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Understanding the Elements of a Strong Research Compliance Program

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AGENDA

- Introductory perspectives on the life sciences and clinical research
- Overview of the main regulatory bodies that preside over the life sciences
- Defining clinical research
- The challenges associated with the practice of life sciences and how compliance programs help address them

Introductory Perspectives

Introductory Perspectives on Clinical Research
History and Ethics

- The experimentation that enabled the virtual eradication of polio came at a cost.
  - In 1936, one researcher conducted clinical trials that provoked severe allergic reactions, but no immunity, while another researcher's clinical trials resulted in fatalities
- Even well-intentioned clinical researchers without guidelines and parameters may lose sight of the possible harms their efforts may cause.
- A consideration of the risks to human participants--as well as the possible benefits to society--is essential to the ethical conduct of clinical research.

Introductory Perspectives on Clinical Research Benefits

- The transformative impact of clinical research on humanity is undeniable.
- Benefits of conducting research:
  - Participation in the advancement of science and enhancement of a clinicians understanding, diagnosis, treatment, and prevention of disease.
  - Enhancing patients access to new medications and keep doctors attuned to the latest research and therapeutics.
  - Generate additional revenue streams.
  - Becoming a so-called "Center of Excellence".
  - Advance an academic or hospital mission.
  - Marketing and enhancement of reputation, brand, perception – positive buzz and publicity.
  - Advancing the professional profile of clinicians through publication with meaningful professional organizations.
  - Opportunity to drive clinical programs by attracting patients who might not otherwise trek to a specific hospital.

9/13/2016 5

Introductory Perspectives on Clinical Research Challenges and Risks

- Costs of developing infrastructure (admin staff, IRB, labs, systems).
- Patient recruitment and retention.
- Investigators compensation models often do not allow for significant time to be invested in research pursuits.
- Financial compensation (funding) may be too low.
  - Requires hospitals and investigators to be budget savvy – to understand the full costs of conducting research and demand adequate compensation.
- Compliance expectations on an organization supporting human subjects research are considerable (e.g., operational, regulatory, market, reputational risk).
- When a community health system is spread over wide geographic areas with several outpatient facilities; can create challenges for billing and other operations.

9/13/2016 6

Introductory Perspectives on Clinical Research Challenges and Risks

- COI: Balancing patient needs with desire to spur enrollment.
- Many physicians don't fully understand the regulations & laws.
  - Complexity make clinical trials difficult to manage and oversee
  - Direct: FDA, OHRP, CMS
  - Tangential: HIPAA, radiation safety, poison prevention & packaging
  - Potential false claims act violations (billing compliance)
  - Liability concerns
    - Related to concern over medical malpractice
    - Importance of indemnification in contract negotiation
    - Ethics
    - Stark/anti-kickback
  - Financial disclosure may deter participation by physicians
    - Physician Payments Sunshine provision embedded within PPACA

Introductory Perspectives on Clinical Research Ethics

- Experimentation in medicine has occurred since the dawn of the practice of medicine both in the US and abroad.
- Clinical research is the nexus of healthcare compliance, patient care, hospital administration and scientific inquiry.
- Human Research Protections is an extension of the concept Primum Non Nocere….*first, do no harm*
- Ethical treatment of humans is the backbone of clinical research
  - Ethics ensure that safety and wellbeing are just as important as results and revenue.
  - Ethics encourage volunteerism.

Overview of Main Regulatory Bodies

Federal Agencies and Clinical Research

- In the United States, several federal regulatory agencies and bodies promulgate regulations under, and monitor compliance with, laws governing clinical research, including:
  - National Institutes of Health (NIH)
  - Food and Drug Administration (FDA)
  - Office for Human Research Protections (OHRP)
  - Office for Research Integrity (ORI)—all within HHS
  - Office of Management and Budget (OMB).
- Because the regulatory agencies have different jurisdictions, mandates and priorities, the laws administered and regulatory requirements imposed by multiple federal agencies often prove applicable to and overlap in a single research study.

Federal Agencies and Clinical Research

- Moreover, individual states have enacted their own laws.
- Federal standards provide a framework, states may "gap-fill,"opting for more (but not less) stringent requirements.
  - Example: A state may adopt supplementing rules that extend protections to human subjects or to require heightened security measures for the protected health information collected during the conduct of research.

Federal Agencies and Clinical Research

- Often, private institutions and organizations develop rules material to the management of clinical research
  - For example, imposing specific restrictions as a condition for funding--to supplement or support their specific research missions.
  - The rationale for developing organizational rules and procedures run the gamut; for example, an institution may impose additional protections or restrictions reflecting its religious or ethical mission.
- In addition, Institutional Review Boards (IRBs) may add to the overlapping layers of rules.
  - For example, the thresholds for risk tolerance in research studies individual IRBs use may differ due to regional, demographic, or population-related factors.

Defining Clinical Research

Defining Clinical Research Evolution

- Clinical research is an expansive, complex field that has been defined in several ways.
- One influential source for the definition of and guidelines for clinical research used by federal agencies is the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
- Specific government agencies have also developed similar, but yet different definitions of clinical research.

Defining Clinical Research
OHRP

- *Research* means a systematic investigation, including research, development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
- Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes.
- For example, some demonstration and service programs may include research activities.

Notably, this definition describes "research" and not "clinical research" specifically. In fact, the OHRP does not have a unique definition for clinical research; it applies the Common Rule to its definition by describing "research involving human subjects."

9/13/2016 15

Defining Clinical Research
FDA

- *Clinical Investigation* means any experiment that involves a test article and one or more human subjects, and that EITHER is subject to requirements for prior submission to the Food and Drug Administration.
  - Section 505(i) or 520(g) of the [Federal Food, Drug, and Cosmetic Act, as amended (secs. 201–902, 52 Stat. 1040 et seq. as amended (21 U.S.C. 321–392))]
- OR is <u>not</u> subject to requirements for prior submission to the Food and Drug Administration under these sections of the act.
- The results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.
- The term does not include experiments that must meet the provisions of part 58 [21 C.F.R. Part 58], regarding non-clinical laboratory studies.

FDA also clarifies the definition by identifying terms it deems to be synonymous in different contexts (E.g., research, clinical research, clinical study, study, and clinical investigation).

9/13/2016 16

Defining Clinical Research
NIH

- Patient-oriented research, including epidemiologic and behavioral studies, outcomes research, and health services research.
- Patient-oriented research is research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) in which a researcher directly interacts with human subjects.
- It includes research on mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies, but does not include in vitro studies using human tissues not linked to a living individual.

Excludes from its definition research involving the collection or study of existing, publicly available or de-identified data, documents, records, pathological specimens, or diagnostic specimens.

Defining Clinical Research
Four Phases

- Clinical trials of an experimental drug, treatment, device, or intervention are most commonly classified by--and proceed through--four phases:
  - *Phase 1:* Testing in a small group of people (i.e., 20-80) to determine safety, metabolic and pharmacologic actions in humans (e.g., determine a safe dosage range and identify side effects).
  - *Phase 2:* Study in a larger group of people (several hundred) to determine efficacy and further evaluate safety.
  - *Phase 3:* Study to determine efficacy in large groups of people (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions, to monitor adverse effects, and to collect information to allow safe use.
  - *Phase 4:* Studies done after the intervention has been marketed. Designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Only the first three phases are specifically defined in FDA regulations, while "Phase 4" is a colloquial term that is nevertheless used by federal agencies, even if it is not specifically defined in the CFR.

Introduction to Clinical Research and Life Sciences Compliance

Clinical Research & Life Sciences Compliance
Informed Consent and Human Subject Protections

- Human subjects should be informed, clearly understand, and voluntarily enroll in studies as required by regulation.
- Best characterized as a process, informed consent includes a variety of tools, such as:
  - Informed consent document
  - Subject recruitment materials (including advertising/marketing materials)
  - Verbal instructions delivered to the subject and his or her family
  - Written materials
  - Question/answer sessions
  - Showing of the subject's agreement and volunteerism, which is best documented by the subject's signature on a written agreement.

Clinical Research & Life Sciences Compliance
Informed Consent and Human Subject Protections

- Many organizations have incorporated human subject protections, and specifically the informed consent process, into their clinical research compliance programs.
- Established procedures for training, periodic reporting, anonymous ways of reporting concerns and issues, employee discipline, and prompt follow-up, as well as auditing and monitoring provide advisable checks and balances.

In the past, clinical research monitoring was typically limited to issues related to funding of federal grants, time and effort reporting and the like.

Given federal investigations trends and stringent determination letters from OHRP, the auditing and monitoring of human subject protections has become a necessary part of the compliance process.

9/13/2016 21

Clinical Research & Life Sciences Compliance
Research Patient Billing

- Clinical research billing is a critical compliance concern for institutions that conduct research studies.
- Most research organizations were created as clinical- and treatment-focused organizations.
  - They were not constructed with a view toward research, nor were their billing systems created with research in mind.
  - Therefore, many have supplemented established systems with improvised clinical research billing processes intended to capture charges to the research study and ensure that only allowable services

Each organization usually tries to develop a billing process that fits within its own research dynamic.

Clinical research billing processes usually present dramatic changes for investigators, clinical trial coordinators, registration staff, and billing staff.

Organizations will likely find it necessary to plan for significant training on new procedures.

9/13/2016 22

Clinical Research & Life Sciences Compliance Research Patient Billing

•Institutions must manage the following clinical research billing risks:

- •Billing for services that are already paid by the sponsor
- •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 & Life Sciences Compliance Effort Reporting

- The federal government is always focused on time and effort reporting and other mechanisms by which dollars flow from the federal government to investigators and research institutions, resulting in several widely publicized cases.
- Consequently, effort reporting is a major area of compliance interest.
- However, its management and its implications are complex thus exacerbating the challenge for research administrators.

Research institutions often undertake an initial assessment of the systems and procedures currently in place as an important first step before settling on a final implementation strategy and rolling out an education plan.

Because effort reports play a pivotal role in documenting cost sharing commitments, the research institution usually develops policies and procedures to address the type of cost sharing it will allow as well as an institutional reporting policy.

Clinical Research & Life Sciences Compliance Conflicts of Interest

- The enforcement focus on COI has heightened recently.
- OHRP and Congress have pursued investigations, suspended the distribution of research funds, and issued fines and penalties for organizations that have run afoul of the regulations.
- Government agencies have considered COI a matter affecting both the integrity of the research study and the stewardship of federal resources.
- The mere appearance of a COI may damage a person's or a research organization's reputation.

What Should Research Organizations Do To Deal with COI Risks?

Assess existing COI infrastructure. Develop, vet, and disseminate organizational COI policies. Devise and implement a reporting, evaluation, and management process review by an internal conflict of interest committee (COIC).

9/13/2016 25

Additional Research Compliance Risk Areas

- Use of Subcontractors and management of sub-recipients and the research they do.
- Access and use of Protected Health Information for research purposes.
- Research Pharmacy compliance with FDA laws and regs.
- Oversight of INDs and IDEs and ensuring that the responsibilities of a research "sponsor" are met.
- Compliance with Good Clinical Practice Standards
- And many more…..

9/13/2016 26

Clinical Research & Life Sciences Compliance The Need for a Programmatic Approach

- The myriad regulatory schema, oversight agencies and enforcement all reinforce the importance of an effective clinical research compliance program.
- A strong clinical research compliance program should be multifaceted.
- To be effective, it must safeguard the integrity of the research, protect resources, and shore up the reputation of the organization and individuals conducting research.
- Another high priority of a research compliance program is to ensure that human subjects who volunteer to participate in clinical research are fully informed of the risks and benefits of the research study in which they are participating.
- Developing and maintaining a robust compliance program may not be easy, but it is an essential component of clinical research.

Research Compliance and Clinical Research

What is Compliance?

Compliance is a comprehensive program that helps institutions and their employees conduct operations and activities ethically; with the highest level of integrity, and meet legal and regulatory requirements.

Research Compliance Motivators

- Research volume and complexity are increasing
- The number of research constituents is increasing
- Broader, multiple and nontraditional collaborations
- Shift from “traditional” funding to alternate funding sources and sponsors
- Numerous areas exist for potential non-compliance
- Increasing focus on requirements/enforcement
- The risks associated with non-compliance are high
- Changes in healthcare regulation/system
- Increasing external access to information

Research Compliance Environment

Fiscal	Research Conduct
• Award monitoring • Cost sharing • Cost transfers • Direct charging practices • Effort reporting • Pre-authorized spending authority • Program income • Service and recharge centers • Sub awardee management • Other support	• Animal subject protections • Human subject protections • Conflicts of interest • Biosafety & select agents • Environmental health & safety • Laboratory safety • Invention licensing, disclosure & reporting • Scientific misconduct & research integrity • Data and information security

Case for a Research Compliance Program

- Good business practice
- Expected as part of a comprehensive compliance program
- Enhances public trust
- Meets expectations of internal and external constituents
- Establishes institutional expectations and accountability
- Provides real time insight into current issues which facilitates identification and prevention of significant compliance issues
- Reduces negative impact of having non-compliance identified by external regulators or agencies
- Reduces/prevents civil/criminal enforcement by regulatory agencies
- Provides structure for continuous quality improvement
- Promote 'engagement' between research administration office and research community
- Helps ensure research integrity and high quality data

Characteristics of an Effective System for Research Oversight

- Proactive
- Objective
- Consistent
- Authoritative
- Autonomous
- Transparent
- Accountable

Common Contributors to Compliance Problems

- Inadequate resources
- Lack of understanding of roles and responsibilities
- Inadequate training and education
- Outdated or nonexistent policies and procedures
- Inadequate management systems (e.g., effort reporting, financial management)
- Perception that internal control systems are not necessary
- Poor communications between components

The Challenge

Develop a research compliance program that:

- Establishes a culture of consciousness
- Promotes ethical conduct
- Ensures that regulatory requirements are met
- Make operational sense
- Is achieved with the least burden possible

Critical Program Elements

- Leadership
- Organizational Compliance Structure
- Written Policies and Procedures
- Effective Training and Education
- Effective Lines of Communication
- Evaluation Process
- Responding to Detected Offenses
- Established Disciplinary Guidelines

Leadership

- Governing authority oversight
  - Knowledgeable about content and operation of the program
  - Exercise oversight regarding implementation and effectiveness
- Designated high-level individual with overall program responsibility
  - Has adequate authority and resources
  - Reports directly to governing authority or subgroup
  - Committee/Advisory Council
- Defined delegation
  - Overall program responsibility
  - Specific area responsibility
  - Day-to-day responsibility

Organizational Compliance Structure

- Identify compliance requirements
- Define functional components of the program
- Designate/confirm responsibility
  - Policy and Procedure section
  - Roles and responsibilities matrix
- Compliance vs. Operations
- Ensure communication and education

Policies and Procedures

- Describes roles, goals, standards and expectations
- Documented
- Current/Updated
- Clear/Concise
- Consistent – internal and external harmonization
- Reviewed
- Implementable
- Accessible
- Known
- Archived

Training and Education

- Required vs. optional
- Known
- Focused
- Current/comprehensive
- Consistent
- Targeted
- Multiple formats
- Adult education
- Tracked and enforced

Effective Lines of Communication

- Expectations, requirements, policies, and structure of the program
- Between program components
- Sentinel event reporting
- Mechanisms to report questions, concerns or complaints

Responding to Detected Offenses

- Investigative process for all concerns, complaints and non-compliance
- Roles and responsibilities clearly identified
- Mechanism for gathering complete information
- Opportunity for input by all parties
- Regulatory determination process
- Corrective action plan
- Reporting procedures

Evaluation Process

- Based on
  - Risk analysis
  - Internal incidents, review, monitoring, and audits
  - External audits, reviews, enforcement actions
  - New or developing programs, regulations, guidance or risk
  - Best practice benchmarking
- Types
  - Program assessment
  - Monitoring
  - Quality Review
  - Auditing

Established Disciplinary Guidelines

- Clear, known process
- Defined, empowered deciding official or group
- Possible/allowable consequences
- Internally and externally consistent
- Defined range of actions/escalation
- Enforced
- Appeal process (if any)
- Punishment vs. Corrective Action

Questions?