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Barriers (Threats) to Clinical Research*

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Clinical research encompasses a wide range of scientific investigations including case reports on a single patient, case series, retrospective studies, prospective studies, and multicenter randomized clinical trials. These activities aim to enhance our understanding of medical conditions with the intention of helping patients.

Clinical research is time-consuming, challenging, and expensive, and with current practice pressures, it can be a daunting task. An increasing number of regulatory obstacles produce further challenges to performing clinical research. Both evidence and opinion indicate that these regulatory obstacles have adversely affected the conduct of clinical research. Ninety-one percent of the audience who attended the symposium at the 2007 Annual Meeting of the American Orthopaedic Association (AOA; a clinical meeting of senior orthopaedic surgeons) in Asheville, North Carolina, characterized this threat as moderate or severe. When the attendees were presented with three negative statements about their institutional review board, which described it as (1) cumbersome, bureaucratic, and difficult to deal with; (2) more interested in protecting the institution than the patient; and (3) causing delays and unnecessary costs, 66% felt that all three applied to their board. This reflects the deep sense of frustration many clinicians have with the current regulatory process and their belief that institutional review boards are clearly obstructive to clinical research.

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This symposium explores the barriers and obstacles to clinical research provided by the Health Insurance Portability and Accountability Act (HIPAA) and by institutional review boards and presents the position that change is necessary to minimize the problems and the expense they create. Clinical research requires substantial funding, particularly for large-scale multicenter trials, which limits the number and quality of these important clinical experiments. Issues related to the funding of orthopaedic trials from the perspective of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) are reviewed. Finally, high-quality clinical research needs clinician researchers trained in the methods of large clinical trials, and this type of expertise must be developed, mentored, and financially supported with protected time.

Importance of Clinical Research

The majority of orthopaedic surgeons agree that clinical research is critically important to our specialty and benefits patients. Most attendees (73%) at the 2007 AOA meeting rated clinical research as being more important than basic-science research. The results of well-designed clinical studies should guide clinical practice, and they are the foundation on which evidence-based medicine is built[1-8].

Although prospective randomized studies are traditionally deemed to be the best study designs, the value of prospective cohort studies and retrospective studies should not be underestimated. As a result of these latter types of studies, major risk factors (or independent predictors) of a disease may be identified and perhaps modified for better prevention of that disease[5,6,9,10]. Prospective studies, on the other hand, help to evaluate the result of an intervention on eventual outcome. These studies, when randomized, double-blinded, and placebo-controlled, have the highest regard among clinicians and are the hallmark of level-I evidence. These studies require extensive investment of time, effort, and money that precludes many institutions from engaging in these projects regularly and limits the number that can be reasonably performed.

History of Institutional Review Boards and HIPAA

The Nazi physician trials in 1946 publicly exposed atrocities committed under the guise of experimental human medical research and resulted in the 1947 Nuremberg Code of human research[11]. The code established the important requirements that a subject's participation be informed and voluntary, and that such research must be scientifically valid and conducted solely for the benefit of society as a whole. The World Health Organization in 1964 expanded the guidelines for human participation in medical research, which was published as the Declaration of Helsinki[12].

The United States was not immune to grossly unethical human subject experimentation. Examples include the World War II-era study on syphilis patients at the Tuskegee Institute[13], which denied available and effective treatment to subjects, and the Willowbrook State School studies on the natural history of hepatitis that coerced parents into enrolling their mentally retarded children in a study that had no potential benefit for participants. Responding to these human rights violations, Congress passed the 1974 National Research Act[14]. Human research practices were studied further from 1974 to 1978[15], and the Belmont Report of 1979 expanded the guidelines governing human medical research[16]. That report defined the conduct of human subject research in the United States. It set the boundaries between clinical practice and research and established three ethical principles to be applied to all research involving human subjects, namely, respect for persons, beneficence (defined as the act of doing or producing goodness and charity), and justice.

The Clinical Center of the U.S. National Institutes of Health (NIH) produced the first federal policy to protect human research subjects in 1953. This effort established a review mechanism, the institutional review board, which represents the research accountability system in the United States[17]. Institutional review boards were further expanded in the 1970s to ensure compliance with the ethical principles of the Belmont Report.

The U.S. Department of Health, Education, and Welfare, now the Department of Health and Human Services, approved Title 45 of the Code of Federal Regulations, Part 46, Protection of Human Subjects, in 1951. These regulations were extended to cover all federally supported research and were renamed the Common Rule in 1991[18]. Congress passed the Health Insurance Portability and Accountability Act (HIPAA) in 1996, partly in response to privacy concerns of individuals whose sensitive health data might be compromised during electronic transmission. The regulations developed by the Department of Health and Human Services are collectively called the Privacy Rule. The deadline for compliance was set for April 14, 2003. This rule defined protected health information as any data that could be traced to an individual, patient, or human subject. This rule placed any query with use of protected health information under the review requirements and monitoring of the institutional review board. Additionally, the earlier Common Rule was subsumed by the Privacy Rule, and the scope of coverage was expanded to all protected health information research, including quality improvement endeavors.

The Effect of HIPAA on Clinical Research

The Privacy Rule

The Privacy Rule defines a class called "covered entities," which are all entities that electronically transmit any protected health information. These include health-care clearing houses, health plans, and providers (hospitals, clinics, and medical practices). Researchers who are nonclinical and employed by universities, medical

centers, clinics, or practice groups are included. Some data, including medical consultations, medical referrals, and communication with referring providers, are exempt from the Privacy Rule. Billing and collection functions, and hospital activities such as administrative oversight and quality assurance activities, are exempted.

HIPAA requires that all so-called covered entities establish a privacy board to monitor any research activities; existing institutional review boards may serve as the privacy board. The institutional review board is to ensure compliance with the Privacy Rule in all cases of human research. In this way, HIPAA and institutional review boards are closely intertwined.

The Privacy Rule impacts any research involving the protected health information of any deceased or living subject. The rule has been incorporated into the institutional review board process of most institutions. The use of any protected health information requires prior written authorization. The data that constitute protected health information are of a broad variety and include any data that could identify an individual, such as zip code, locale, Social Security number, and medical record number as well as other information. All subjects must grant prior written authorization to use their protected health information. The investigator may not reuse the protected health information without prior written authorization, and the data may not be reused in any subsequent studies.

The Department of Health and Human Services has charged its Office of Civil Rights to ensure compliance with the Privacy Rule. At this time, the intent at this office is a cooperative approach toward compliance. Compliance complaints come to the office by way of a whistle-blower or by conducting compliance reviews of covered entities.

Privacy Rule violations may be civil or criminal. Civil violations are essentially administrative errors with fines of $100 to a maximum of $25,000 per year per violation. Criminal violations, which are defined as knowing, wrongful disclosure of protected health information, can incur fines to a maximum of $250,000 per year per violation. The Privacy Rule sets a minimum federal standard for the protection of protected health information for all citizens; it preempts or overrides state laws that are below that standard. If state laws are more restrictive than the federal laws, the Department of Health and Human Services will require that the state law be fully addressed in that jurisdiction.

The Impact on Clinical Research

Maintaining patient and human subject privacy is a laudable goal, but it must be reconciled with the unintended consequences of regulation on the conduct of clinical research. There is concern that the Privacy Rule creates a substantial bureaucratic and financial burden that discourages valuable research. As the Privacy Rule has been applied, a number of concerns, including increased costs of research[19] and difficulties in obtaining consent, especially for registries[20-30], have been identified. In a study from the Canadian stroke registry, Tu et al.[23] found that the requirement for informed consent to participate in the registry resulted in a participation of <50%. A report on the Program to Improve Care in Acute Renal Disease was considered a failure because the rate of participation was only 52%[26]. Armstrong et al. had a similar experience with the University of Michigan Acute Coronary Syndrome registry, where participation in the registry was 96.4% before HIPAA and decreased to 34% after HIPAA[19]. In a survey of 875 epidemiologists, Ness found that the HIPAA Privacy Rule was perceived to have a substantial negative influence on clinical health-related research, adding uncertainty, cost, and delay. The results of that study were published in the *Journal of the American Medical Association*[31] and reached the lay press. An op-ed piece published in the *New York Times* highlighted how a checklist policy, which was improving handwashing by health-care workers and decreasing the number of infections, was withdrawn because of a bureaucratic need for consent[32]. Continued monitoring of the quality and amount of research conducted since the advent of HIPAA is necessary to identify the consequences of this legislation and its regulations. Unfortunately, fundamental changes in regulations that will mitigate the potentially chilling effects on clinical research seem unlikely to be forthcoming in the near future.

The Effect of Institutional Review Boards on Clinical Research

Structure and Function of Institutional Review Boards

The duties of institutional review boards include ethics consultation, education, peer review of research protocols, clinical trial monitoring, and the protection of the safety and welfare of research subjects[33]. Additional roles include monitoring of adverse events that may arise during execution of the research proposal. Institutional review boards maintain the authority to sanction and enforce noncompliant investigators with rejection of a proposal or termination of an investigation.

Institutional review boards are composed of individuals with medical, legal, scientific, behavioral, and bioethics expertise as well as lay members of the public. The committee size of the institutional review board varies but needs to be a minimum of five. The committee usually convenes at regular and predetermined intervals to review protocol submissions. There are three types of reviews: full review (requiring a quorum of members), expedited (which may be done by administrative members of the institutional review board), and exempt. The type of review a submission will need, and to some extent the approval process, is influenced by the inherent risks to subjects, the anticipated benefits, the importance and scientific merit of the knowledge to be gained, and the informed consent. Generally, full reviews are done by two members of the committee, preferably including one member with relative expertise on the subject matter. The

review process involves scrutiny of the protocols, consent forms, adverse events, amendments and/or revisions to protocols, recruiting advertisements, and matters of noncompliance. Each institution usually has a safety and monitoring board or committee that is charged with overseeing the conduct of research and the reporting of adverse events.

Not all institutional review boards are the same, but the central mission of all of them is identical, namely, to ensure the safety and interests of human subjects in accordance with the federal regulations. There are two broad types of institutional review boards: institutional or local boards and central or commercial boards. Every institution involved in government-funded research is mandated to have a local institutional review board. Central institutional review boards, on the other hand, are usually governed by private and commercial entities. Although different in some aspects, both types of institutional review boards must adhere to similar procedures governing research[34] and ensure the protection of human subjects involved in research. Commercial institutional review boards work under contract, and systems of accreditation are designed to ensure protection for human subjects. While they are efficient, commercial institutional review boards have been criticized because of the inherent conflict of interest when a committee is performing reviews for the entities that fund the review process.

Barriers Created by Institutional Review Boards and Solutions

There is a wide variation among institutional review boards with regard to the number of required forms for submission, the number of days from submission to approval, and the process of approval[35]. There is no national standard for consent language and for items required for institutional review board approval. In addition, an abundance of clinical research has resulted in increased workload and time constraints for those who safeguard human subjects[36]. The review process of the institutional review board may be considered as arduous and as a barrier for timely research, and the fact that obtaining institutional review board approval delays initiation of a study cannot be disputed[37]. Studies have proposed implementing a centralized review for multicenter investigations and for practice-based research whose principal investigators are not affiliated with an institution[38]. Another possibility to reduce the turnaround time for institutional review board submissions may be accomplished by expanding the committee membership or the number of institutional review board meetings. Finally, recognition of an institutional review board approval issued by another institution (cross reciprocity) may be a very important solution to the delays that are often encountered in launching multicenter studies. In 2002, a pilot program developed by the National Cancer Institute established a central institutional review board that provided review of protocols for multicenter phase-3 clinical trials[39]. The central institutional review board currently provides protocol and consent form review to local institutional review boards by means of an institutional review board authorization agreement. Similar central institutional review boards that would oversee the conduct of NIH-funded research would drastically reduce the time required to obtain institutional review board approval prior to initiation of a study. With central institutional review boards in place, the redundancies, staff time, and inefficiencies would be improved without sacrificing any protection of health-related information or protection of human subjects. Although attractive in concept, the implementation of central institutional review boards has met with some resistance, most important of which is the unwillingness of institutions to relinquish control. The local institutional review boards are particularly concerned with the issue of indemnification when or if research subject injury may occur. These local issues must be solved to eliminate barriers to clinical research.

Other methods to reduce the delays in the institutional review board approval process relate mostly to preparation of the institutional review board submission (Table I). By ensuring that all elements of the institutional review board application are in place, the investigator can prevent delays in approval. The institutional review board commonly requests that the application be modified for improperly designed consent forms, poor study design, unacceptable risk to human subjects, and questions on the ethical or scientific merit of the study[35].

Funding Clinical Research—Opportunities and Challenges

High-quality clinical research, particularly that involving multicenter trials, is expensive and competes with basic-science research for available funds. Investigators face challenges in obtaining adequate funding. However, currently there are more opportunities to fund clinical research than there have ever been in the past. The primary federal agency in the United States for conducting and supporting medical research is the NIH, a part of the U.S. Department of Health and Human Services. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is an institute of the NIH that supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases. In this section, the challenges to funding clinical research from the point of view of the NIH and specifically NIAMS are presented.

Funding Decisions

The core mission of the NIH is basic-science research, and this mission comprises 60% to 70% of the investment of NIAMS. A substantial amount of research in orthopaedics is supported by private industry and is predominately funneled to clinical research. To maintain a balance, government funding is tipped toward basic-science research. Bridging a relationship between the NIH and private industry has the

TABLE I Elements of a Successful Institutional Review Board Submission

Prior to Submission	Submission	After Approval
• Contact institutional review board to obtain guidelines • Determine the type of review required (full, expedited, or exempt) • Ensure that all personnel named on the submission have completed local institutional review board training and have filed conflict-of-interest statement • Obtain relevant signatures • Check deadlines for submission in advance	Elements of protocol and consent: • Use local forms and/or format • Be succinct • Use lay language (readable at a 6th to 8th grade level) • Define acronyms • Proofread and spell check • Provide background for research • Avoid irrelevant details about drug or device development • Provide alternatives including patients' ability not to participate in research • Define the difference between research and ''standard of care'' • Include number of visits and duration of visits • Ensure that consent of patients is obtained in long-term follow-up studies • Cite all extra tests that may be required • Explain who will cover the extra costs • Include statement about conflicts of interest and indemnification • Provide information for a contact person (usually the principal investigator)	• Report all adverse effects • Watch expiration of approval and file resubmission in advance

potential to more cohesively and collaboratively provide funding for the most important clinical research studies.

Identifying the most compelling research questions is an important part of the NIAMS mission. The process must be selective because important clinical research is very expensive. What are the optimal types of clinical studies to fund? Can nonrandomized case-control and cohort surgical studies provide usable and meaningful information? These questions are particularly important in a surgical field in which randomized studies of surgical compared with nonsurgical intervention are so difficult to conduct. The NIH has input from a number of different groups. Roundtable discussions every year allow various medical communities to influence funding directions taken by the NIH. Meetings at retreats address issues and subjects critically important to the NIH and of interest to our specialty groups. Input is obtained from professional lay organizations, and at least annually the director of NIAMS meets with representatives from the orthopaedic community. There is input from NIH program directors as well as many others from within the NIH and the federal government through systematic program review.

The planning process helps to guide research directions, but investigator-initiated proposals are the most important source for clinical research. The majority of funding decisions evolve from the grants written by investigators and from investigator participation in review panels. They inform the process and prioritize research that must be funded. A proposal must be relevant to the NIH research mission, but the peer-review process determines whether the outcome will make a difference. After the peer-review process, the NIH must decide if it can afford to support the study. Is the study so compelling that it needs to be supported? These are difficult decisions, and the core process that guides them is peer review.

How Much Funding Is There?

Federal money for musculoskeletal research comes not only from NIAMS but also from other NIH federal institutes and agencies. In 1999, the NIH budget (for NIAMS) was a little over $300 million with two-thirds of it going to investigator-related research. Compared with the rest of the NIH, NIAMS allocates more of its budget toward investigator-initiated research projects with a philosophy that the research community and the investigators will identify the ideas that are clinically most important.

A massive increase in the NIAMS budget over a five-year period after 1998 to 1999 has led to investments in clinical research that previously could not have been considered. In osteoarthritis, an enormous research effort has been generated and the results will be used by clinicians across the world to identify biomarkers and correlate magnetic resonance imaging with clinical outcomes of osteoarthritis, particularly of the

knee. The SPORT (Spine Patient Outcomes Research Trial) study on lumbar disc disease has produced results that have been published[40], and more will be available in the next year. These types of studies need continued support and have only been possible through these new investments in NIAMS.

Obstacles to Funding Orthopaedic Clinical Research

Few investigators are appropriately trained to initiate and lead these complex investigations, particularly in surgical subspecialties in which it is difficult to take the time to obtain adequate training. A postdoctoral-funded fellowship in clinical research in orthopaedic surgery, which is cosponsored by the Orthopaedic Research and Education Foundation (OREF) and NIAMS, does not attract applications because too few clinically active orthopaedic surgeons can, or choose to, participate in the required 75% full-time-equivalent commitment. To entice more applications, NIAMS has decreased the time commitment required for candidates from surgical specialties to 50%.

Initiating multicenter research trials is a big challenge for the NIH. For example, trials with twenty different centers and twenty different institutional review boards present substantial obstacles. An eighteen-month lag between the initiation of an institutional review board application at a site and the enrollment of patients is common. Centralizing an institutional review board process for multicenter studies is important not only for investigators but also for major funding agencies like the NIH.

Obstacles to a Major Clinical Trial

Clinical Trials Are Complex and Expensive

The expense, effort, and dedication required to receive federal funding for an orthopaedic clinical study are illustrated for a multicenter outcome network investigating the prognosis and predictors of outcomes after anterior cruciate ligament reconstruction. This project was developed in 2001 at seven sites. The coordinating center was Vanderbilt University and consisted of two coinvestigators in the Health Services Research Center, one in the Biostatistics Department, and a research staff consisting of two research coordinators, a research analyst, and an editorial assistant. Additionally, there were two consultants, one an engineer and the other a pediatric sports medicine orthopaedic clinician-scientist. Core funding of $1,369,000 to support the infrastructure of the project was raised from small competitive grants through the OREF and NFL (National Football League) Charities, unrestricted educational gifts from corporations (Aircast and Smith and Nephew), and an internal tax on the three sports medicine orthopaedic surgeons at Vanderbilt (John E. Kuhn, Eric C. McCarty, and Kurt P. Spindler). The participating orthopaedic surgeons and the outside sites did not receive financial support.

Data on anterior cruciate ligament reconstruction were prospectively collected with two-year follow-up outcomes achieved in >85% of the first 1000 procedures. Only at this point did the investigators begin to seek federal funding. A series of NIH grants were submitted beginning February 1, 2004. The grant was eventually funded on a revision submitted March 1, 2006, with a 12% budget cut with total direct costs allocated over four years at $1.2 million.

In the first three years, 1600 patients had been enrolled, and 85% had two-year follow-up. The principal investigator spends one day each week coordinating the study and conducts a monthly conference call with all of the participating orthopaedic surgeons and coinvestigators. The entire team meets three times each year. A research coordinator is responsible for the database, patient enrollment, institutional review board requirements, grants, and follow-up, and another research coordinator is responsible for the next phase (funded by the NIH grant) for onsite follow-up of a nested cohort within the study at three of the sites.

Successful NIH funding for this clinical research grant required tremendous support. The effort necessary to succeed raises the question: How does orthopaedics increase the quantity and quality of clinical research and the number of orthopaedic clinician-scientists as principal investigators on grants through the NIH, such as an RO1 research grant? An RO1 is the major research project grant program of the NIH, which supports individual specified research projects. It is the most commonly used NIH grant program, with awards generally lasting three to five years.

Inadequate Training for Orthopaedic Clinician-Scientists

Inadequate education, training, and support of orthopaedic clinician-scientists are an obstacle to orthopaedic clinical trials. There are a lack of training programs for clinical research design, insufficient grant-writing instruction at the NIH RO1 level, ineffective collaborations and mentorship, and finally a lack of adequate salary support.

A national course to train orthopaedic clinician-scientists to be effective principal investigators on clinical studies is needed. The course would need experienced orthopaedic researchers and effective collaborators in health service research, biostatistics, engineering, imaging, and rheumatology. The goal would be to guide a cohort of serious orthopaedic researchers to be successful at the level of NIH RO1 funding. Funding for this course could be arranged in a collaborative effort between the American Academy of Orthopaedic Surgeons (AAOS) and orthopaedic specialty societies, NIH, and industry. Establishing a national course could also increase the numbers of orthopaedists who are qualified to be effective study section reviewers. The time commitment required to be a reviewer on an NIH study section is substantial, and some minimal level of compensation by the orthopaedic community is warranted.

Lack of Support for Clinical Investigation

Orthopaedic clinician-scientists typically have inadequate financial support for research efforts. The clinician can

generate substantial profit margins for the medical center by doing clinical work, and not surprisingly there is often little enthusiasm for protected time away from this lucrative activity. The OREF does not support salaries for the orthopaedic surgeon but fully supports their PhD coinvestigators. The NIH base salary cap of approximately $191,300 provides incomplete salary support for the orthopaedic clinician. This issue is not unique to orthopaedics since physicians in other surgical disciplines, procedure-based specialties, and radiology can easily earn several times the NIH cap by doing clinical work. The lack of competitive salary support discourages this type of investigator. One solution would be for the orthopaedic societies to devise mechanisms to provide adequate compensation for qualified members to participate in clinical research. The AAOS could take a leadership role, by partnering with subspecialty societies, industry, and academic centers to provide matching supplemental salary for an orthopaedic surgeon who is a principal investigator in an NIH-funded clinical trial. As noted, the salary cap on an NIH grant is approximately $191,300. A principal investigator usually must devote a 20% effort, effectively dedicating one day a week to the funded research. A 20% effort with a cap of $191,300 is about $36,000 per year of salary support. If the effective cap were raised to $360,000, the $36,000 given by the NIH would need to be matched with another $36,000, nearly eliminating the financial penalty to the investigator and his or her department. Creating sufficient compensation for investigators would be a solid step toward eliminating barriers to future high-quality clinical research in orthopaedic surgery.

Overview

In summary, both opinion and evidence indicate that barriers and obstacles to clinical research exist in orthopaedic surgery. The HIPAA rules are unlikely to be modified, given the importance of patient privacy in the electronic age. However, the negative effect of these rules on database research must continue to be assessed. We must make sure that, in the local interpretations of the Privacy Rule, protection of the individual subjects can be accomplished while still prioritizing the benefits of this type of research for the community at large. Efforts to reduce redundancies in the institutional review board submissions and truncate the need for multiple institutional review board approvals for multicenter trials must be pursued with a coordinated approach. Central institutional review boards could streamline the approval process at each institution, but they can do so only with changes in indemnification matters and local institutional protocols. This would streamline multicenter clinical research and eliminate an important barrier to large clinical trials, but local institutional review boards will need to relinquish full oversight of a project performed on patients at their institution.

High-quality clinical research is expensive and competes with basic-science research for available funds. Although NIAMS uses internal and external advisory groups to decide on optimal directions for clinical research, the majority of funding goes to investigator-initiated proposals. Obstacles to funding these trials include identifying appropriately trained investigators and the difficulties with multicenter institutional review board processes. To increase the amount of effective clinical research in orthopaedics, potential orthopaedic clinician-scientists must be provided more extensive education and training when they are young investigators. An ongoing national course, which should include nonorthopaedic mentors and collaborators who are established principal investigators in the research community, could accomplish this goal. Inadequate salary support for the orthopaedic clinician-scientist must be addressed by the OREF, orthopaedic societies, and all of us in the community of orthopaedics. This effort could place orthopaedics in a leadership role in medicine in general and substantively decrease barriers to high-quality clinical research.

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