A Wake Up Call for Investigators Involved In Human Subject Research
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In recent years, research at many academic medical centers has outpaced growth of the research infrastructure. One area greatly impacted by the growth is Institutional Review Boards or (IRBs). IRBs review clinical trial protocols and other research studies with the goal of protecting the interests of study subjects who participate in these trials. During the past twelve months alone, the increasing volume of protocols and tightening regulatory requirements have resulted in the suspension of clinical research at approximately ten prominent research institutions. Moreover, the Office for Human Research Protections (OHRP) was administratively reassigned to the Department of Health and Human Services and out of the National Institutes of Health as a way to heighten the profile of this office. In addition, the Department of Health and Human Services has proposed fines for failure to maintain compliance with human subject’s research regulations. These fines (up to $250,000 for investigators and $1,000,000 for institutions) demonstrate the agency’s commitment to enforcing existing statutes. The suspensions, related media and regulatory scrutiny, and recent regulatory activities have motivated the clinical research industry and IRBs specifically to seek external consulting to assist with compliance-related efforts.

The typical topics included in OHRP reviews from the past include: investigator roles and responsibilities, training and education, financial conflict of interest, financial management of sponsored projects, clinical trial data safety and monitoring, Bayh-Dole Act/Invention and Patent Reporting, clinical gene transfer research, and hazardous waste disposal efforts. These efforts have extracted millions of dollars in fines and penalties, including suspension of human subject research.

Most recently, as a result of the death of a healthy research volunteer and a recent site visit, the OHRP suspended Johns Hopkins University’s (JHU) Multiple Project Assurance and ordered all human subject research to be suspended. The study in question related to “Mechanisms of Deep Inspiration-Induced Airway Relaxation” and the use and study of “hexamethonium”. The OHRP review led to 31 total findings. Seven of the findings related to the specific study, and 24 of the findings related to human subject protections under MPA M-1011. The result of the findings included the suspension of all activities under MPA M 1011, exclusion per the regulations—i.e. “continue experimental protocols when stopping would be detrimental to the subject’s well-being.”

The specific findings related to the trial in question included:

- The investigator failed to learn of the known association of hexamethonium and lung toxicity
- Hexamethonium is not FDA approved currently for use in humans
- Inhalation was never an approved route of administration
- The investigator used a lab grade drug
- No request was made for information regarding pharmacology and toxicity of inhaled hexamethonium in animals or safety in humans
- There was inadequate informed consent—the consent form did not indicate that hexamethonium was experimental and not approved; hexamethonium is referred to as a medication in the consent form; the consent form did not include a plan for escalating dosages; the consent form did not adequately describe foreseeable risks; and there was not prompt reporting of unanticipated events

The selected findings related to the IRB procedures included that:
- Quorum and membership require clinical review
- The key eight elements of informed consent were missing
- Protocols were reviewed in groupings
- There were conflicts of interest with IRB members
_ There was inappropriate use of expedited procedures
_ There was difficulty in the level of informed consent documents
_ The IRBs and staff were overworked
_ There was a failure to document specific findings regarding children and prisoners
_ Approval letters were issued prior to conditions being met
_ There was a lack of documentation of meeting of specific conditions when waiving or altering informed consent
_ There were inconsistencies in adverse consent reporting

As a result of these activities at JHU and other institutions, institutions that conduct human subject research have conducted evaluations of their internal controls and compliance with OHRP, FDA and other regulatory requirements. Risk assessments of human subject research can include a multitude of activities, but at a minimum, should include the following work steps:
_ Interviews with the President of the investigators responsible for the trials under review, lab coordinators involved in the trials under review, other key administrative staff members including representatives of the Clinical Trials Office, representatives of any Clinical Review Organization (CRO) involved in the studies in question, and other key academic leaders for research
_ Reading of any documentation from any CROs involved in the studies in question
_ Analysis of all IRB files for all protocols involved in the studies to be reviewed
_ Reading of all minutes of the IRB meetings related to the studies to be reviewed
_ Listening of all audiotapes of IRB meetings related to the studies to be reviewed
_ Reading of all time and effort reports for those individuals who worked on the studies to be reviewed
_ Reading of any adverse event reports or incident reports related to the studies to be reviewed
_ Reading of select medical records for the subjects of the studies
_ Reading of all consent forms for all subjects involved in the studies in question
_ Review of all conflict of interest disclosure forms signed by the study investigators, members of the IRBs, and other relevant staff members related to the studies in question
_ Reading of all multiple project assurances related to the studies in question
_ Review of any other relevant documentation related to the studies in question
_ Reports and recommendations for corrective action
_ Ongoing monitoring and assessments of compliance

The risk assessments should be designed to ensure that grantees have adequate internal controls, and that grantee’s provide adequate oversight of individual research grants. Grantees should develop a process to review progress reports and financial reports of grants on an ongoing basis, as well as audit reports, and correspondence related to grants. Moreover, site visits should be performed as necessary to ensure that documentation reflects actual practice.

Finally, a thorough review of research billing should also be performed to ensure that a sound process exists to prevent billing to both research grants and subject insurance as well. Although these efforts are not a guarantee that the government will not come calling, they certainly demonstrate due diligence in attempting to maintain a best practice environment for conducting human subject research.