Review Article

Basic Principles for Conducting Human Research in Orthopaedic Medicine

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Abstract

Researchers and clinicians operate in an increasingly complex clinical and regulatory environment in which understanding the principles governing human research is essential. However, most orthopaedic surgeons have not received in-depth training in regulatory requirements and scientific research methods. Ensuring that research is conducted in accordance with state and federal laws and ethical principles is essential to guard compromising patient information and avoid severe penalties for noncompliance. The researcher must understand the regulations for compliance and proper data management, including the requirements of the Health Insurance Portability and Accountability Act, proper application of informed consent, use of the Institutional Review Board, and data protection guidelines. Tools such as a regulatory binder can assist investigators in complying with requirements, maintaining regulatory standards, and ensuring a robust study design and conduct.

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Orthopaedic research is fundamental to addressing the healthcare challenges of aging populations worldwide. Although orthopaedic surgeons are the front line for research in orthopaedic medicine, most have not received in-depth training in regulatory requirements and scientific research methods. Moreover, it is difficult for most practicing surgeons to devote significant amounts of their time to clinical research.

Knowing the legal requirements, being able to apply the relevant rules and regulations, and having knowledgeable support staff are all essential to properly conduct and manage a clinical research program. Here, we present a research guide for orthopaedic surgeons and clinical research coordinators who conduct orthopaedic clinical research, providing detailed information on research regulations and compliance, Institutional Review Board (IRB) procedures, and the basic principles of data handling and security of protected health information.

Overview of Research Regulations

Orthopaedic investigators must develop an understanding of basic research concepts, laws, and regulations to carry out human subject research and ensure that studies are conducted properly. Human subject research is defined as any systematic investigation that involves a living person, with identifiable private information or data obtained through an intervention or interaction that is designed to contribute to generaliz-

able knowledge.[1] The foundation for quality clinical research entails safeguarding the integrity of human subject research and protecting study participants, while operating in accordance with federal rules and regulations.

History

The current rules and regulations governing good clinical practices (GCP) and human subject protection (HSP) are based on ethical guidelines and a history of clinical research oversight. The research conducted by Nazi physicians is one of the most infamous historical examples of unethical research; they subjected concentration camp prisoners to lethal experiments, and the physicians were subsequently tried at the Nuremberg trials at the end of World War II.[2] The 1947 Nuremberg Code was developed as a result of the trials; it was a set of 10 ethical guidelines for human experimentation that focused on the fundamental rights of research participants and the responsibilities of research investigators.[3]

Additional stories of abuse of authority in the name of science, ethical lapses, and research study scandals led to the formulation of the World Medical Association's Declaration of Helsinki in 1964. This document is the cornerstone of ethical principles for medical research involving human subjects and data and expands the Nuremberg Code guidelines. The declaration morally binds physicians to the fundamental principles of respect for the individual right to self determination, the right to make informed decisions, and the investigator's duty to the patient and to uphold HSP above the interests of science and society.[4]

Ethical documents such as the Declaration of Helsinki and the subsequent Belmont Report of 1979 are the foundation for most of the FDA's mission, as described in the Code of Federal Regulations (CFR). The Belmont Report articulates three core ethical principles governing clinical research: respect for persons (ie, protecting autonomy and allowing informed consent), beneficence (the research must maximize benefits and minimize risks), and justice (the research must not exploit any group to benefit another).[5]

Failure to comply with clinical research laws and regulatory requirements can result in severe consequences. Patients can experience unfavorable outcomes or have their private information compromised. The established ethical and regulatory framework applies to all human subject research, including investigator-initiated and industry-sponsored research. In addition, adherence to local state laws governing clinical research is imperative for research teams. State regulations can differ with regard to specific aspects of human subject research such as informed consent; researchers should be aware of and observe state regulations. It is important to note that the principal investigator (PI) be responsible for compliance with all related federal and state laws and regulations, code of ethics, and GCP; therefore, it is critical that the PI be aware of the responsibilities associated with the role and consider these responsibilities each time a new study is initiated.

The Office for Human Research Protections (OHRP) and the FDA have the authority to suspend research at institutions.[6] In 2001, OHRP suspended federally funded research at Johns Hopkins University School of Medicine, halting approximately 2,400 research protocols for inadequate protection of human research subjects.[7] Noncompliance can also result in fines, withdrawal of investigator funding, and lawsuits.[8]

Scientific Misconduct and Conflict of Interest

The well-established relationship between industry and academia has become increasingly complex. Although this relationship has proven to be beneficial in translational research settings, it has created a variety of situations that have the potential to lead to ethical compromises. These issues most commonly involve scientific misconduct and conflict of interest. Scientific misconduct includes activities such as falsification of data and/or plagiarism.[9] Conflict of interest is defined as a "conflict between the private interest and the official responsibilities of a person in a position of trust."[10] Examples of such circumstances include situations in which the investigator of a product also holds an equity position in the company that produces the product or situations in which a lecturer may receive considerable research or consultant funding from a company that markets a product mentioned in the lecturer's presentation.

In these situations, ethical questions arise regarding whether these relationships and funding sources will influence the judgment of the investigator; concerns over balancing personal gain versus the standards of objectivity and intellectual honesty may have to be considered. In general, although there have been cases of scientific misconduct, the area of conflict of interest has been most problematic, resulting in the development of institutional disclosure policies and other guidelines. Financial disclosure and authorship criteria should be consistent with the criteria established by the International Committee of Medical Journal Editors.[11]

Because of the increasing complexity of clinical and regulatory environments, an understanding of the rules and regulations for conducting hu-

man research is essential for the orthopaedic research investigator to avoid patient harm, misconduct, and the costly penalties of noncompliance.

Institutional Review Boards

IRBs are ethics committees that review and monitor human subject research. The primary purpose of the IRB is to ensure that necessary measures are in place to safeguard the privacy, confidentiality, rights, and privileges of human research subjects. The OHRP and the FDA regulate IRBs, which can be categorized as one of three types: local, central, or commercial. Local IRBs are typically affiliated with an institution or organization that conducts research (eg, university, hospital) and are located at or near the study site. Central IRBs are commonly used for large, multisite clinical trials. Commercial IRBs are commercial or independent boards; they are paid, contracted agencies not affiliated with an institution or hospital.

In accordance with Department of Health and Human Services (DHHS) regulations 45 CFR 46.103(b) and 46.109(a), IRBs must review and approve all nonexempt human subject research before initiation. Ensuring HSP is the responsibility of the IRB that reviews research protocols. IRBs have the authority to review, approve, and disapprove research studies. They also may request modifications of human subject research. Currently, federal regulations do not require IRB review of privately funded protocols unless they are subject to FDA regulation. However, institutions designated on a federal-wide assurance formally commit themselves to comply with regulation 45 CFR part 46 through an approved contract with OHRP, and their IRBs may oversee HSP for all institutional research regardless of funding status. The commitment to the OHRP does not reduce the medical, ethical, and legal responsibilities of private investigators who are subject to institutional policies and regulations. There is a legal requirement, however, for IRB review of all federal-funded research. Table 1 lists the requirements for human subject research applications submitted to the IRB and the basic review criteria used for approval.[1] DHHS regulations 45 CFR 46.103 and 45 CFR 46.113 grant IRBs the authority to suspend or terminate approval of research that is not conducted in accordance with federal law and IRB requirements or that has been associated with unexpected risk to subjects, serious or continuing noncompliance, or inadequate reporting.[1,12]

In research protocols that involve human subjects, the IRB can employ one of three levels of review, including exempt, expedited, or full board review[12] (Table 2). Because the IRB makes the final determination of the proper review category, consulting the IRB early in study development can aid the researcher in selecting the correct

Table 1

Basic Institutional Review Board Application Requirements and Review Criteria

1. A complete description of proposed research
2. Potential risk to anticipated benefits analysis, ensuring that risks to subjects are minimized
3. Outlined risks are reasonable relative to the anticipated benefits
4. Equitable selection of subjects in terms of gender, race, and ethnicity
5. Scientifically valid research design and methods
6. Description of the process of obtaining and documenting informed consent
7. Plan for adequate data collection, storage, and safety monitoring
8. Appropriate safeguards for protection of vulnerable subjects (eg, children, prisoners)
9. Adequate subject privacy and confidentiality provisions

Table 2

Institutional Review Board Levels of Human Subjects Research Review

Level of Review	Description	Research Example
Exempt	No risk or minimal risk research that falls under one or more categories outlined in 45 CFR 46.101(b), which is not subject to IRB continuing review	A retrospective chart review of pre-existing, de-identified data such as evaluation of databases made by authorities such as Medicare
Expedited	Minimal risk research that meets 45 CFR 46.110 requirements and falls under one or more categories outlined in 21 CFR 56.110	A questionnaire-based survey of patient attitudes toward hip replacement before surgery
Full board	Research that does not qualify for exemption or expedited review	A randomized, investigational trial of a knee prosthesis device before FDA approval

CFR = Code of Federal Regulations, IRB = institutional review board

review type for submission and understanding the policies and procedures of the IRB as they apply to the specific study being designed. After approval of the study, there are provisions to monitor ongoing research to ensure HSP remains in place after initiation of the study; this is referred to as continuing review.

IRBs are responsible for conducting a continuing review of studies at intervals appropriate to the degree of risk, but at a minimum of once a year. Continuing review of research includes consideration of adverse events, unanticipated problems, risk assessment, interim findings, and any recent literature or new information relevant to the research study. Expedited and full board review studies are subject to continuing review, and their IRB approval must be renewed at least annually. Continuations provide the IRB the opportunity to review study progress and reassess HSP. No project can be continued past the approved performance period. It is the PI's responsibility to submit the required continuing review information for timely IRB continuation approval to prevent noncompliance and/or a lapse in study conduct.

Studies Exempt From IRB Review

Studies that are considered exempt from review still require review by the IRB chair or designee to certify that they qualify for exemption. The IRB does not actually approve exempt studies but makes the determination that the research falls under one of the six federal exempt categories listed in 45 CFR 46.101(b).[1] Exempt research includes educational research; educational tests, interviews, surveys, or public observation in which personal identifiers are not collected; studies that use existing publicly available or anonymous datasets or specimens; research on public benefit or service programs; and taste and food quality studies. Research that uses de-identified laboratory specimens or data, anonymous interviews or surveys, and retrospective chart reviews in which all data are de-identified before any analyses are conducted are also exempt. Data anonymization removes any subject identifiers and linking codes. Exempt research involves no risk or minimal risk of harm to subjects and their protected information. The regulatory definition of minimal risk is based on the assessment that the probability and magnitude of any harm or discomfort anticipated in the research is not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Studies that may place subjects at risk of criminal or civil liability; that may be damaging to financial standing, employability, or reputation; or that involve vulnerable populations do not qualify for exemption. Vulnerable populations include prisoners, pregnant women, fetuses, neonates, cognitively impaired persons, children, students, and employees. These populations require additional consideration or protections; therefore, studies that involve these groups are not eligible for exemption.[1] Exempt research is not subject to continuing review unless the study is modified to change the exemption determination or there is unanticipated, increased risk to the study participants.

Studies That Qualify for Expedited IRB Review

Research eligible for expedited review must involve no more than minimal risk of harm to subjects and protected information and fall under at least one of the nine categories for expedited review listed in 45 CFR 46.110 and 21 CFR 56.110.[1,13,14] In general, expedited review does not apply to studies that involve vulnerable populations; that involve treatment of patients with anything other than standard care or risk to study subjects (eg, prospective collection of data or specimens through noninvasive means); and that involve behavioral research. Although studies approved by the IRB's expedited review procedures have a low risk of harm to human subjects, the studies must still follow the applicable regulations for human research, including appropriate consent procedures. Research that involves a medical device cleared or approved for marketing and used in accordance with its labeling may qualify for expedited review according to 21 CFR part 812.[15] Expedited review may also be used when requesting minor changes to a previously approved research protocol. Changes are considered minor if they do not affect HSP and/or human subjects' discomfort, risk, and benefit. Expedited research is subject to continuing annual IRB review and approval.

Studies That Require Full Board IRB Review

Any proposed research that does not fall into either the exempt or expedited review categories requires a full board review. This level of review is the most rigorous and takes longer to approve than does an exempt or expedited review because it requires the full IRB board to convene and make a decision. Research in this category may include studies that involve treatment interventions with greater than minimal risk, studies that include vulnerable populations, or studies that involve sensitive topics such as criminal behavior or sexuality. Research that requires full board review is subject to continuing annual IRB review and renewal.[12]

Proper Administration of Informed Consent

Prior to conducting any research-related procedures, informed consent must be obtained voluntarily from persons eligible to participate in the study. Informed consent for a research study is distinct in process and content from informed consent for standard treatment (eg, surgical procedures) or standard Health Insurance Portability and Accountability Act (HIPAA) consent. The purpose of clinical informed consent is to provide the patient with enough information about a procedure or treatment to enable them to make a decision regarding the proposed care.

Research informed consent has two essential parts: the process and the proper documentation. For research studies, the informed consent process begins from the time of initial contact with a potential study subject. It helps to ensure the rights, safety, and welfare of research participants and helps each study subject fully understand the study itself and what his or her participation entails. Basic requirements of the process include presentation of the research purpose, procedures, risks, potential benefits and, most importantly, the rights of the study participant. The subject's agreement must be documented via a signed and witnessed informed consent form that has been approved by the IRB unless an oral consent process or the need for consent is waived by the IRB. Persons responsible for obtaining a subject's informed consent include clinical investigators and their IRB-approved designees. The informed consent process is interactive and ongoing throughout a study, and new questions from the subject and/or study-related information can be presented anytime while the study is conducted. The signed informed consent document is critical to regulatory compliance, and the period for record retention is dictated by sponsor contracts or FDA and DHHS regulations.

The informed consent document provides a summary of the clinical research study and serves as the basis for conversations between the subject and research team. Oral or written consent must be presented in a language understandable to the subject and cannot contain any exculpatory language that waives or appears to waive the subject's legal rights. If informed consent is presented orally, a witness and written summary of the process are required. Before submitting a study for initial review by the IRB, investigators should determine the local IRB requirements for informed consent documents. Many IRBs have standard language or formats for consent elements, including voluntary participation, confidentiality, compensation, and answers to questions.[16]

Under limited circumstances, the IRB may grant a waiver of informed consent or written documentation of informed consent. This is granted only when the study's risk assessment profile is low and obtaining consent is not practicable. The specific situations allowing waiver of informed consent are identified in 45 CFR part 46.116 and include (1) research that involves no more than minimal risk; (2) cases in which waiver or alteration of consent will not adversely affect the rights and welfare of the subjects. Waivers of informed consent are also allowed for (3) research that cannot practicably be performed without the waiver or alteration of consent and, when appropriate, (4) for studies in which the subjects will be provided with additional pertinent information after participation.

An example of waiver of consent that may be approved by the IRB is the use of de-identified medical records to retrospectively evaluate the factors that influence the need for blood transfusion. In this case, researchers are collecting limited data that is assigned a random code with a link available only to researchers, and the data are maintained in a secure database. The research does not affect clinical care because the patients have been discharged from the hospital.

According to 45 CFR 46.117(c), the IRB can also waive the requirement for obtaining signed consent if the board determines that (1) the only record linking the subject and the research is the consent document, with the principal risk being the potential harm caused by a breach of confidentiality, or (2) the research presents no more than minimal risk of harm to human subjects and involves no procedures for which written consent is normally required outside of the research context.[1]

Data Handling

Distinguishing between data used for medical practice and that used for human subject research is imperative, especially when there is overlap. Clinical care includes diagnosis and/or treatment intended to improve the well-being of an individual patient with a reasonable expectation of success. Research activities are designed to test a hypothesis that may ultimately contribute to generalizable knowledge.[5] The determination of what constitutes human subject research depends on the type of information collected, the manner and procedures for information collection, and how the information will be analyzed and disclosed.[12]

Practicing clinicians and researchers must be aware of the HIPAA Privacy Rule, which specifically outlines

Table 3

Health Information Portability and Accountability Act Direct Identifiers[17]

1.	Names
2.	All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geographical codes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
	A. The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people
	B. The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3.	Telephone numbers
4.	Facsimile numbers
5.	Electronic mail addresses
6.	Social security numbers
7.	Medical record numbers
8.	Health plan beneficiary numbers
9.	Account numbers
10.	Certificate/license numbers
11.	Vehicle identifiers and serial numbers, including license plate numbers
12.	Device identifiers and serial numbers
13.	Web Universal Resource Locators
14.	Internet Protocol address numbers
15.	Biometric identifiers, including finger and voice prints
16.	Full face photographic images and any comparable images
17.	Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification
18.	All elements of dates (except year) for dates directly related to a person, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.

the requirements for protecting each patient's personal information, and the circumstances under which protected health information (PHI) can be used or disclosed for research purposes. PHI is defined as individually identifiable health information that includes demographic and other information related to the health of an individual treated at regulated institutions (ie, "covered entities") and that is transmitted or maintained in electronic media or any other form. The Privacy Rule applies only to covered entities, which are defined as (1) healthcare providers; (2) health plans; and (3) healthcare clearing houses that transmit health information for which the DHHS has adopted a standard. Covered entities may use or disclose PHI only as permitted under the Privacy Rule provisions; failing to follow these provisions can subject both persons and institutions to civil or criminal monetary penalties, loss of funding, and even imprisonment. The Privacy Rule establishes federal standards to protect the privacy of the information and outlines specific procedures for researchers to access and use PHI for research.

According to the Privacy Rule, health information that is de-identified may be used or disclosed without restriction. De-identified health information is not considered PHI and is not subject to the state and federal privacy laws. De-identification requires removal of all 18 information categories specified as direct identifiers[17] (Table 3). HIPAA also outlines a third method of maintaining privacy, referred to as a limited data set. Under this method, 16 of the 18 specified identifiers are removed, with security provisions in place to safeguard the remaining data. A limited dataset can include dates relating to a person, other codes or numbers not listed as direct identifiers, and geographic data limited to town, city, state, and zip code, but no street address. This dataset may be used for research, but the remaining data are considered PHI and are subject to HIPAA regulations.[18]

Data handling for collaborative research involving more than one institution typically requires a formal written agreement between academic, government, or industry organizations when institutional rights and responsibilities are affected. A confidential disclosure agreement, material transfer agreement (MTA), or data transfer agreement (DTA) are examples of contractual documents that are required to permit data transfer of human subject data. The agreements delineate data confidentiality, access, and use of the data generated; they also define intellectual property rights in accordance with applicable federal requirements and institutional policies. An MTA or a DTA may require IRB approval before limited datasets or disclosure of human subject data can be transferred for research under an IRB-approved protocol in which individual authorization for disclosure has not been obtained.[18] A separate MTA or DTA may not be required when data handling and transfer are addressed in the study protocol or funding agreement or in the context of a larger contractual agreement.

Any clinical research study that in-

Table 4

Fundamental Regulatory Binder Requirements

1.	Study protocol (original IRB-approved version and any amended versions)
2.	IRB documentation (applications, amendments, board roster, correspondence)
3.	Laboratory documentation (CLIA certification, normal values/ranges, accreditation, certification of analysis)
4.	Subject screening and enrollment log
5.	Informed consent and assent forms (original IRB approved copy and any amended versions)
6.	Adverse events and reportable events
7.	Data safety and monitoring
8.	Study personnel documentation (training documentation, roles and responsibilities, delegation of authority, financial disclosure, curricula vitae, licenses/certifications)
9.	Investigational brochure/package insert/device manual[a]
10.	Sponsor documentation (contact information, protocol, correspondence, agreements)[a]
11.	FDA forms 1571/1572, or investigational device exemption[a]
12.	Funding information (grant applications, budgets, contracts)[a]
13.	Monitoring logs and reports[a]
14.	Drug/device accountability log[a]

CLIA = clinical laboratory improvement amendment, IRB = institutional review board
[a] Additional sections for external, industry-sponsored or FDA-regulated studies

volves intervention that changes the standard care of treatment, which represents more than minimal risk, should have a safety monitoring plan. Several different monitoring practices can be adopted based on the size and complexity of the research study, but the plan should be commensurate to the degree of risk involved. In many cases, the PI is responsible for monitoring patient safety and data integrity, which should be reviewed on a regular basis. The PI is also responsible for ensuring research data security to prevent accidental theft or modification of data, breaches of confidentiality, and premature release or unblinding of data. One method to secure data and ensure confidentiality is encryption, whereby data are encoded. Other security practices that should be implemented include backing up data and storing it in a separate location from the original, securing computers and storage devices with locks, and password protection for all computers and electronic media. Use of portable data storage devices should be avoided to prevent data compromise and loss.

Compliance With Regulations

All orthopaedic investigators are responsible for their personal compliance with all applicable laws and regulations. GCP guidelines require a complete and up-to-date regulatory binder, standard operating procedures for trial conduct, and a dated clinical study protocol.[19] Implementation of a research compliance program is an important responsibility of all healthcare institutions. Programs must be implemented in ways that promote lawful and ethical research conduct, thereby minimizing the potential risks to research subjects and the risk of serious noncompliance penalties. Compliance efforts benefit institutions, investigators, and, most importantly, human research participants. Requirements for successful implementation of compliance programs include establishing standards for conducting research, personnel training, ongoing monitoring of research conduct, and enacting corrective action plans to address any deficiencies noted. The PI of each study is responsible for ensuring that all co-investigators and study personnel comply with regulations and the IRB-approved protocol as well as documenting all study-related material and correspondence in a secure regulatory binder that is updated throughout the study and safely stored after study completion.

Some of the most common compliance issues include failure to properly follow regulations in all their detail, failure to follow the study plan, and inadequate training or experience of study personnel.[6] The regulatory binder provides the PI with an essential tool for managing the study, maintaining regulatory compliance, and ensuring high standards for human subject research. All studies should have a regulatory binder assembled before study initiation. During audits and inspections, the regulatory binder is often the first document reviewed. The regulatory binder is used to store and organize essential documents that are individually and collectively permit the evaluation of the study data and quality. Table 4 lists basic regulatory binder requirements.[19] Although the PI often delegates the maintenance of the regulatory binder to a qualified research coordinator, regulatory compliance is ultimately the PI's responsibility. Compliance tools and programs are useful in ensuring that investigators adhere to applicable laws and regulations, which is essential to the ethics and integrity of a clinical study.

Summary

With increasing regulatory oversight of human subject research, orthopaedic researchers must commit themselves to the highest standards of integrity and ethics in research and abide by all laws and regulations. Understanding the basic principles for conducting human research in orthopaedic medicine can ensure proper study conduct and avoid the potential personal and institutional consequences of noncompliance. Orthopaedic physicians and their research team members are responsible for acquiring the necessary clinical research knowledge to effectively conduct human subject research from study design to data handling and execution. A high level of scientific integrity in clinical research is integral in the development of innovative orthopaedic care solutions and contributes importantly to medical knowledge.

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Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 2, 8, 9, and 12 are level V expert opinion.

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