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Donnetta Horseman (dhorseman@coh.org, linkedin.com/in/donnetta-horseman-193a388/) is Senior Vice President, Chief Ethics and Compliance Officer at City of Hope, based in Duarte, CA.

Gabriella Neff (gabriella.neff@moffitt.org, linkedin.com/in/gabriella-neff-91b95b13) is Research Compliance Officer at H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

Dawn N.L. Pittinger (dawn.pittinger@moffitt.org, linkedin.com/in/dr-dawn-n-l-pittinger-31824148) is Research Financial Compliance Officer at H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

Research compliance fundamentals and risks

by Donnetta Horseman, Gabriella Neff, and Dawn N.L. Pittinger

Research is fundamentally different from other operational activities of a healthcare organization and, at times, can be overwhelming. Research compliance and the regulatory environment surrounding research are increasingly complex and apply when conducting research in a healthcare setting. This article outlines the various compliance issues and regulations specific to research.

Human subject research and protection

The Nuremberg Code of 1947 initially created human subjects research protections in response to the horrific and cruel experiments in Nazi concentration camps during World War II. The subsequent Declaration of Helsinki[1] (1964) and *The Belmont Report*[2] (1979) further strengthened protections and established the three fundamental ethical principles for research involving human subjects:

1. *Respect for persons* – respecting the autonomy of and equally protecting all individuals, including persons with diminished autonomy;
2. *Beneficence* – protecting subjects from harm by maximizing possible benefits and minimizing potential harms; and
3. *Justice* – individuals should be equitably represented in research by fair distribution of the risks and benefits.

The International Conference on Harmonization and Good Clinical Practice was established in 1976 to further protect human subjects by establishing international ethical and scientific quality standards for designing, conducting, recording, and reporting clinical trials involving human subjects.

The U.S. Department of Health and Human Services (HHS) regulates human research supported by federal funds

and the use of investigational drugs, biologics, and devices. HHS Office of Human Research Protection was created in 2000 to lead HHS efforts to protect human subjects and provide oversight of the "Common Rule," which is the short name for "The Federal Policy for the Protection of Human Subjects." The Common Rule represents the accumulation of all human research protection principles. Compliance with these standards provides assurance that the rights, safety, and well-being of trial subjects are protected and that clinical trial data is credible.[3]

FDA regulations

Over the years, regulations relating protecting the US public evolved simultaneously with human subjects' protections. The Food and Drug Administration (FDA) was established in 1906 to enforce food, drug, and cosmetic protections for the US public. But as science and clinical trials advanced, new ethical and regulatory challenges were discovered, requiring updates to clinical trials' ethical and legal framework.[4]

Following World War II, medical research expanded, as did new ethical concerns surrounding protecting research subjects in clinical trials—particularly after the Nuremberg experiments. In 1947, a randomized controlled trial to treat pulmonary tuberculosis with streptomycin was conducted in Britain and triggered ethical concerns around placebo versus active treatments.[5]

In the late 1950s, thalidomide was given to pregnant women to treat nausea. It was discovered to cause severe birth defects and infant deaths within a few years and was banned in Europe. As a result of this tragedy, the US and countries worldwide adopted requirements for systematic testing of pharmaceutical products for developmental and reproductive toxicity before marketing. Consequently, in 1962, the Kefauver–Harris Amendments were passed, strengthening the FDA's controls over drug trials and changing how new drugs are approved and regulated.

And finally, in 1980, the FDA transferred under the purview of HHS, where it currently has oversight of the protection of human subjects, institutional review boards (IRBs), investigational drugs, investigational devices, biologics, the safety of the nation's food supply, cosmetics, and products that emit radiation. Understanding of and compliance with these regulations is necessary to ensure that clinical trials are conducted appropriately, and human subjects are protected.[6]

Animal use and welfare

HHS Office of Laboratory Animal Welfare (OLAW) oversees the care and use of animals in research in any public or private organization, business, or agency. No substitute exists to match the complexity of the human structure or function. Without an existing replacement, animals will play a critical role in helping researchers test potential new drugs and medical treatments for effectiveness and safety.

Animals are used in scientific research because they are biologically similar to humans. In fact, mice share more than 92% of human DNA. In addition, animals are susceptible to many health problems like humans—such as cancer, diabetes, and heart disease. Studying animals throughout their life span and across several generations can be vital in understanding how a disease progresses and how to treat it.

Any institution using animal research requires an Institutional Animal Care and Use Committee (IACUC), which oversees the use of vertebrate animals in research, teaching, and testing committees. OLAW has embraced the three Rs (replacement, reduction, and refinement) as guiding principles of animal research to give researchers practical and ethical methods for using animals in research:[7]

- **Replacement** refers to achieving a research goal or objective without conducting animal experiments. Methods are employed whereby animals are replaced with suitable alternatives.
- **Reduction** refers to using methods that allow researchers to obtain comparable levels of information using fewer animals.
- **Refinement** refers to practices that reduce or eliminate the animals' pain, stress, and discomfort during experimental procedures and with the animals' daily social and physical environments.

Federal awards and grant expenditures

Managing a research portfolio that includes federally sponsored awards requires additional oversight due to the complexity of the regulations and the severity of consequences for noncompliance.

Allowable versus unallowable costs, time and effort reporting, subrecipient monitoring, cost transfers, and dealing with direct and indirect costs accounting concerns create challenges that need addressing through a solid and effective compliance program. Compliance should routinely audit awards and grant compliance to ensure adherence to the regulations.

Foreign influence

The US government has had growing concerns about inappropriate influence by foreign governments over federally funded research. In 2018, the National Institutes of Health (NIH) sent letters to thousands of academic medical centers and universities requesting investigations into faculty who had potential involvement in research outside the US, specifically in the People's Republic of China. The primary concerns were:

- Shadow labs were being established, supported by substantial funding for research conducted abroad;
- Faculty working full-time in the US were committing to working substantial amounts of time, and often full-time, in an institution in another country; and
- Benefits to faculty were significant, such as sign-on bonuses, additional salaries, housing, personal bank accounts, lab space, lab equipment, and lab personnel.

These benefits were touted as rewards for training foreign personnel, authoring papers, and developing patents and intellectual property in China. The NIH inquiry resulted in hundreds of investigators nationwide being terminated, including some False Claims Act (FCA) allegations. Some investigators have been charged and sentenced to prison as a result.

US export control regulations

Export controls are regulations affecting the export of goods, software, and technology designed to protect national security. Activities affected by export controls include:

- Any research projects involving controlled technology with an international student or researcher who may be collaborating with researchers in the US;
- Sponsored projects involving a global sponsor;
- Shipping research equipment or biologicals outside the US;
- Transactions involving sanctioned countries or parties; and

- Sharing proprietary information, technology, or software with a foreign national.

The oversight agencies for export control include:

- **Department of State** – governs military technology;
- **Department of Commerce** – governs dual-use technology (technologies that can be used for civilian purposes but may have a military use as well). Examples include chemicals, microorganisms, toxins, and marine navigation equipment; and
- **Department of Treasury** – prohibits transactions by sanctioned countries or individuals.

Even US organizations that do not have an international presence must ensure compliance with export control regulations.

Research integrity and misconduct

Research integrity and misconduct intersect as aspects of research that affect ethics and have consequences. Research integrity encompasses a set of moral principles for professional behavior that guide investigators/researchers regarding the practice, learning, training, publishing, and communication of science. Research misconduct is defined by HHS Office of Research Integrity (ORI) as fabrication, falsification, or plagiarism in proposing, performing, reviewing, or reporting research results in connection with U.S. Public Health Service (PHS) funded research. Under the policy, three distinct elements must be met to establish a finding of research misconduct.[8] Consequently, ORI is very specific that research misconduct does not include honest error or difference of opinion.

Research integrity is essential as it provides the ethical foundation for research, ultimately guiding investigators/researchers to avoid incidents of research misconduct or other ethical issues. Conducting research with integrity ensures that:

- the aims of the research are supported;
- the values needed for collaborative work are promoted;
- public support and sustainability for research are maintained;
- human and animal subjects are protected, and compliance with the laws that govern them are adhered to; and
- Investigators/researchers understand the expectations and are held accountable for their actions.

Although not required, except for NIH-funded projects, responsible conduct of research education and training can help prevent, identify, and address research misconduct and other ethical issues. ORI published a document entitled *Introduction to the Responsible Conduct of Research* that describes the federal rules and provides guidance on the accepted practices for responsible conduct of research.[9] In this document, ORI describes the nine core areas of responsible conduct of research.

A robust research compliance program is vital for organizations conducting research to ensure that research integrity and misconduct issues are addressed through appropriate policies, procedures, and education.

Conflicts of interest

Conflicts of interest refer to situations where financial or other personal considerations may compromise or appear to compromise a researcher's professional judgment in conducting or reporting research. Investigators engaged in PHS-supported research must disclose all significant financial interests to their institutions, including reimbursed and sponsored travel. This ensures objectivity and allows the organization to implement a conflicts-of-interest management plan. The investigator is the project director, and they are responsible for ensuring that all aspects of research (design, conduct, reporting) are unbiased by any conflicting financial interest. Conflicts of interest are not necessarily harmful but need to be managed appropriately. Management activities may include:

- Publicly disclosing financial conflicts of interest (to your institution, to the IRB, to staff working on the project, and when presenting or publishing research);
- Directly disclosing financial conflicts of interest to participants of a research study (usually within the informed consent);
- Appointing an independent monitor to protect the design, conduct, and reporting of research against any bias;
- Modifying the research plan;
- Changing personnel or responsibilities from participation in all or a portion of the research;
- Reducing or completely eliminating the financial conflict; and/or
- Removing the relationship that caused the financial conflict.

Conflicts of interest disclosure statements must be made before applying for PHS research funding, updated at least annually, and within 30 days of discovering or acquiring a new significant financial interest. A robust conflicts of interest program is crucial to an effective compliance program.

Clinical trial billing

Navigating and complying with applicable regulations around clinical trial billing is one of the most complex operational and regulatory challenges faced by organizations conducting clinical research. Clinical research billing noncompliance is a high-risk area watched heavily by the Department of Justice and HHS Office of Inspector General due to historical FCA violations.[10]

Accurately billing for clinical trial services requires a collaborative effort across multiple departments to achieve compliance. Lack of adequate controls can increase the risk of FCA violations, insurance fraud allegations, and improper billing, which could result in severe penalties, reputational damage, loss of federal funding, or jail time.

Research billing compliance refers to the adherence to applicable federal and state laws, regulations, institutional policies, and billing rules governing research-related activities performed as part of a clinical trial or clinical research study separate from the direct clinical management of the patient. Compliance with research billing regulations aims to prevent fraud, waste, and abuse and protect the financial integrity of the organization and its clinical research participants.

Infrastructure, collaboration, and communication are vital to maintaining oversight and addressing compliance with the research billing life cycle. Research billing compliance oversight includes but is not limited to the following areas:

- billing for items or services paid for by a sponsor or other agency to prevent double billing

- billing for items or services promised free to the participant in the informed consent form
- billing for items or services completed for research purposes only and not billable under the Centers for Medicare & Medicaid Services Clinical Trial Policy[11]
- documentation of billing designations for items or services performed as part of the clinical research study
- identification of subjects enrolled in a clinical research study
- charge capture and a claims review process for all research participants
- charge segregation
- processing claims with payer-mandated research coding
- processing of protocol, budget, or contract amendments
- claim denials
- inadequate financial accounting and reconciliation

Clinical research billing compliance infrastructure refers to the processes, procedures, and controls in place to accurately set up a clinical research study, document the responsible payer and appropriate billing designations, document the costs associated with clinical research studies, and effectively conduct accurate back-end reconciliation. The impact of clinical research billing infrastructure is critical to ensuring that clinical research studies are conducted compliantly from a financial perspective. It helps reduce the risk of noncompliance, control costs, generate revenue, and streamline processes—all of which are essential for the successful completion of clinical research studies.

The impact of clinical research billing infrastructure can be significant in several ways:

1. **Compliance:** Proper clinical research billing infrastructure ensures that all costs associated with the study are billed appropriately and in compliance with applicable regulations and guidelines. This helps reduce the risk of noncompliance, which can result in financial penalties and legal consequences.
2. **Cost control:** Clinical research billing infrastructure helps accurately track and document study-related costs, which can help control expenses and ensure that the study stays within budget. This is particularly important in more extensive studies where costs can quickly escalate.
3. **Revenue generation:** In some cases, clinical research billing infrastructure can also help generate revenue for the organization. For example, if a pharmaceutical company sponsors the study, the organization can charge the sponsor for items or services conducted for research purposes only and provided as part of the study protocol.
4. **Streamlined processes:** A well-established clinical research billing infrastructure can also help streamline clinical research studies' billing and documentation processes and reduce risk of noncompliance. Additionally, streamlined processes can reduce administrative burdens and free up resources for other tasks.

Additional considerations for why a robust research billing compliance program is necessary and could benefit the organization include the following:

1. **Legal compliance:** Research institutions must comply with federal, state, and local regulations and guidelines for billing research-related services. Noncompliance can result in significant financial penalties, loss of funding, and legal action.

2. **Ethical standards:** The billing of research-related services is subject to ethical standards, including informed consent, privacy, confidentiality, and protecting participants, including vulnerable populations. Adhering to these standards is imperative to maintaining the integrity and credibility of the research study and the organization's reputation.

Knowledge of research billing compliance fundamentals can benefit staff in several ways. The following are some possible benefits:

1. **Avoiding legal and financial penalties:** Compliance with research billing regulations can help the organization avoid legal and financial penalties resulting from noncompliance.

2. **Maintaining ethical standards:** Research billing compliance helps ensure that the research is conducted ethically and with integrity. This can help staff avoid any ethical breaches or harm to study participants.

3. **Protecting institutional reputation:** Noncompliance with research billing regulations can harm the reputation of the institution conducting the research. Complying with these regulations can help staff maintain the institution's reputation and credibility.

4. **Reducing errors and inefficiencies:** Proper compliance with research billing regulations can help staff avoid mistakes and inefficiencies in the billing process. Proper compliance can result in faster payments, reduced administrative costs, improved financial management, and increased quality.

5. **Facilitating communication with sponsors:** Compliance with research billing regulations can help staff communicate more effectively with sponsors and other stakeholders involved in the research. This can lead to better relationships with sponsors, activation timeline improvements, and more successful collaborations.

Finally, effective clinical research billing compliance programs can help improve the financial sustainability of clinical research programs. Institutions can maximize their revenue and reinvest these funds into future research projects and staffing by ensuring that research services are appropriately billed and reimbursed.

Conclusion

Clinical research billing is a necessary process that ensures the ethical and legal management of clinical research studies' financial aspects, protects study participants' economic well-being, and provides organizational compliance with federal and state regulations while improving the financial sustainability of clinical research programs. Understanding the complexities of research billing compliance can help the organization avoid legal and financial penalties, protect participants, protect the organization's staff, maintain ethical standards, protect institutional reputation, and reduce errors and inefficiencies.

Takeaways

- Research compliance is extremely important and complex.
- Compliance with these human subject research protection standards provides assurance that the rights, safety, and well-being of trial subjects are protected, and clinical trial data is credible.
- A robust research compliance program is vital for organizations conducting research to ensure that

research integrity and misconduct issues are addressed through appropriate policies, procedures, and education.

- Effective clinical research billing compliance programs can help improve the clinical research programs' financial sustainability.
- Noncompliance can result in significant financial penalties, loss of funding, and legal action.

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