Regulatory and Ethical Issues in Inflammatory Bowel Disease Research

The zeal of clinician-researchers to advance the science and improve care must be tempered by the necessity to conduct research studies on patients with inflammatory bowel disease in strict accordance with federal regulations and also maintain high ethical standards in the patient–physician relationship. Conflicts of interest, both non-financial and financial, must be recognized and managed to insure the safety of research participants and the integrity of scientific studies.

FEDERAL REGULATIONS AND IBD RESEARCH

Therapeutic trials in IBD must satisfy the rules of two masters—the Office of Human Research Protection (OHRP) and the Food and Drug Administration (FDA). Ironically, the regulations for these two federal agencies are not always in sync. The OHRP operates under the Common Rule of the Code of Federal Regulations (CFR) (45 CFR Part 46) which governs the operations of 17 federal agencies that include the Department of Heath and Human Services (DHHS) which oversees the OHRP, as well as the Veterans Administration. Noticeably absent from the list of federal agencies that adhere to the Common Rule is the FDA, which operates under different federal codes, 21 CFR Parts 50 & 56.

The separate regulations for the OHRP and the FDA differ in 4 aspects concerning human research (Table 1). The OHRP defines a human subject as a living individual from whom there is collection of data from interaction or intervention. In contrast, the FDA defines a human subject as an individual who is or becomes a participant in research either as a recipient of a test or article or as a control. This difference between the OHRP and the FDA on the definition of a subject may cause confusion regarding storage and future use of tissue samples from study subjects.

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which the OHRP regulates, but is not an area of concern for the FDA, since tissue doesn’t fit the definition of a human subject. The two agencies also differ in their view towards emergency use of medications or devices. The OHRP does not recognize any exception to institutional review board (IRB) approval and therefore the recipient of an emergency use drug or device for which there has not been IRB approval is not considered a research participant, and the data from that subject may not be used in a research study, and may not be published. In contrast, the FDA recognizes emergency use of research drugs or devices as acceptable when the subject’s situation is life-threatening, when there is no standard acceptable treatment, and when there is insufficient time for IRB review and approval. Emergency use guidelines from the FDA require written informed consent and although the consent form is noted by the IRB, it is not approved by the IRB. Usually, a pharmaceutical or device company requires an acknowledgment from the IRB that the proposal for emergency use drug or device has been reviewed with confirmation that the IRB agrees, even though the IRB can’t officially approve the emergency use. Another difference in the OHRP and the FDA is in the requirements for reporting adverse events. The OHRP requires reporting of all adverse events (AEs), and not just serious adverse events (SAEs). By convention and as a practicality, AEs that are not SAEs are reported in summary form with progress reports to the IRB. In contrast, the FDA only requires reporting of serious or unexpected adverse events (SAEs) from studies in which drugs are used under an investigational new drug exemption (IND), and other AEs need not be reported. All research centers that use the study drug under the same IND must be notified of the SAEs from all other studies and study sites. This requirement includes all SAEs, related and unrelated to the study drug, which creates a tremendous workload for investigators to file the multitude of reports for studies that use an investigational drug that is being tested at multiple sites and in different studies, and sometimes for different diseases. The FDA has a different set of requirements for reporting adverse events in studies in which there is an investigational device exemption (IDE). When using an IDE, any unanticipated event, whether an AE or an SAE, related to the device or unrelated, must be reported and all centers using the device under the IDE must be notified. FDA approved devices used in IBD include wireless capsule endoscopy, high definition endoscopy, and chromoendoscopy for identification of dysplastic mucosa. Column apheresis is a current example of an IDE device used in IBD research. The final difference—and perhaps it is just a technicality—between the OHRP and the FDA has to do with the consent form. The FDA requires a statement that the agency can review the subject’s medical records, but the OHRP has no requirement for such a statement. This difference has been superseded by the Health Insurance Portability and Accountability Act (HIPPA) which requires that all research subjects are informed that their health related information may be reviewed by federal representatives.

For investigators using experimental therapies for IBD, the discrepancy in the rules of the OHRP and FDA are most apparent in the conflicts that occur in seeking approval from the local IRB for a multicenter industry-sponsored trial. The FDA provides guidance on the design and conduct of clinical trials, but the FDA does not routinely mandate all of the specific details of the study design. This leaves room for differences in interpretation of the general guidelines by the industry sponsor and the IRB regarding what measures are required to insure the safe conduct of a study. For example, the industry sponsor may decide that a data and safety monitoring board (DSMB) is not necessary in a particular treatment trial, and the company notes that the FDA did not require a DSMB. However, the local IRB may determine that the potential risks of the investigational agent are either unclear or potentially serious and that a DSMB is required. Unless the inves-

Table 1
Regulatory Differences: Office of Human Research Protection (OHRP) and The Food and Drug Administration (FDA)

| • Definition of a human research participant |
| • Emergency use of a drug or device |
| • Adverse Event reporting |
| • Information in the consent form on who has access to the participant’s data |
tigator is able to get the sponsor to add a DSMB, or persuade the IRB to forego the requirement, the study can’t be done at the local site. Similar conflicts may arise regarding the need for overall study stopping rules, with or without a DSMB in place, or regarding the frequency of follow-up testing to monitor for safety.

**ETHICAL ISSUES AND IBD RESEARCH**

The clinical investigator who conducts therapeutic trials in the treatment of IBD faces a number of potential conflicts of interest, both non-financial and financial. Unique aspects of IBD, including the onset at a young age and the lifelong nature of the disease, often strengthen the physician–patient bond and can accentuate some of these conflicts. Unlike infectious or malignant disease for which therapy may be curative or the disease may be fatal in a few months or years, physicians have an ongoing relationship with their patients with IBD that involves not only treatment, but also serving as the patient’s advocate. Examples include writing letters in support of insurance coverage for off-label use of prescription drugs, authorizing special arrangements at school or work to deal with symptoms, and providing justification for a patient obtaining disability payments.

When the clinician-advocate becomes the clinician-investigator by offering the patient participation in a therapeutic trial, it can be more difficult for both the physician and the patient to make an objective decision about entering a study. The concepts of clinical equipoise and therapeutic misconception illustrate some of the issues the clinician-investigator faces. In addition, non-financial and financial conflicts of interest can influence the patient–clinician/researcher relationship.

**ETHICAL ISSUES IN IBD RESEARCH**

**Clinical Equipoise**

The justification for randomized therapeutic trials is embodied in the concept of clinical equipoise, which exists when there is disagreement and uncertainty among experts as to the preferred treatment for a medical condition (1,2). Usually, the disagreement is based on high quality evidenced-based data. However, the clinician often makes decisions about therapy for situations in which there is little evidence-based data and uses all available resources, including personal practice experiences to make the best possible decision for the individual patient. Although the clinician may accept the concept of clinical equipoise, he or she may have a strong preference for one therapy over another and find it difficult to recommend that a particular patient consider enrolling in a randomized therapeutic trial. In IBD studies, this conflict is often resolved by performing add-on studies, in which patients are maintained on current therapy and randomized to adjunctive new therapies, which may include a placebo arm.

**Therapeutic Misconception**

Patients may misinterpret information about experimental therapy as highly likely to be beneficial, even though their physician has explained that they may receive placebo. This misunderstanding of the difference in clinical care and research has been termed “therapeutic misconception” in which the patient assumes that their trusted physician will only recommend treatment that will likely improve their condition (3). Therapeutic misconception may occur not only when the clinician is also the researcher, but when the treating physician refers a patient to a clinical research study, with the implication that the referral was made because entry into the study is the best treatment option. The physician who takes care of IBD patients should take extra care in explaining the inherent uncertainty of the outcome in a research study to deal with the potential for misunderstanding on the part of the patient.

**Non-Financial Conflicts of Interest**

Although reports of financial conflicts of interest in medical research are appearing with increasing frequency in the press, non-financial conflicts of interest (Table 2) are also a potential risk to the integrity of clinical research (4). The clinician-researcher has an ethical obligation to recognize these potential conflicts and manage them. Excessive zeal in recruiting patients to complete a study, such as by disregarding some of (continued on page 31)
the inclusion or exclusion criteria, cannot be justified by the need to advance the science or advance the researcher’s career. Institutional Review Boards must insure that safety measures are not only detailed in the protocol, but are properly monitored and that unsafe actions are reported and resolved.

Financial Conflicts of Interest

Remarkable advances in medical care have been achieved through the partnerships of academic medical centers with industry, to transfer discoveries and develop new drugs and devices. The U.S. government encouraged this relationship with the Bayh-Dole Act of 1980. As a result, clinician–researchers and their medical institutions often have financial conflicts of interest related to patents, and also royalties, consulting agreements, and research grants from industry (5,6). A financial conflict does not imply guilt, but it does require management to insure disclosure of the conflict to potential research subjects and to peers. Management of the conflict may require restriction of the researcher from some aspects of a study, such as prohibiting leadership, informed consent, participation in study procedures or data analysis, or authorship. Many academic centers have conflict-of-interest policies for investigators in clinical trials (7). Ultimately, the responsibility for disclosure of conflicts of interest rests with the investigator, who must report his or her financial relationships fully and accurately.

I have no financial conflicts of interest regarding this manuscript.

—William J. Tremaine

References

SUMMARY

The physician who treats patients with inflammatory bowel disease and also performs clinical research trials should be versed in the regulatory and ethical issues that arise. The differences in requirements between the OHRP and FDA can be confusing for the clinical investigator, particularly regarding emergency use of a drug or device, specific requirements for safety monitoring during a study, and adverse event reporting. There are ethical conflicts for the clinician-researcher involved in IBD research that are unique to patients with long-term illnesses, as the physician not only prescribes therapy, but also serves as the patient’s advocate to employers, schools, insurance companies, and for other social issues. The clinician-researcher must take special precautions to insure that these conflicts to do not adversely effect the patient’s management.

Table 2

Non-financial Conflicts of interest

- Desire to advance the science
- Investigator’s personal benefits
  - Career advancement
  - Enhanced reputation
  - Grant acquisition

Adapted from Levinsky (4)