

# ACCP WHITE PAPER

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## **Ethical Issues Related to Clinical, Translational, and Health System Research**

American College of Clinical Pharmacy

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## **Background**

In 2005, the president of the American College of Clinical Pharmacy (ACCP), Joseph DiPiro, Pharm.D., charged the ACCP Publications Committee with updating the College's 1993 White Paper on Ethical Issues in Clinical Pharmacy Research. The purpose of this update was to highlight the current state of ethical issues associated with the responsible conduct of research by clinical pharmacy investigators. High ethical standards are traits the public expects from health care providers. Pharmacists in particular have long been among the most respected and trusted members of our society. Patients and other health care professionals look to pharmacists for reliable and unbiased information regarding drug therapy. With this trust comes great professional responsibility that extends well-beyond direct patient care. As pharmacists, we should hold our colleagues and ourselves to the most rigorous ethical standards in all of our professional activities, including patient care, research, and education. Unfortunately, reports of questionable behavior among health care professionals, including pharmacists, have become commonplace in the last 10 years. For some individuals, the lines between right and wrong have become blurred by greed or pressure to perform. Sometimes unethical conduct is engaged in knowingly, while at other times ignorance or sloppy practice is blamed. Regardless of the motivation or awareness of an individual's unethical behavior, such actions not only damage the sacred trust bestowed on us by the public but can also compromise the well-being of our patients. Therefore all health care professionals need to be well versed in bioethical issues and strive to conduct themselves appropriately.

In 1993, the American College of Clinical Pharmacy published a white paper, Ethical Issues Related to Clinical Pharmacy Research.<sup>1</sup> Many of the perspectives and much of the guidance provided in this publication, while more than a decade old, are still of value today.

However, as the clinical sciences advance, new challenges have emerged that require heightened vigilance by individual investigators and clarification/interpretation by scientific and lay societies. In this paper, we attempt to identify the emerging threats to scientific integrity and provide investigators with guidance to minimize their risk for impropriety as the result of their conduction of clinical, translational, or health services research. The bioethical dilemmas that are commonly encountered by those evaluating health care quality improvement initiatives that border on research and those who serve on institutional or organizational review boards will also be addressed. Although many issues discussed are relevant across health care professions, we have attempted to highlight the significance of specific quandaries as they pertain specifically to pharmacy researchers. Ethical interaction with industry throughout the range of clinical pharmacy activities, including research, is the focus of a separate, recently updated white paper, *Pharmacists and Industry: Guidelines for Ethical Interactions*.<sup>2</sup>

### **Perspective on the Issues**

In a 2005 survey, more than a third of researchers in the United States admitted to engaging in ethical misconduct within the past 3 years.<sup>3</sup> The investigators who carried out the study warned that because most attention is focused on high-profile, serious cases, the broader threat from “minor misdeeds” is under appreciated. The anonymous survey of 3247 early- and mid-career researchers who were funded by the National Institutes of Health (NIH) revealed that although less than 1.5% admitted to falsification or plagiarism; 15.5% said they had changed the design, methodology, or results of a study; 12.5% admitted overlooking others' use of flawed data; and 7.6% said they had circumvented “minor” aspects of the regulations designed to protect human subjects who participate in research (Table 1). Clearly, despite decades of focused attention on the standards for ethical scientific conduct and the mandated educational and

certification processes for clinical researchers relative to human subjects' protection and privacy, ethical concerns in clinical research have not been eradicated. In fact, many would argue that the situation is worse in 2007 than in the past.

### **Obligations for Research Integrity**

Obligation may be defined in many ways. An obligation may represent something that must be done out of legal or moral duty. Alternatively, an obligation may also be defined as assistance or a debt owed in return for something given. At a basic level, an obligation consists of at least one party who feels a sense of accountability to another person or party. Although a sense of obligation or duty would seem to be a desirable characteristic for a clinical researcher, one must be clear about the hierarchy of his obligations.

As pharmacists, our professional activities should reflect the Code of Ethics for the profession.<sup>4</sup> This code was developed to “state publicly the principles that form the fundamental basis of the roles and responsibilities of pharmacists. These principles, based on moral obligations and virtues, are established to guide pharmacists in relationships with patients, health professionals, and society.” At the heart of the code is a stated commitment to the trust and welfare of the patient. This obligation to the patient is the foundation on which our profession is based and should be never be compromised. When clinical scientists downplay the significance of this duty or displace it as their guiding obligation, they place themselves at risk of unethical behavior.

Even though pharmacists' obligation to patients and society remains foremost in their minds, it is reasonable to expect those involved in the conduction or evaluation of research to feel a sense of obligation to other entities. Eagerness, enthusiasm, and self-motivation can be outward manifestations of an investigator's or evaluator's sense of obligation. While these

outward manifestations can be admirable traits, eagerness to please a sponsor, overzealousness regarding a project, or self-motivation to succeed may ultimately blind investigators to their primary obligation. Although it is not inherently wrong for clinical investigators to develop secondary obligations to sponsors or their careers, it is imperative for them to constantly reassess what is the primary driving force behind their actions. Without conscious self-evaluation, one's sense of obligation can easily become blurred or distorted.

## **Patient-Related Issues**

### ***HIPAA Compliance and Use of Clinical Databases***

A variety of regulations come into play for the investigator who is conducting research involving human subjects. Historically, Institutional Review Boards (IRBs) focused their review solely on the adequacy of informed consent: the “common rule” as described in the Code of Federal Regulations 45 CFR 46. Subpart A governs research on human subjects if it is funded by 1 of 18 federal agencies, while the “FDA rule” is applicable for all non-federally funded research that is to be conducted for drug approval or marketing.<sup>5,6</sup> The Health and Human Services (HHS) Privacy Rule established a set of national standards for the protection of certain health information as part of the implementation of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.<sup>7</sup> This legislation was designed to protect the public from abuses that had been noted in the past such as unauthorized disclosure and use of identifiable information for fallacious purposes. The Privacy Rule<sup>8</sup> established a set of national standards for the use and disclosure of protected health information (PHI), which is generally defined as individually identifiable health information, by covered entities (i.e., health plans, health care clearinghouses, and health care providers who transmit health information in electronic form with HHS such as Medicare claims).<sup>9</sup> Examples of PHI include, but are not limited to, information such as a

patient/subject's name, address, birth date, and social security number (Appendix A). The Privacy Rule thus created an additional consideration for many investigators and new responsibilities for IRBs since they, along with privacy boards, are authorized to review requests for the use of PHI. The Privacy Rule specifically permits authorization for the use of PHI to be combined with informed consent.<sup>8</sup> The Privacy Rule applies regardless of funding source and restricts covered entities from disclosing PHI in electronic or other form.

Before the establishment of the Privacy Rule, registries and data banks provided invaluable information about a variety of conditions such as the natural history and responsiveness to therapy of certain diseases, the prevalence of various diseases in the general population, and population effects of unsuspected toxins, to name just a few. According to the Privacy Rule, access to this information now requires a patient's authorization for the release of PHI. In many cases, previously existing regulations did not require informed consent or consent to access patient information. Now, to obtain PHI from a database or repository or to reuse it in the future, regulations require the researcher to obtain the authorization of each individual whose health information is to be procured or to obtain a waiver of this requirement from the IRB or privacy board. In addition, regulations specifically prohibit the combination of authorizations for various projects.<sup>8</sup> The Common Rule contains no equivalent prohibition.<sup>5</sup>

While the requirements embodied in the Privacy Rule seemed reasonable, its implementation in 2003 was fraught with concerns. Although an IRB or privacy board may waive the requirement for patient authorization and an IRB is allowed to modify or waive the requirement for informed consent, the existence of these two processes and sets of criteria have complicated, and in many people's perspective, hindered the conduct of clinical research.<sup>10,11</sup> A survey

conducted by the Association of American Medical Colleges found that the Privacy Rule had the following effects on research:<sup>12</sup>

- Research subjects were confused and distracted by having to *consent* to participate in research (as per the Common Rule) and *authorize* use of their PHI (as per the Privacy Rule).
- Collaborations became more difficult because the Privacy Rule now requires prior authorization for PHI to be shared among institutions a condition that was not required under the Common Rule.
- The perceived quality of research was diminished.
- Research costs increased because of the authorization requirements, which require a subject to assent before each separate disclosure of their PHI. The Common Rule had been interpreted to allow a one-time consent for research.

The interaction of the Privacy Rule and the Common Rule was addressed by the Secretary's Advisory Committee on Human Subjects Protection (SACHRP) in 2004. They recommended 9 changes to the Privacy Rule based on commentary from representatives of the Association of American Medical Colleges, the National Committee on Health and Vital Statistics, and a number of academic health science centers (Table 2).<sup>13</sup> These recommendations were approved by Secretary Thompson in December 2004, and SACHRP staff was requested to move forward with the implementation of as many of these as possible. This dialogue indicates continuing problems associated with the implementation of HIPAA in the context of research involving human subjects. Conflicts at the interface of new regulations and modifications thereof with existing practices may continue to arise and investigators need to remain vigilant to assure that they are in compliance with all relevant expectations.

### ***Informed Consent***

The tenets of informed consent is comprised of at least three elements: provision of information, assessment of a potential subject's understanding and capacity to make sound decisions, and assurance of freedom to exercise choice to participate in research without external pressure or coercion. Informed consent should represent the investigator's respect for the patient's autonomy and the right of patients to bring their values and beliefs into making health care decisions that affect them.<sup>14</sup> A complete discussion of the history and use of informed consent has been provided previously.<sup>1</sup> The emerging challenge herein is the scope and quality of IRB reviews as society begins to embrace the perspective that even minimal risk is unacceptable if the proposed investigation is scientifically flawed and thereby unlikely to yield benefit.

### ***Vulnerable Patient Populations***

Researchers have an obligation to protect the autonomy and well-being of subjects who are socially, physically, and economically powerless or disadvantaged. At the same time, however, there is a responsibility to conduct research in these populations so that informed treatment decisions can be made. Historically, these populations of subjects were underrepresented in clinical research due to a number of factors. A thorough discussion of the multiplicity of these factors and other issues, many of which are not ethical in nature, associated with the conduction of research in vulnerable populations has recently been published.<sup>15</sup> The subsequent discussion focuses on the ethical concerns that have arisen from recent experiences in the conduct and evaluation of research.

### ***Children***

Most children do not have a legal right to make decisions regarding their medical treatment or their participation in a clinical investigation. This authority routinely lies with a

parent or legal guardian. Since the parent or guardian is agreeing not for him or herself, but for a child, the concept becomes that of informed permission or "consent by proxy." The concept of consent by proxy assumes that the parents are best suited to make decisions for their child. Prior to attempting to gain consent, the investigator should make an attempt to assess the individual's interest in the child's welfare, emotional stability, and ability to make sound decisions that are in the best interest of the child.<sup>16</sup> If an investigator feels that a parent or guardian is incapable of making sound decisions, he or she has an obligation to request that others assist in the making appropriate decisions. In some instances, a psychologist or psychiatrist may be required to evaluate the competence of the parent or guardian. In the event that a parent or guardian is found to lack the necessary decision-making capacity, the courts may become involved. The court may assign a guardian *ad litem* (someone who is appointed by the courts to protect the safety and welfare of the child) solely to make medical decisions for the child. In most cases where this happens, the parent retains custody of the child.<sup>15-17</sup>

Minors who are self-supporting and/or not living at home, married, pregnant or have children, or in the military may be declared by a court of law to be emancipated, thus allowing them to make their own health care decisions. An emancipated minor may be treated as an adult for all purposes including medical treatment and informed consent.<sup>15,17</sup> In some states, unemancipated minors are given health care decision-making authority when seeking treatment for certain medical conditions such as pregnancy, sexually transmitted diseases, or substance abuse. In these situations, a minor is able to give consent to treatment or participation in an investigation without permission of the parent or guardian.<sup>15,17</sup>

### *Critically Ill*

In 1999, 20% of all deaths in the United States occurred in intensive care units (ICU).<sup>18</sup> Owing to the severity and acuity of the illnesses encountered by patients admitted to the ICU, disease-induced physiologic alterations make these patients unique with regard to their reaction to various medications. In addition, the high degree of morbidity and mortality associated with critical illness underscores the need for clinical research in these patients. One of the primary challenges in conducting research in this patient population is the difficulty in obtaining informed consent owing to unconsciousness or altered mental status. For an unconscious patient, informed consent must be obtained for an individual responsible for making treatment decisions for the patient. It is widely accepted that many patients and their surrogates agree to participate in clinical research in the critical care setting in hope of a cure, extension of life, or reduction in pain and suffering. Some individuals may be at peace with the imminence of their death or death of a loved one and agree to participate to contribute to the quest for knowledge that may help others in the future. However, patients or patient representatives should provide consent only after they have been informed and demonstrate that they have a full understanding of study procedures and how the procedures could influence patient outcomes.<sup>19,20</sup> It is not ethical to create or propagate a false belief regarding the impact of treatment on a patient's outcome for the purpose of securing research participation.

Distress and helplessness also contribute to the vulnerability of critically ill patients. Apart from anxiety, discomfort, and disease/medication-induced altered mental status, the potential for dependence out of desperation raises concern about the patient's ability to give informed consent to participate in clinical research. Apart from the questions of mental clarity, some patients may feel obligated to grant consent out of gratitude or out of fear that the quality

of their care could suffer. Researchers have a responsibility to reassure patients or their decision makers that their quality of care will not be affected if they elect not to participate in a study.

Another caveat regarding informed consent in this population is that consent may be implied in emergency situations where delaying care to obtain authorization would result in serious or permanent harm. As a result, caregivers routinely obtain implied consent for life-saving procedures; however, extrapolation of emergency consent procedures to clinical research needs to occur only under strict guidelines and review.<sup>20</sup> Even in the most critical of these settings the concept of informed consent has been withheld as evidenced by the recent decision by an FDA advisory panel to not grant a waiver of consent for the United States Navy to administer an investigational blood substitute for trauma victims.<sup>21,22</sup>

### *Illiteracy*

Almost one-half of American adults read at or below the 8<sup>th</sup> grade level.<sup>23</sup> People with low literacy skills come from a variety of backgrounds, races, and socioeconomic classes and usually have no visible signs of disability. Clues that suggest limited literacy include patients claiming to have forgotten their glasses, bringing in family members for appointments, or filling out forms or questionnaires incompletely or inaccurately.<sup>23,24</sup> Low literacy skills are more prevalent among persons over 65 years of age and inner city minorities. The high prevalence of literacy problems among these groups makes them vulnerable owing to poor understanding of health-related and consent information.<sup>23,24</sup> Researchers need to develop consent forms that are written at a reading level of comprehension that is commensurate with the level noted among the population they are likely to encounter. The average literacy of adults receiving Medicaid is at the 5<sup>th</sup> to 6<sup>th</sup> grade level. Utilizing computer software applications that assess reading level such

as the Flesch-Kincaid Grade Level embedded in word processing software can help with this process.<sup>25-27</sup>

Many patients with low literacy prefer to receive health information verbally rather than in a written form. The use of non-text methods such as cartoons and videos to convey information has been employed successfully by researchers when attempting to inform or educate low literacy patients.<sup>28</sup> The use of these methods requires the utilization of audiovisual documentation of consent—a process that many IRBs may not be comfortable with or willing to allow investigators to employ.

### **Pharmacogenomic Issues**

Clinical trials should include enough individuals from various ethnic or racial backgrounds for statistical analyses of the heterogeneity of a response to a particular therapy. However, enrolling patients who self-identify as a particular race is not ideal, since race is a somewhat subjective term that is often left to the interpretation of the individual.<sup>29</sup> Identifying genotypic and phenotypic characteristics or markers is a more precise method for identifying factors that might determine treatment response.<sup>29,30</sup> Currently, pharmacogenomic profiling is most often prospectively utilized during phase 1 trials.<sup>31,32</sup>

Stratification of clinical trial subjects into subgroups on the basis of genotype poses several ethical challenges. The use of genotyping as an inclusion or exclusion criteria for participation in a clinical trial could lead to a loss of the benefits associated with research participation, subject selection biases, or unfair representation in the trial, similar to the historical under representation of women, ethnic minorities, children, and the elderly.<sup>33</sup> If studies are designed to target specific pharmacogenetic characteristics that are associated with specific ethnic groups, members of other groups may feel as if the drug development process

discriminated against the unstudied populations.<sup>33,34</sup> In addition, selection bias introduced into studies may affect extrapolation of safety and efficacy to other groups.

When subjects are enrolled into studies for which genetic information is to be collected, the informed consent process should clearly define the overall objective of the study, the subject's role in the study, and intended use of genetic samples for analyses. The informed consent should indicate who will have access to genetic data and the conditions under which data access is possible during and after completion of the study. Subjects should be assured that no disclosures of genetic information are authorized outside of those indicated in the informed consent.<sup>34,35</sup> The sensitive nature of knowledge about a subject's pharmacogenetic profile has become apparent. Unfortunately, the responsibilities of the investigator and the ethical dilemmas created as a result of knowing the details of an individual's genetic code are not entirely clear. For instance, at the completion of a study new, preliminary information becomes available which suggests that individuals with a particular genotype are at risk of developing a certain disease. If an investigator notes that several subjects have this particular genotype, are they obligated to disclose the potential link to disease predisposition, even if the data are preliminary? What if potential employers and insurers then attempt to use genetic information as a means to deny employment or to limit access to health care even if the disease has not manifested? Researchers must be able to demonstrate to IRBs that procedures are in place to decrease the risk that genetic data may become part of the study subject's permanent medical record. Limiting access to the de-identifying coding keys of databases to a trusted third party reduces the likelihood of disclosing data to any party including study subjects and researchers.<sup>36,37</sup> Unfortunately, the same steps that are employed to protect subject confidentiality may also make it easier for unethical researchers to cover up data fabrication.<sup>38</sup>

## **Ethnic Minorities**

Minorities and low-income persons are more likely to use public institutions for medical care, thus making them accessible to researchers for clinical or translational research. Of interest, however, participation of patients of various ethnic minorities in clinical trials, especially prevention trials, has been dismal.<sup>39</sup> Since health care providers often rely on clinical guidelines and large clinical trials when determining the appropriateness of therapy for a patient, if patient populations are not well represented in these data sets, treatment decisions can be biased.<sup>39-41</sup> As a result of concerns surrounding the paucity of data in various racial and gender groups, the NIH issued guidelines in 1994 for the inclusion of women and minorities as subjects in clinical research.<sup>42</sup> This NIH initiative assumed that investigators truly understand the barriers to minority patient enrollment in clinical trials. Although we now have a better understanding of some of the barriers to minority recruitment such as the patient's beliefs about clinical research and Western medicine, communication problems between the investigator and patient, and mistrust and fear of research institutions, the research community has made little progress in the intervening years toward the resolution of this critical issue.<sup>43-47</sup>

To achieve better participation, researchers must give special attention to factors that may influence the decision of each individual to participate. Ethnic community members suggest that many individuals express a desire to establish a relationship with researchers before they agree to become part of a clinical investigation.<sup>47,48</sup> Researchers must learn to recognize and be sensitive to cultural dynamics that influence research subjects' quality of life. It is important to recognize that there is an inherent dignity in all cultures that legitimates a patient's customs and practices.<sup>47,48</sup>

## **Conflicts of Interest**

Conflicts of interest, real or perceived, arise when an individual's professional and/or personal interests have the potential to affect his or her ability to act in an unbiased manner. Significant conflicts may also arise as the result of the evaluation of research data that ultimately leads to the generation of clinical practice guidelines. Although many conflicts arise secondary to financial relationships with the biotechnology, device, or pharmaceutical industry, investigators may also allow their personal goals, friendships, or prejudices to compromise their judgment.<sup>49,50</sup> These competing interests can make it difficult to maintain impartiality when carrying out professional responsibilities, especially in the arena of clinical research. Conflicts of interest can result in the clinician making decisions that are not in a patient's best interest and can also compromise standards of scientific integrity.<sup>51</sup> In addition, even though an individual's intentions may not result in an impropriety, having a real or potential conflict of interest may bring into question the motivation behind statements made or conclusions formulated by the investigator or the one evaluating the data. This may propagate a perception of impropriety and allow critics to question the ability of that individual to act fairly in a given situation. Investigators associated with high-profile research are particularly susceptible to such scrutiny by peers and even the lay press.<sup>52</sup>

The key to managing a potential conflict of interest is to determine if the situation will interfere or give the appearance that it interferes with one's ability to exhibit unbiased, independent judgment when involved in a given activity. One must be sure that there is no compromise of trust before engaging in any activity where a potential conflict of interest exists. In many instances, the perception of a conflict of interest is unavoidable. To maintain the integrity of the researcher and the related work, individuals are commonly asked / required to

disclose any potential conflicts of interest by signing a conflict of interest statement. However, the conflict of interest disclosure process itself is flawed and the assumption should never be made that disclosure negates problems created by a conflict of interest.<sup>51</sup>

Knowing that one has a potential conflict of interest requires knowledge by the subject and sound professional judgment. To remain objective concerning a potential conflict of interest, one can solicit input from a trusted colleague so as to avoid a potentially career-ending situation. Knowing how to manage a conflict of interest is critical. It is best to avoid the situation if possible and, if not, to ensure that all affected parties are aware of the conflicts so that one's professional integrity is not compromised. In addition, it is prudent for the individual to consult with his/her institution and granting agencies to discuss their policies regarding conflicts of interest.

## **Investigator and Trial Oversight**

### ***Institutional Review Boards***

Most issues related to the ethics of conducting clinical research can be addressed by following published standards for the protection of human research subjects. Current federal regulations in effect in the United States, Title 45 Part 46 of the Code of Federal Regulations, mandate that all protocols be reviewed and approved by institutional committees responsible for the protection of human subjects.<sup>5</sup> These regulations apply to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal agency. However, approval from an IRB does not relieve the researchers of the responsibility of safeguarding the health and welfare of the study subjects. This responsibility ultimately lies with the study investigators. The IRB's role in recent years has expanded to encompass some new issues, while for others there has been an increase in the degree of scrutiny. Thus, they now must

devote more time to such issues as the privacy of personal medical information; investigator and institutional conflicts of interest; critical evaluation of investigator–initiated, unfunded research; assurance that clinical trials are registered; and the design of the clinical or translational investigation.

### ***Data Safety Monitoring Boards***

Data safety monitoring boards (DSMBs) are necessary to provide appropriate oversight and monitoring of the conduct of clinical trials.<sup>53</sup> The purpose of DSMBs is to ensure safety of study participants and the validity and integrity of the data. A wide variety of clinical trials require safety and data monitoring, including safety, physiologic, and dose-finding studies (phase 1); efficacy studies (phase 2); and efficacy, effectiveness, and comparative trials (phase 3).

Data safety monitoring boards should function as an independent entity separate from the oversight conducted by the investigators and the IRB. It is the responsibility of each medical center to ensure that systems are in place to provide appropriate monitoring of trial data and study participant safety. The composition and role of the DSMB should be clearly defined: frequency of the meetings, whether the meetings will be held in an open or closed forum or public or private capacity, and the frequency and content of meeting reports. The composition of a DSMB should be multidisciplinary and include but not be limited to bioethicists, biostatisticians, experienced clinicians, and any other individual as deemed appropriate.

### **Investigator-Initiated Unfunded Research**

Research is often initiated without funding within the context of gathering pilot data to test a new hypothesis or as a quality improvement initiative.<sup>54</sup> Although the pharmacy literature is essentially silent on the conduct of unfunded research, several years ago this topic was highlighted in the medical literature.<sup>55-57</sup> Stein et al. reviewed original articles in 23 internal

medicine and neurology journals.<sup>58</sup> They determined that 78% of journals published at least one unfunded study and 23% of all published research had no explicit funding. Almost 30% of these studies involved procedures that appeared to be performed for research purposes and not as part of routine care, such as electroencephalograms and laboratory tests. In 7% of studies, direct clinical costs were not accounted for by the investigators. These findings raised concerns whether the research subjects involved in these studies had provided informed consent and were aware that some study-related costs could be passed onto them. Since publication of these articles detailing the extent of unfunded research, journals now commonly require both a listing of research funding sources and documentation that informed consent was given by study subjects, as well as the fact that the investigation was approved by an IRB.<sup>58</sup>

The costs and sources of support for unfunded research pose ethical questions. Because all research accrues costs, the absence of grant funding for a project simply means that alternative payment mechanisms must be sought. Research support unassociated with investigator-initiated grant awards exist as money obtained through university-based patient care revenues, charitable contributions and endowments, grants awarded to institutions rather than to individual investigators, industry-supported institution-based contracts, and hopefully to a very limited degree as the result of billing the cost to the study participant.<sup>55</sup> In addition, indirect costs paid by federal research grants are a form of research support. Indirect cost revenues are intended to cover services provided by the institution that cannot be identified directly as line-item costs on grants and can be used for a variety of expenses. Although the specific uses for these dollars vary from institution to institution, their use is regulated by federal law and subject to audit. It is thus extremely important that use of indirect cost revenues be in compliance with existing federal laws and institutional policies. Individual researchers should not assume it is legal and ethical to

use infrastructure resources provided through indirect costs from an existing federal grant to support other projects. The planned use of infrastructure resources should be discussed and approved with the institution's financial and/or grants office.

Who else ultimately pays for unfunded research? Unfunded research represents opportunity costs for health care institutions when money that could have been generated through time spent in clinical practice is rerouted to research.<sup>58</sup> While spending professional time doing research is compatible with the mission of pharmacy schools and medical schools, hospitals, managed care organizations, and ambulatory practice sites may not be in financial positions to subsidize professionals' time in this manner. The costs of certain types of relatively inexpensive research (i.e., survey research) can be "buried" in departmental budgets and overhead.<sup>58</sup> However, conducting tests or procedures in an unfunded study that are not part of routine patient care can generate substantial costs. In some cases, these costs have been passed on to study participants or third-party payers, a practice that is clearly not ethical.<sup>58</sup>

The principal investigator (PI) in an unfunded research project is usually conducting an investigator-initiated study. In situations where the study is an investigator-initiated clinical trial that falls under the regulations of the FDA, the PI is acting as both the sponsor and the investigator (i.e., as a sponsor-investigator) and must comply with all applicable federal regulations that apply to both the investigator and the sponsor. The PI and the institution where he or she is employed assume all the responsibilities and all the risks associated with being the study sponsor. In addition, the PI bears the responsibility for developing all aspects of the trial. These include, but are not limited to, developing the protocol, recruitment plan, randomization process, unblinding procedures, data collection tools and procedures, quality assurance plan, consent form and privacy authorization documents, informed consent plan, patient safety and

monitoring plan, training plan and materials, and data analysis plan, as well as submitting the protocol to obtain IRB approval. In some circumstances, the sponsor-investigator is also responsible for the application, attainment, and maintenance of an investigational new drug application (IND) or investigational device exemption (IDE) from the FDA.

### **Clinical Trial Registration**

Although hundreds of clinical trials are conducted each year, research results are not always published in a timely fashion and in some instances never made available to other clinicians and the public. This is due in part to the bias of researchers, pharmaceutical companies, and journals to publish only trials that yield a positive result.<sup>59</sup> This and other problems inherent to the current method of clinical trial data reporting led to a mandate by the International Committee of Medical Journal Editors (ICMJE) that all clinical trials be registered in a public accessible clinical trials registry prior to initiation if the investigators want it to be considered for publication in one of the ICMJE journals.<sup>60</sup> The mandate does not apply to phase 1 or pharmacokinetic studies.

The Institute of Medicine recently released a report entitled, *The future of Drug Safety: Promoting and Protecting the Health of the Public*, in which they called upon Congress to “require industry sponsors to register in a timely manner at [clinicaltrials.gov](http://clinicaltrials.gov), at a minimum, all phase 2 through phase 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to the FDA as part of a new drug application, supplemental new drug application, or to fulfill a post-market commitment.”<sup>61</sup> The committee recommended also that “this requirement include the posting of a structured field summary of the efficacy and safety results of the studies.”

Currently, there are several web sites, including ones sponsored by the National Library of Medicine ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and the World Health Organization ([www.who.int/ictrp/registration/en/](http://www.who.int/ictrp/registration/en/)) that meet all the requirements to be considered valid registries. These requirements include the following: a unique identifying number, study hypothesis, primary and secondary outcomes, eligibility criteria, statement of intervention and comparison, key trial dates, funding source, target number of subjects, and contact information for the principal investigator.

### **Clinical Trial Design**

The randomized controlled trial (RCT) design is the gold standard for prospective trials and is the most effective way to control for overall study bias.<sup>62</sup> This design, however, is not suitable to evaluate the differences between combinations of treatments, assess equivalence, or detect the influence of multiple variables.<sup>62</sup> Therefore, the increased financial, regulatory, and scientific burden necessary to answer various research questions often limits the use of the RCT design. Controlled clinical trials and use of alternative study designs must be carefully constructed to ensure the study is conducted ethically. The appropriate primary outcome measure, control group selection, treatment characteristics, and patient selection can aid in maintaining research subject equipoise.

### ***Appropriate Outcome Measure***

Determining the primary outcome measure *a priori* will allow for sample size calculations and will dictate data collection and post-study results reporting.<sup>63</sup> Outcome measures should be selected based on what is important to both patients and practitioners.<sup>64</sup> Use of therapeutic endpoints that are not comparable to that of previous trials will not provide the additional information necessary to decipher controversies between treatments. When choosing a

study endpoint, the investigator must use care to ensure that the endpoint will answer the scientific question in a meaningful way and/or provide the basis for further research. Research questions that are redundant or expose subjects to unnecessary harm should be avoided. Clinical trials involving long observation periods with serious conditions where the primary outcome measure is mortality should employ an independent DSMB. The DSMB should review periodic interim analyses of treatment outcomes at predetermined time points and provide guidance to the investigator, IRB, and sponsor about when a trial should be stopped or modified.<sup>65,66</sup> Trials should not only be stopped or modified based on excessive toxicity, but also when study treatment shows significant benefit beyond the standard of care.

### ***Control Group Selection***

Response to pharmacological intervention is dependent on several variables, specifically the features and setting in which the treatment is administered.<sup>67</sup> Active controls are necessary when there is a proven, effective treatment for the condition being studied. In cases where the study treatment appears to be superior to what is currently available, investigators must rely on alternative study designs such as a crossover design and blinded interim analysis to maintain ethical consideration of all participants. Placebo controls have clear cost and scientific advantages over active controls. They allow for smaller sample sizes, where the difference between treatment groups will be significant, and limit bias. However, today a significant number of diseases have proven treatment options and the use of placebo controls is ethically controversial. Their use should be limited to specific situations, for example where there is no proven effective treatment or where standard of care is no better than placebo for the condition being studied.<sup>1,67</sup>

### ***Patient Selection***

Defining the appropriate patient population to maximize treatment generalizability has become ethically complicated with advances in genetic testing. Identification of probable responders and non-responders may make it ethically necessary to administer treatment based on the genetic probability of response.<sup>68</sup> An example of the successful application of therapy based on genetic identification is randomization based on the presence of human epidermal growth factor receptor-2 (HER2) in patients with breast cancer.<sup>69</sup> Investigators must take care in the interpretation of pharmacogenetic testing and phenotypic expression, as marked variability still exists in systemic dose exposure and subsequent response even when the known genetic traits are characterized.<sup>68</sup> Significant challenges such as patient/provider education, legal ramifications, regulation of specific tests, and ethical implications of obtained knowledge currently limit use of genetic information in clinical trials (see discussion in previous section).

### ***Treatment Characteristics***

Medication doses used in both the active and control treatment arms should be provided in accordance with the standard of care. Subtherapeutic doses of active drug used in the control arm will bias trial results in favor of the alternative hypothesis. Conversely, suprathreshold doses in either treatment arm will result in unnecessary exposure and may lead to an increased incidence of adverse events and side effects. Investigators must ensure that treatment dose, route, and administration are optimal for a standard comparison, as well as comparison between treatment groups. In addition, selection of active control and treatment controls must be chosen to ensure both patient and investigator blinding. Therapeutic decisions made in a clinical trial situation because of the investigator's attempts to guess or presume what treatment group the patient is in will lead to bias. In a blinded trial, to maintain results validity, investigators should

make every effort to conceal treatment arms, for example by using a central laboratory system to read results and dictate changes in study drug. Techniques used to maintain blinding should be delineated prior to trial execution and communicated in results reporting.

### **Scientific Integrity**

Integrity in scientific research seeks to promote accuracy, honesty, and truthfulness in the conduct and reporting of that research. Compromise of scientific integrity manifests in a variety of ways, including data fabrication, fraud, deception, falsification of data or results, or plagiarism. Although most investigators would not intentionally manipulate data in an attempt to mislead others, it is virtually impossible for researchers to remain completely objective. As a result, researchers can introduce bias into their studies unintentionally. Such an act of unintentional bias is generally considered a form of scientific error. In contrast, if an investigator intentionally manipulates data to yield a specific result, this is intentional bias and is a form of fraud. Unfortunately, being able to discern an individual's intent can be difficult.

Misconduct in science is not a victimless practice. Misconduct can harm patients and others outside the scientific arena when falsified results become the basis for medical treatment. This is especially worrisome when one considers that clinical guidelines, governing the diagnosis and treatment of patients, may contain information that lacks objectivity. When this happens, the untoward effects are multiplied many times in patients. Society pays the price when scientific misconduct squanders public funds that could be applied in other areas. Scientific misconduct can also result in a ripple effect when others use research results to prevent or hinder certain areas of scientific inquiry or use published data to disparage other therapies. In the realm of clinical, translational, and health system research, this is seen when the marketing of a therapeutic entity drives the science, rather than science driving the marketing of drugs.

Falsification of data or results by misreporting data is not acceptable. It is a common practice among some investigators to review data and detect outliers. Once identified, outliers are generally not included in further data analyses. Justification for this practice is founded on the premise that if a data point significantly deviates from the norm then something must be abnormal or wrong with that data point. As a result, exclusion of outlying data points will result in stronger statistical outcomes. Although this practice can seem to be rational, it has the potential to dismiss valid and important observations that may signify rare population characteristics. Therefore, it becomes a fine line between ensuring the quality and integrity of data and unethical data manipulation.

The results of a particular investigation of a drug, device or clinical practice may have a dramatic impact on the future viability of the drug, device, or clinical practice. A linked consequence may be the likelihood of the investigator receiving funding for future projects involving a product depends on the favorability of the results of previous studies. This reality can put an investigator in an unenviable position if the study results make a sponsor's product look inferior to a competitor. In such a case, the sponsor can attempt to pressure the investigator to manipulate or suppress data.<sup>70</sup> In extreme cases, a sponsor may threaten legal action against an investigator if he or she proceeds with publication of a study with unfavorable findings.<sup>71,72</sup> Such cases have highlighted the importance of contracts between sponsors and investigators/institutions. These cases make it clear that the conditions of data ownership and rights of publication should be clearly identified and spelled out in a written contract prior to the initiation of a research project, with the intent to protect the investigator's scientific autonomy.

Even if data ownership and rights of publication are clearly outlined, sponsors can still attempt to influence a study by requiring specific methods or inclusion/exclusion criteria that

may intentionally bias study findings. Although agreeing to participate in marketing studies is not unethical, investigators should approach participation in such studies with caution. Even though investigators openly disclose funding sources and conflicts of interests, they should be aware of the possibility that the sponsor may attempt to lend validity/prestige to the study by using the investigator's name or the name of their institution.

## **Conclusion**

Objectivity of researchers, their ethical construct, and the resultant scientific integrity of that research are the foundational values of clinical and translational investigations and the basis for public trust. All researchers must be led by the data, not by other interests that might undermine the scientific integrity of their work. Everyone in the pharmacy, medicine, and nursing profession know of and appreciate the rewards of scientific research. Successful research brings valued publications, advancement of careers, grant renewals for institutions, and the professional satisfaction of accomplishment. Most important is the discovery and development of new drugs, devices, and clinical interventions that save lives and alleviate suffering. A commitment to scientific integrity is optimized when one's education and training in scientific practices and the ethical conduct of research is begun early and continued throughout their career.

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**Table 1: Breach of ethical conduct by medical scientists.**

**Percentage of scientists who say that they engaged in the behavior listed below within the previous 3 years (n=3247)**

<b>Top ten behaviors</b>	<b>All</b>	<b>Mid-career</b>	<b>Early-career</b>
1. Falsifying or ‘cooking’ research data	0.3	0.2	0.5
2. Ignoring major aspects of human-subject requirements	0.3	0.3	0.4
3. Not properly disclosing involvement in firms whose products are based on one’s own research	0.3	0.4	0.3
4. Relationships with students, research subjects or clients that may be interpreted as questionable	1.4	1.3	1.4
5. Using another’s ideas without obtaining permission or giving due credit	1.4	1.7	1.0
6. Unauthorized use of confidential information in connection with one’s own research	1.7	2.4	0.8 ***
7. Failing to present data that contradict one’s own previous research	6.0	6.5	5.3
8. Circumventing certain minor aspects of human-subject requirements	7.6	9.0	6.0 **
9. Overlooking others' use of flawed data or questionable interpretation of data	12.5	12.2	12.8
10. Changing the design, methodology or results of a study in response to pressure from a funding source	15.5	20.6	9.5 ***
<b>Other behaviors</b>			
11. Publishing the same data or results in two or more publications	4.7	5.9	3.4 **
12. Inappropriately assigning authorship credit	10.0	12.3	7.4 ***
13. Withholding details of methodology or results in papers or proposals	10.8	12.4	8.9 **
14. Using inadequate or inappropriate research designs	13.5	14.6	12.2
15. Dropping observations or data points from analyses based on a gut feeling that they were inaccurate	15.3	14.3	16.5
16. Inadequate record keeping related to research projects	27.5	27.7	27.3

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Martinson BC, Anderson MS, de Vries R. Scientists behaving badly. Nature 2005; 435:737-38.,

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**Table 2.** Summary of Secretary’s Advisory Committee on Human Subjects Protection

Recommendations on the HIPAA Privacy Rule (Approved by Secretary Thompson on December 29, 2004).<sup>13</sup>

<b>Topic</b>	<b>SACHRP Recommendations</b>
Accounting requirements for research	Recommendation I: The disclosure of protected health information (PHI) for research purposes should be expressly exempted from the Final Privacy Rule’s accounting requirements, and instead, Covered Entities should be required to inform patients in the Notice of Privacy Practices that their PHI may be used and disclosed for research purposes without their express authorization only in limited circumstances where additional safeguards are in place.
Standards for de-identification	Recommendation II: The Department should review the standards for de-identification of data in order to reduce the number of data categories that must be eliminated for data to be regarded as de-identified. Among those data categories that should be strongly considered for deletion from the de-identification standards are zip codes, geographic subdivisions, and dates. While the specific addresses of persons should not be included in de-identified information, more general areas of residence, work or origin, may, in fact, be essential to epidemiologic and other studies of, for example, disease incidence. Additionally, most dates, including admission and discharge dates, provide essential endpoints for much research without directly identifying the individual.
Research recruitment	Recommendation III: Rather than focusing on the distinction between internal and external researchers created by HIPAA’s artificial organizational rules, the Department should key any distinction in the ability of researchers to use PHI to contact subjects without the additional requirement of Institutional Review Board (IRB) waiver or a business associate agreement around whether the Covered Entity exercises effective control over the researcher through application of its policies and procedures. Specifically, SACHRP recommends that the existing distinction be removed between, on the one hand, all researchers who are affiliated with the Covered Entity, through membership in the Covered Entity’s workforce, making them internal to the Covered Entity for HIPAA purposes, and on the other hand, those who otherwise are subject to the Covered Entity’s policies and procedures, for example, by virtue of being a member of the Covered Entity’s faculty or medical staff or by being in an organized health care arrangement with the Covered Entity. SACHRP also recommends that additional guidance be provided so that the Department’s interpretation of HIPAA does not result in a weakening of existing privacy protections under the Common Rule.
Research authorizations	Recommendation IV: When an IRB has considered and approved a research consent form that permits consent to certain future uses under the

Common Rule standard, the Final Privacy Rule should likewise permit subjects to authorize the use and disclosure of their PHI for the same future uses. Any subsequent research using the PHI that goes beyond the scope of the authorization to future uses or disclosures would require IRB or Privacy Board waiver of the Privacy Rule's Authorization requirements, or subsequent authorization from each subject.

Recommendation V: The Department should revise HIPAA's compound authorization rules to permit the combining of research authorizations into one form when researchers seek to bank data and materials collected as part of an underlying clinical trial; however, in order to promote patients/subject choice, the rules should require that subjects be given the ability to opt in to the banking portion of the authorization.

Recommendation VI: The Department should revise the categories of research for which authorization is not required, so that those categories are consistent with research determined by an IRB or other appropriate institutional authority to be exempt from the requirements of the Common Rule.

Transition provisions

Recommendation VII: The Department should revise the transition Rules to grandfather not only research that received IRB waiver of informed consent under the Common Rule prior to HIPAA's compliance date but also research that did not receive IRB review or oversight as a result of having met an exemption under the Common Rule.

Applicability abroad

Recommendation VIII: The Department should clarify, if legally possible, that PHI collected from foreign nationals outside the United States by researchers engaged in international research who are affiliated with Covered Entities is not subject to HIPAA's requirements solely as a result of the researcher's affiliation with the Covered Entity. Alternatively, SACHRP recommends that there be guidance as to how research conducted outside the United States can be insulated from HIPAA's applicability so that Covered Entities and their affiliated researchers can continue to participate in this important research without triggering HIPAA's requirements.

Public health

Recommendation IX: The Department should revisit both the definition of public health authority as well as the exception for uses and disclosures for public health activities. The revisions should serve to broaden them sufficiently to ensure that federal and state agencies whose primary purpose is the prevention or control of disease, injury, or disability or the analysis of data in alliance with public health and public benefits agencies fall under this exception, even if the legal authority establishing such agencies does not explicitly authorize them to compel the collection of PHI in the course of their duties.

**Appendix A. Identifiers Considered Individually Identifiable Health Information  
(Protected Health Information).**

1. Names;
2. All geographic subdivisions smaller than a state (e.g., street address, city, county) with the exception of the first three digits of a zip code;
3. All elements of dates (except year), including birth date, admission date, discharge date, date of death; and all ages over 89;
4. Telephone numbers;
5. Fax numbers;
6. Electronic mail (e-mail) addresses;
7. Social security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web Universal Resource Locators (URLs);
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including finger and voice prints;
17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic, or code that could be used alone or in combination with other information to identify an individual.