications
  - Administration of investigational item or service
- QUESTION: Will the item or service be used for the clinical management of every patient enrolled in the research study?

# Proposed Clinical Research Policy

- Qualifying Research Study
  - 13 standards must be met (language still in flux)
  - No “deemed status” and IND status does not matter
  - Standards are certified by either the sponsor or the investigator
  - Certification is registered with CMS
  - Certification status of study will be publicly available
  - Study only needs to be self-certified once in a multi-site study

# Proposed Clinical Research Policy

- Status of therapeutic intent:
  - If therapeutic benefit is a primary objective, then study will meet standard
  - If therapeutic benefit is a secondary objective, then will meet standard if disease investigates a “life threatening” disease
  - CMS is still working on specific language



# Practical Effects of Proposed CRP

- 2 Medicare coverage rules will be active – enrollment date of first subject will determine which rule
- Very broad jurisdiction over any “prospective” study that includes an informed consent
- All research studies are treated exactly the same whether funded by government, industry or self-funded
- Industry efforts underway to advocate for less complexity
- Stay tuned!

# Things That Providers Can Do to Help Manage Clinical Research Billing Compliance

- Develop databases of research studies and patient enrollees.
- Begin going-forward coverage analyses on research studies before signing clinical trial agreement to ensure adequate sponsor funding for items and services that cannot be billed.
- Use coverage analysis as billing tool once patients are enrolled.
- Assess state of existing studies and begin process of developing coverage analyses as compliance safeguards.
- Work with team of operational personnel to determine how best to implement controls to ensure that third-party payors are not billed for items and services indicated in the coverage analysis as not billable.
- Identify what is happening in your State – Medicaid and commercial payors.
- Educate research personnel and investigators.
- Develop auditing and monitoring program to ensure safeguards are working.
- Keep a close watch on CMS developments!

# Clinical Trials Reimbursement

Emerging Medicaid Issues

# Medicaid Programs

- Operated by State agencies
- Receive Federal subsidies and State provides remaining funding
- Federal false claims laws apply to Medicaid claims – HHS-OIG has authority to investigate and review Medicaid compliance
- States are incentivized to adopt State false claim laws and State whistleblower actions
- The Deficit Reduction Act provides increased funding for both Federal and State agencies to audit, monitor and investigate Medicaid claims
- Medicaid investigations are proliferating as a result

# Medicaid & Research Billing

- The Federal device trial regulations and the CTP/CRP do not apply to billing clinical research services to Medicaid programs
- Each Medicaid program is allowed to develop its own rules on how to approach clinical research billing
- Most Medicaid programs are silent on the issue and coverage needs to be interpreted from the overall structure of the State program and basic principles that the State employs or seek guidance and clarification from the State agency

# Medicaid & Research Billing

- Interpretation of Medicaid rules:
  - Example: State program excludes from coverage “investigational items and services” as well as “research activities” but another section of rules provides blanket coverage for “medically necessary” items and services unless specifically excluded.
  - Possible approach: Services during a research study that are for the clinical management of the patient would still be covered because they are not solely for research purposes.
  - Practical approach: Follow the CMS rules since they are slightly more conservative than the example’s approach and instituting one approach provides operational efficiencies.

# Medicaid & Research Billing

- What to do?

- Check State Medicaid program coverage rules to see if they address clinical research services
- If State does not address research services, consider consulting State agency or can clear interpretations be made from the structure of the Medicaid rules?
- Does the State have separate initiative that imposes research coverage rules on all non-Federal payors in the State (about 20 States have such laws and they closely mirror the CTP)
- Do commercial payors have a clear policy or do payor contracts address research services?



## Where Do Other Compliance Challenges Arise

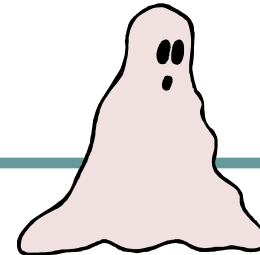


# Potentially Problematic Conduct

- Exists in all aspects of research administration and conduct
- Private plaintiff and government interest is heightened in the event of explicit and intentional misconduct and/or bad outcomes
- Understanding how to identify potential problems and where to go to resolve them can help reduce or eliminate exposure

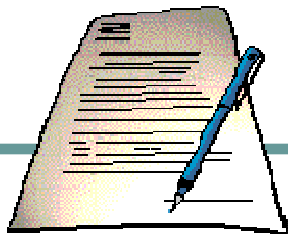
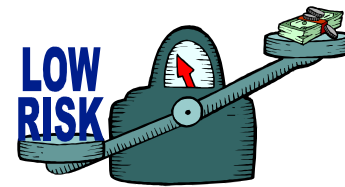
# Recruitment and Enrollment Issues

- False statements or misrepresentation to induce potential subjects to participate
- Payments to recruiting doctors and staff (depending on circumstances)
- Enrollment of ineligible subjects (without advance IRB approval)
- Ghost subjects
- Fabricated or falsified results for qualifying tests (e.g., blood work, radiological scans, physicals, etc.)



# Informed Consent Issues

- Forged or falsified documents
- Failure to disclose investigator/institutional conflicts of interest
- Failure to disclose risks
- Circumvention of procedures (e.g., “sign here” at back of form, inducing potential subject to enroll without actual consent)



# Approvals and Oversight

- Approval process violations
- False statements to sponsors, CROs, IRBs, regulators, etc.
- Failure to disclose research, appropriate information about the research, or changes in the research to the IRB
- Non-compliance with IRB requirements, including IRB-approved protocol and consent

# Conduct of Study

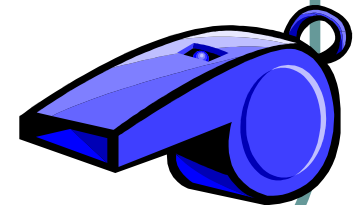
- Fabrication, falsification, or plagiarism in proposing, conducting, or reporting on the research
- Billing for non-covered services
- Double billing (e.g., to grant/sponsor and to payor)
- Waivers of copayments and deductibles
- False statements in federal grant applications or FDA 1571/1572
- Sham research



How Are Problems Identified and Enforced?

# Sources of Inspections and Investigations

- Routine inspections
  - Federal oversight agencies
  - Cooperative groups
  - Sponsors/CROs
  - Accreditation organizations
  - Institutional officials
- For-cause investigations
  - Patient/subject complaints and litigation
  - Advocacy organizations
  - Internal discoveries
  - Whistleblowers (note on whistleblower protections)
- Note on OIG Workplan



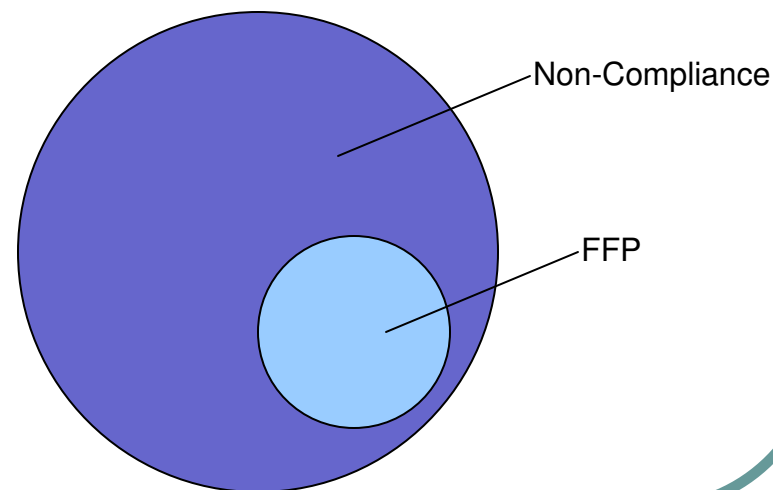
# Sanctions Against PI's for Non-Compliance or Misconduct

- Institutionally imposed sanctions (Local Enforcement)
  - Suspension or termination of protocols
  - Disqualification from research leadership or activities
  - Medical staff/clinical privileges implications
  - HR sanctions up to and including dismissal
- Regulatory sanctions (OHRP, FDA, NIH, etc.)
  - Suspension or termination of protocols
  - Disqualification from research leadership or activities
  - Civil fines and penalties
- Criminal enforcement (FDA, DOJ)
  - Fines
  - Imprisonment



# Non-Compliance and Misconduct

- Non-Compliance
  - Failure to comply with laws, regulations, protocols, informed consent documents – may be intentional or unintentional
  - “Serious” and “continuing” non-compliance is reportable to federal funding agencies and FDA, for studies subject to their oversight
- Misconduct (“FFP”)
  - Fabrication
  - Falsification
  - Plagiarism





# Common Challenges and Practical Solutions

# Common Themes in Non-Compliance Investigations and Practical Solutions

- Problem: PI delegation to co-investigators or research staff unable or unwilling to comply with the rules (PI is accountable)
- Solutions
  - Assure adequate funding of research administration
    - Hire qualified, dedicated, well-organized staff
    - Support development and implementation of department-wide procedures to avoid having to re-invent the wheel for every study
  - Assure research staff takes advantage of available training opportunities; encourage certification
  - Try and do so yourself
  - Don't include as co-investigators colleagues who are unwilling to abide by the rules.

# Common Problems & Solutions

- Problem: IRB approval delays, initiation of study prior to IRB approval
- Solutions
  - Assure study staff build relationships with IRB staff to maintain open communications
  - Respond promptly to IRB requests for additional information or revisions
  - Assure you have a copy of the IRB approval in hand before enrolling *any* subject (or determining eligibility, collecting data, etc.).

# Common Themes & Solutions

- Problem: Enrollment of ineligible subjects.
- Solutions:
  - Assure protocol eligibility criteria are clear and that anyone responsible for enrollment understands them.
  - Use criteria that are as flexible as possible without sacrificing scientific validity. You will be held to the rules you write.
  - If an ineligible subject is a good candidate for participation, get prior IRB (and sponsor, if applicable) approval to enroll (i.e., an amendment), or assure one of the recognized exceptions exists:
    - Emergency use (exception is narrow, requires concurrence of an outside physician and report to IRB and sponsor within 5 days)
    - Clinical treatment off-protocol (not an option for unapproved drugs or devices; data may not be collected or reported for study-related purposes)

# Common Themes & Solutions

- Problem: Other protocol non-compliance
- Solution:
  - Write clear protocols
  - Assure CRA, protocol, investigator's brochure (if any), IRB application, and consent form are all consistent
  - Consider using a calendar/chronology tool to map out all study-related visits/procedures and include it in the IRB application to make sure everyone understands what is expected from the IRB to the PI to the co-investigators to the study staff
  - Consider the protocol a rule, not a guideline. Adhere to it carefully except as necessary to avoid immediate hazards to subjects or others. In case non-compliance is found, report it promptly to the IRB (and, for FDA studies, sponsor or FDA).
  - Assure all co-investigators, research staff, and others involved in protocol implementation are trained to the protocol requirements and able and willing to adhere to them. Consider an initiation meeting and regular meetings as long as the protocol is active to assure all are on the same page.

# Common Themes & Solutions

- Problem: Informed consent deficiencies
- Solutions
  - Write a clear document with reasonable readability, to the extent practical
  - Do not begin a protocol-related procedure until you verify that the subject has signed the research consent document and that it is dated and, if required on the form, witnessed. If the subject is unable to sign and an LAR does instead, document the LAR's authority (e.g., parent, legal guardian), as well as the reason why the LAR signed (e.g., patient unconscious, patient sedated, patient incompetent, etc.).
  - Consent is a process. The form simply documents the process. Either consent the subjects yourself or, if you must delegate, assure that co-investigators or responsible research staff are appropriately qualified and competent to provide consent.
  - Don't make ANY changes to the form without prior IRB approval. When IRB does approve, immediately implement the new version (destroy all blank old versions except a file copy or two).
  - Unless a promise is made not to on the face of the document, put a copy of the signed consent into the patient's medical record, in addition to the research record. This will help insure against loss.

# Common Themes & Solutions

- Problem: Adverse event and unanticipated problem reporting – FDA, OHRP, sponsor, and IRB requirements vary
- Solutions
  - Write protocol-specific adverse event reporting guidelines or be prepared to comply with the IRB's.
  - Promptly (typically within 7 days) report ALL deaths to the sponsor and IRB, even if expected and seemingly unrelated to the study intervention (e.g., death due to disease progression).
  - AEs are not always directly reported to the study team – patient medical records should be examined if available (and approved in the informed consent)
  - Note: other information may need to be reported – such as protocol deviations – understand all applicable requirements.



# Common Themes & Solutions

- Problem: Inadequate documentation.
- Solutions:
  - Be organized (or hire people who are)
  - Regardless of whether the trial is sponsored by industry, be prepared for audit. Be sure to maintain all key documents, including:
    - All communications with IRB, other institutional committees or officials, FDA and other government agencies, and sponsors.
    - Informed consent documents, evidence of intervention and follow-up, and anything else the sponsor wants
    - Support for protocol deviations and emergency use
  - Assure appropriate security measures for any electronically maintained records (e.g., secure servers, encryption)
  - Maintain all research records at least 3 years; 6 if they relate to patient care (HIPAA requirement); 2 beyond termination of study or new marketing application, depending on circumstances (for FDA studies) . . . comply with more restrictive local requirements

# Common Themes & Solutions

- Problem: Mishandling things when something goes wrong.
- Solutions
  - Communicate professionally with government and institutional officials at all times (no matter what you are thinking or who you are talking to).
  - “That’s how everyone does it” is not an excuse.
  - Be prepared with at least an initial corrective action plan to assure future compliance, preferably before you are even asked.
  - Secure knowledgeable legal representation for any government inspection or audit (or any other matter where you may not know all the rules or be prepared to properly defend yourself).

# Reality Check

- Understand triggers
  - Plaintiffs' bar
    - Bad outcomes often trigger lawsuits
    - Bad facts (e.g., inadequate disclosure of potential conflicts of interest) creates greater likelihood of litigation and higher exposure
    - Plaintiffs argue that ethical standards serve as controlling legal authority (not much different from a law or regulation)
  - Federal authorities
    - Limited resources force prioritization
    - Note on major sponsor enforcement vs. investigator or sponsor/investigator enforcement
    - Few government-initiated criminal cases (but you don't want to be the first)
- Distinguish less critical concerns
  - Minor protocol deviations
  - Unintentional or unknowing violations

# Links

- OHRP – <http://www.hhs.gov/ohrp>
- FDA – <http://www.fda.gov>

Q&A

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