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REPORT

Looking Back at 2006, Looking Ahead to 2007: 'Expanded Access,' Research Billing, International Research, Grants Accounting, *Catalona,* Gene Therapy, and Central IRBs

By Mark Barnes, Clinton D. Hermes, Katherine Saral, and Ellen Moskowitz

The end of 2006 brought with it a cascade of developments in the regulation and practice of human subjects research in general and clinical trials in particular. Issues that had percolated for some time continued to be relevant during 2006. In the area of conflicts of interest, for example, December 2006 saw the guilty plea of a prominent National Institute of Mental Health (NIMH) scientist, who had accepted consulting payments from private industry even as he was involved in his official duties with the same projects; that scientist also was made to disgorge the consulting fees he had received, and to pay a hefty fine. In being called before a congressional committee, this reportedly was the first National Institutes of Health (NIH) scientist to invoke the Fifth Amendment and to decline to testify.[1] Thus the issue that emerged full force years ago in the aftermath of Jesse Gelsinger's death in a gene therapy trial that allegedly was influenced by investigator and institutional conflicts of interest continued to appear in public media and in medical journal commentaries. Drug and device safety, and the accurate reporting of clinical trial results and adverse events, also continued to attract hefty media exposure: Merck wins and losses in various state court Vioxx-related cases mounted,[2] and bad side effects emerged for such widely touted treatments as drug-coated stents.[3] Access to investigational products also emerged as a leading issue, with the Food and Drug Administration (FDA) proposing new draft guidance on increased access to investigational drugs,[4] at the same time as the U.S. Court of Appeals for the D.C. Circuit agreed to rehear en banc a case brought by a patient treatment alliance to compel FDA to allow easier access to such unapproved investigational drugs, in *Abigail Alliance v. von Eschenbach*.[5] In federal grant administration, 2006 saw multiple settlements of time and effort reporting disputes and grants-accounting investigations, and Yale University was subjected to a significant multi-agency inquiry into its grants accounting practices, including allegations relating to inappropriate transfer of costs from one grant

[1] "Researcher Pleads Guilty to Improperly Taking Fees," *Wall Street Journal,* Dec. 8, 2006.

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[2] "Merck Loses Bid to Reverse Vioxx Ruling," *Wall Street Journal,* Dec. 23, 2006; "Merck Scores Another Vioxx-Trial Win," *Wall Street Journal,* Dec. 16, 2006.

[3] R. Winslow and A., Mathews, "How Doctors are Re-Thinking Drug-Coated Stents," *Wall Street Journal,* Dec. 9, 2006.

[4] FDA, Proposed Rules for Charging for Investigational Drugs and Expanded Access to Investigational Drugs for Treatment Use, Dec. 11, 2006, *available at* http://www.fda.gov/cder/regulatory/applications/IND_PR.htm.

[5] *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006), *en banc reh'g granted*, 2006 U.S. App. LEXIS 28974 (D.C. Cir. Nov. 21, 2006).

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to another.[6] The trends and pending developments are many, but in this article we try to identify these and related industry trends that those involved in designing, conducting, and overseeing clinical trials should monitor in the coming year.

1. Expanded 'Compassionate Use' of Unapproved Drugs for Treatment

In the past two decades, treatment advocates and patient groups, allied in many cases with physicians, have pushed the boundaries of access to unapproved drugs and devices. Indeed, in the late 1980s, AIDS advocates—acting in an environment in which there were no standard treatments available—pushed FDA into expanded access and ''treatment INDs'' (''IND'' representing ''investigational new drug application''), which allow groups of patients to receive unapproved drugs based on promising Phase III or even Phase II trial data. The cause of expanded access has been taken up in more recent years by cancer patients and their physicians. In *Abigail Alliance*, a three-judge panel of the U.S. Court of Appeals for the Federal Circuit, reinstating a case brought by treatment advocates, found a constitutional due process right of access to unapproved drugs—a decision with vastly negative implications for FDA authority over unapproved drugs.[7] In the midst of the continued appeals of that decision, on Dec. 14, 2006, FDA proposed two rules that augur continued changes in unapproved drug access, directly affecting pharmaceutical companies, research investigators, prescribing physicians, and patients.[8] The first rule aims to clarify the provisions under the Federal Food, Drug, and Cosmetic Act (FFDCA) for expanded access to investigational drugs for use in treatment,[9] while the second focuses on the circumstances and criteria under which charging patients for investigational drugs is appropriate.

Access to unapproved drugs outside the context of a clinical trial last was addressed by congressional enactment in the 1997 Food and Drug Administration Modernization Act (FDAMA),[10] which updated the FFDCA to make investigational drugs available to diagnose, monitor, or treat persons with serious or immediately life-threatening diseases. Although FDAMA did not require FDA to issue implementing regulations, the agency decided that such regulations were necessary to supplement a lack of awareness among the public and among physicians in nonacademic medical center settings of compassionate use options, to remedy perceived inequities in the authorization of investigational drugs for treatment use based on the site of treatment[11] and the type of disease treated,[12] and to define more clearly the eligibility criteria, submission requirements, and necessary safeguards that physicians and drug sponsors must adhere to in applying for expanded access use.

Accordingly, FDA's proposed rule reiterates the availability of investigational drugs under the so-called ''treatment IND'' or treatment protocol for large groups authorized by the 1987 regulations and establishes two additional categories of expanded access use: access for individual patients and access for ''intermediate-size'' patient populations. The proposed rule sets forth the criteria, submission requirements, and safeguards for these expanded access categories.

First, the patients for whom the investigational drug is requested must have a serious or life-threatening disease for which there is no alternative therapy. Second, the potential benefits of the treatment must outweigh its potential risks and the risks must not be unreasonable, given the disease to be treated and the severity of the recipient's condition. Third, providing the investigational drug must not interfere with the conduct of clinical trials supporting marketing approval.[13] Satisfaction of each of these criteria is subject to FDA's judgment.[14]

For an application for expanded access for individual patients, the proposed rule presents two additional criteria: the physician must determine that the probable risk to the patient from the investigational drug is not greater than the risk from the disease the drug is meant to treat, and FDA must be satisfied that the patient is unable to obtain the drug under a current clinical trial or other type of IND.[15] The preamble to the proposed rule offers some instances when a patient would be barred from participating in a clinical trial yet still be a good candidate for an investigational drug. These examples are relevant to substantiating compliance with the criteria for certain types of ''intermediate-size'' population expanded access, as well as individual expanded access: trial enrollment is closed, the study site is too distant from the patient, the patient cannot tolerate an active control, the patient is diagnosed with a disease or stage of disease different from that under study, or the patient otherwise is ineligible for the trial.[16] The provision covering access for individual patients also encompasses the access in emergencies that was an explicit part of FDAMA, but notably does not delineate the sorts of events that can qualify as emergencies.[17]

As to an application for expanded access for ''intermediate-size'' patient populations (which FDA anticipates will fall somewhere between 10 and 100 patients), the proposed rule specifies three situations warranting such an application: the drug is not being developed for marketing approval, the drug is being developed, or the drug is already approved but is not being marketed.[18] This focus on the provision, through expanded access, of drugs that are not being tested in clinical trials or already have been approved is an interesting elaboration on the statutory text. Under the regulation, patients could have access to drugs that a drug developer had not submitted earlier for an IND or to

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[6] *Investigation of Yale Research Accounting Seen as Reflection of Government Trend*, 5 Medical Research Law & Policy Rep. 491, July 19, 2006.

[7] *Abigail Alliance*, 445 F.3d at 486.

[8] *See* 71 Fed. Reg. 75147 and 71 Fed. Reg. 75168.

[9] *See* 21 U.S.C. § 360bbb.

[10] Pub. L. No. 105-115.

[11] Critics have argued that use of investigational drugs for treatment was concentrated in academic medical centers. 71 Fed. Reg. 75149.

[12] Criticism often has centered on the fact that treatment use previously has been available only to cancer and HIV-infected patients. *Id*.

[13] 71 Fed. Reg. 75150.

[14] Sponsors and treating physicians might find it worthwhile to distinguish criteria falling under FDA's discretion from those entrusted to physician judgment.

[15] 71 Fed. Reg. 75153.

[16] *Id*.

[17] *Id*.

[18] 71 Fed. Reg. 75154.

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drugs that treat conditions so rare that mounting a clinical trial has never seemed feasible. Also addressed are occasions when supply of a previously approved drug is disrupted because of violations of good manufacturing practice or when a drug is taken off the market for safety reasons. The preamble even suggests that expanded access for treatment use could be authorized for an unapproved drug when an approved drug with the same active ingredient becomes unavailable due to a drug shortage.[19]

The proposed rule contains two additional criteria pertaining to ''intermediate-size'' expanded access. First, the drug must be safe enough at the planned dose and duration to justify a clinical trial in the number of patients expected to receive it. Second, there must be at least preliminary evidence of effectiveness to make the drug a reasonable therapy for its recipients.[20] Together these criteria demonstrate that the intermediate-size population expanded-use authorization cannot be sought as a means to evade review akin to a clinical trial or to launch research in the guise of treatment. The proposed rule suggests that FDA will treat the request for expanded access simply as an application for a smaller clinical trial and require evidentiary grounding to support its authorization.

If the application is submitted to allow individual patient access to investigational drugs, the proposed rule permits a licensed physician, as well as the drug sponsor, to make the submission. As explained in the preamble, the physician will obtain the IND, but will rely on the sponsor's grant of a right of reference to information in its prior IND. The proposed rule does not require that a sponsor agree to give a right of reference. Indeed, the preamble comments that FDA cannot compel a sponsor or drug manufacturer to make an investigational drug or accompanying information available to facilitate treatment use.[21] However, a sponsor or manufacturer might consider it imprudent not to cooperate, and it is likely that sponsors will differ as to their willingness to make unapproved drugs more widely available under these new proposed regulations. Sponsors, investigators, and research institutions certainly have become mindful in 2006 of the risk that subjects in closed trials may demand—and even sue to obtain—continued access to unapproved therapies, as occurred when Amgen decided to end its trials of an unapproved drug for Parkinson's Disease.

The proposed rule imposes several requirements on licensed physicians who directly administer the investigational drug and entities who submit an IND or protocol for expanded access. Treating physicians are considered investigators and submitters are considered sponsors under FDA regulations and must comply with the responsibilities set out in Subpart D of 21 C.F.R. Part 312.[22] Additionally, the proposed rule stipulates especially that investigators must report adverse drug experiences to the sponsor, ensure that informed consent requirements are met and IRB approval obtained, and maintain case histories and drug disposition records. The proposed rule also highlights the onus on sponsors to submit IND safety reports, ensure that administering physicians are qualified, provide physicians with information to minimize risk and maximize benefits to recipients, maintain an effective IND for expanded access use, and maintain drug disposition records.[23] When individual physicians have applied for expanded access in these cases, they become sponsors as well as investigators, and inherit the reporting and monitoring obligations of both.

The safeguards established for intermediate-size population expanded use require that the sponsor monitor physicians' compliance with the protocol. The proposed rule also mandates annual FDA review of the use to determine whether it is interfering with the clinical development of the drug, or, if no trial currently is occurring with which the expanded access use might compete, whether it should be converted to a full clinical study geared toward marketing approval.

With comments due on the proposed rule by March 14, 2007, the proposal likely will be finalized by the middle of 2007. Although the use of investigational drugs for treatment is not a novel practice, it most likely will increase following FDA's creation of an enhanced regulatory framework for obtaining permission for this type of use. It is likely that the rule, depending on its final shape, will ignite further controversy over premature FDA approval of drugs or stimulate advocates of drug access to argue that access to life-saving drugs remains too restrictive. Pending in the background is the possibility that the revolutionary three-judge ruling in *Abigail Alliance* will be affirmed in 2007, resulting in ''expanded access'' that would dwarf FDA's own proposed expansion. Above all, investigators, sponsors, research institutions, and institutional review boards must remain vigilant in 2007 as to the provisions in protocols and informed consent forms, and to discussions relating to subjects' continued access to unapproved therapies—because promises made may, in this environment, become promises enforced by law.

2. Clinical Trial Costs: Charging for Investigational Drugs

With settlements at Rush University Medical Center, the University of Alabama, and other institutions over the past two years having focused on the issues of charging for services and items rendered in clinical trials, the Centers for Medicare & Medicaid Services (CMS), the Department of Health and Human Services Office of Inspector General (HHS OIG), and FDA have focused attention on how costs for clinical trials are allocated and collected. The second rule that FDA proposed on December 14, 2006, contains amendments to the regulations governing charges for investigational drugs, and thus relates directly to the larger issue of how clinical trial and drug and device development costs are allocated among sponsors, government programs, private third-party payers, research institutions, and patients/subjects. The recent proposed FDA revision relates to new circumstances in which charging for investigational drugs is appropriate, sets forth the criteria for charging, and explains what types of costs are recoverable. It is this area of FDA jurisdiction that directly overlaps with larger Medicare- and Medicaid-related concerns about the appropriateness of charging for research-related drugs, items, and services.

The impetus for the proposed revision is threefold. First, FDA realized that its assumption when the regu-

[19] *Id.*
[20] *Id.*
[21] 71 Fed. Reg. 75153.
[22] 21 C.F.R. § 312.50 *et. seq.*
[23] 71 Fed. Reg. 75152.

lations originally were published in 1987—that most requests would be to charge for a sponsor's drug being tested in a trial—was incorrect. In fact, the more common request has been to charge for an approved drug that would serve as the active control or a combination treatment in a trial of another drug. Other frequent charging requests have come from noncommercial investigators who have needed approved drugs to carry out comparative drug studies or to assess the safety or efficacy of these approved drugs in treating different indications. (One should note that in investigator-initiated studies, the investigators are in fact the sponsors for purposes of these and other FDA rules, and physician-sponsors and their institutions should understand that ''chargeability'' of these drug costs to patients and to public and private third-party payers is an essential part of clinical trial costing, planning, and informed consent.) Second, FDA needed to update the charging regulations to reflect the proposed addition (described above) of two more categories to ''expanded access'' for treatment. Third, FDA decided that the nature and extent of acceptable charges required clearer definition—such as how manufacturing, research, development, and handling costs might be factored into such charges.[24]

Several requirements from the 1987 regulations would continue under the new proposed rule. The sponsor must provide to FDA a written explanation justifying the necessity of a charge and explaining why it should not absorb the costs as a normal aspect of conducting a clinical trial. Certain conditions of charging remain consistent, including the sponsor's agreement not to engage in commercial promotion or advertisement. Under the proposed rule, FDA continues to have the right to withdraw authorization to charge if it concludes that charging is interfering with the development of the drug for marketing approval or that the sponsor no longer is meeting the criteria allowing charging.[25]

What is quite new in this proposal is its delineation of specific criteria that FDA will use to evaluate a clinical trial sponsor's explanation for why charging is necessary. When the sponsor seeks authority to charge for the very drug under review, the proposed rule requires evidence that a drug's potential clinical benefits offer significant advantages over available products, evidence that a trial is necessary for development of the drug, and evidence that charging is necessary for the trial to be conducted.[26] The criteria are less stringent when the sponsor seeks authority to charge for an approved drug that is a crucial component of a clinical trial for another drug, either as an active control or as a concomitant therapy, or where a noncommercial sponsor seeks to charge for an approved drug in order to test the drug for another indication. In both cases the sponsor need only show an adequate trial design and affirm that the manufacturer is not providing the approved drug for free.[27] Interestingly, although the preamble states that the relaxed criteria for allowing sponsors to charge for an approved drug when the trial focuses on a new indication are intended to ease the burden on small, noncommercial sponsors, there is no explicit restriction in the proposed rule. Conceivably, a sponsor of any size and orientation could get permission to charge in the course of conducting a trial to demonstrate the efficacy of an approved drug for an off-label use.

Also new in the proposed rule are the criteria for charging for the three types of expanded access to investigational drugs for treatment use. Here FDA, attuned to the danger of interference with the development of drugs for marketing approval, hones in on the treatment INDs that have the greatest potential to upset enrollment in clinical trials. To assure FDA that charging is not a hindrance to conventional methods of drug development, sponsors of treatment INDs would be required to give evidence of sufficient enrollment in clinical trials, adequate progress towards marketing approval, and plans that specify development milestones in the coming year. The proposed rule circumscribes charging practices further by limiting the authorization to one year and to the number of patients who may receive the drug under the expanded-access submission.[28]

Finally, the proposed rule marks out the direct costs, for which charging is permissible. Direct costs are: per-unit manufacturing costs; acquisition costs; shipping, handling, and storage costs; and costs of monitoring an expanded-access protocol. Indirect costs, which may not be recouped through investigational drug charges, are: expenditures for manufacturing plants and equipment; costs incurred to produce the drug for commercial sale; and any other costs that would have been realized in the absence of a clinical trail or expanded access use.[29]

Like the proposed rule for expanded access to investigational drugs, the proposed charging rule is open for comment until March 14, 2007, and likely will be finalized by mid-2007. As proposed, the rule appears designed to restrict ''chargeability'' so as to prevent sponsors from accelerating the recovery of their costs prior to marketing approval. Although the rule undoubtedly will undergo revisions following the comment period, its current articulation seems well-tailored to FDA's goal of promoting drug development and therapeutic access that until now might have been stymied by the lack of financial incentives. In the interim, during 2007, given this increased attention to charging for investigational drugs in clinical trials and in treatment INDs, it would be wise for sponsors, investigators, IRBs, and research institutions to assure that in their investigational studies, charging for drugs is addressed in protocols and in subject informed consent. Experience has shown that, because of investigators' ignorance of these rules, they may not be respected in all cases.

3. Research Billing Requirements: Medicare as Secondary Payer Controversy Remains Unresolved

During 2006, issues around reimbursement for medical services provided in the course of clinical research continued to evolve and have remained a focus of CMS policymaking and of internal compliance for both industry and research institutions. Some mark the Rush University Medical Center case as the starting point for regulatory activity in this area: in November 2005, federal prosecutors announced that Rush University Medi-

[24] 71 Fed. Reg. 75169.
[25] *Id*.
[26] 71 Fed. Reg. 75171.
[27] 71 Fed. Reg. 75172.
[28] *Id*.
[29] 71 Fed. Reg. 75173.

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cal Center had agreed to pay more than $1 million to settle allegations of improper billings to the Medicare and Medicaid programs related to clinical research. The government has focused on the area of clinical trial reimbursement, scrutinizing billing practices to ensure that the government is not charged for care for which it does not pay under current coverage policies or for which reimbursement is available from the sponsor.

Proper third-party (including Medicare) billing requires clear demarcation in billing systems and clinical trial agreement budgets between services that are ''research-only,'' ''standard-of-care,'' and billable to a third-party payer. Failing to conform to these standards could result in liability under the federal False Claims Act and possibly other federal and state laws. Important for this issue in the year ahead is the advent on Jan. 1, 2007, of new requirements for health care providers that receive more than $5 million in annual Medicaid reimbursement. Imposed by the Deficit Reduction Act of 2005, this law now requires health care providers to adopt specific compliance policies and workforce training that describe for employees the False Claims Act, whistleblower protections, and the availability of financial rewards for notifying federal and state authorities of illegal billing practices.[30] The act also provides financial incentives for state governments to adopt state False Claims Act equivalents.[31] Given that many previous research billing investigations have been triggered by internal whistleblowers, the advent of these new requirements in 2007 will make even more risky any improper, ambiguous, or marginally acceptable clinical trial billing practices.

In September 2000, CMS issued its National Coverage Decision (NCD) clarifying the extent to which Medicare will cover the routine health care costs of Medicare beneficiaries enrolled in ''qualifying'' clinical trials of drugs. That document has received wide attention in compliance and research circles: its many, confusing requirements (including Medicare coding requirements) often have stumped research institutions that have tried to comply with it and commercial sponsors that have tried to respect it in study agreements and study budgeting. In December 2006, responding to dissatisfaction with the NCD's ambiguities, CMS convened a meeting of its Medicare Coverage Advisory Committee to hear and respond to proposals from CMS staff on potential changes to the NCD. Among those potential changes put forth at the December 2006 meeting—and supported by clear majorities of the Coverage Advisory Committee—were:

- removing the status of IND–exempt studies as ''deemed'' automatically to have the desirable characteristics for an NCD ''qualifying trial'';
- extension of such deemed status to trials that had been approved by *any* federal agency—not just the Centers for Disease Control and Prevention (CDC), NIH, the Agency for Healthcare Research and Quality, CMS, the Department of Defense, and the Veterans Administration, as exclusively specified in the original NCD;
- clarification that deemed status would include trials that have been reviewed and approved as scientifically sound by centers or cooperative groups funded by a federal agency;
- extension of ''qualifying trial'' status to otherwise eligible humanitarian device exemption (HDE) protocols;
- adding a requirement that to be qualifying under the NCD, a trial must be registered at clinicaltrials.gov—the NIH registry of clinical trials;
- adding a requirement that to be qualifying under the NCD, a study protocol explicitly must address plans for the release and diffusion of study results, including negative results; and
- adding a requirement that to be qualifying under the NCD, a trial must enroll ''sufficient numbers'' of ''relevant subpopulations,'' as defined by gender, race/ethnicity, age, and ''other factors.''

In 2007, we likely will see CMS finalize new guidance for these qualifying clinical trials, and in the ways described above, by using its third-party payer funding leverage, CMS is poised to intervene in clinical research protocols in unprecedented ways, relating to study populations and dissemination of study findings. CMS also has indicated that it is likely to adopt coding requirements for *all* clinical services delivered to subjects of qualifying trials—not just those services whose coverage depends directly on the NCD. This too would mark a compliance revolution in 2007, requiring retooling of billing and claims processing for services delivered to patients enrolled in clinical trials.

What CMS staff did not address at the December 2006 meeting, however, was the most burning research billing issue of 2006: how to interpret and apply the principles of the April 13, 2004, CMS letter, in which the agency took the position that in the context of clinical trials, the Medicare secondary payor rule[32] renders Medicare payment secondary to treatment expenses potentially payable by a research sponsor. The actual context of that April 2004 letter was a hypothetical clinical study agreement in which an industry sponsor had agreed to pay for costs associated with clinical trial injuries to subjects if third-party payers, like Medicare, were billed for the treatment but denied the claims. CMS opined that in such a case, Medicare should not be billed at all for treatment of study complications, the sponsor having become the primary payer by virtue of that clinical study agreement provision. Under that approach, if a research sponsor promises in its clinical trial agreements and consent forms to pay for certain types of care, e.g., research-related injuries, CMS deems this promise to pay as an ''insurance policy or plan,'' which makes the sponsor, and not Medicare, responsible for payment for that care. Of critical importance is that the CMS interpretation applies regardless of whether the sponsor expressly states that its coverage is secondary to Medicare. The CMS letter also indicated that sponsors or researchers who become aware of prior improper Medicare payment under these circumstances must reimburse Medicare for any payments improperly made by the agency.

The fact is that, for decades, commercially sponsored clinical study agreements often have contained clauses much like, or identical to, the hypothetical clause addressed in the April 2004 CMS letter. Yet until April 2004, CMS had never addressed this issue, nor given

[30] Deficit Reduction Act of 2005, Pub. L. No. 109-171, § 6032, 120 Stat. 4, 73 (2006).

[31] *Id.* § 6031, 120 Stat. at 72-73.

[32] 42 U.S.C. § 1395y(b)(2)(A)(ii).

any indication that such clinical study agreement provisions were inappropriate. Many of these study agreements were entered into before this letter was widely known, and trials continue under those agreements. In short, in December 2006, CMS addressed some parts of the industry confusion around the NCD, but failed to address the question that will continue to plague us daily: how do we provide that sponsors will be payers of last resort, so that research institutions and patients/subjects are not harmed by faulty judgments of what is and is not a clinical trial service appropriately billable to Medicare, Medicaid, and other third-party payers?

4. Some Relief in Sight for 'Engagement' of Institutions and Physicians in Research

In October 2006, the HHS Office for Human Research Protections (OHRP) released a new draft guidance document (to replace two documents created in 1999) as to when persons and entities should be considered to be ''engaging in human subjects research'' and thus subject to the Common Rule (45 C.F.R. Part 46, Subpart A) requirements or other requirements stipulated in an institution's Federalwide Assurance (FWA). Certainty on this question is important to anyone who performs activities that touch upon human subjects research funded by HHS or any of the other U.S. government agencies that have adopted the Common Rule: all institutions, and their employees and agents, engaging in such research (unless exempt under certain regulations) must hold an FWA of compliance with federal regulations, and must certify that the research proposal has been approved by the designated IRB and will be subject to continuing review.[33] The draft guidance, therefore, is critical to assisting institutions in determining whether they must acquire an FWA or obtain IRB approval before starting their work. The issue of whether physician's offices and clinics that only perform follow-up examinations of clinical trial subjects are themselves ''engaged in'' a study has bedeviled many institutions, especially in cancer treatment, where many patients/subjects receive their primary intervention at a medical center but then return home for follow-up care from a local provider. Zealous application of the current ''engaged in research'' standards have required these local medical office and clinic research sites to gain IRB approval and oversight, even when their connection to a study is oblique. A similar bedevilment has occurred in institutions that make databases and specimen banks available to outside researchers: are such institutions ''engaged in research'' by virtue of their release of information or identified specimens, and must they therefore have approval and continuing review of these external studies from their own IRBs?

Although many of the examples in the recent draft guidance conform to the 1999 guidance, there are a few notable changes, additions, and omissions. One salient shift is the decision to characterize as ''not engaged in research'' those institutions that merely release identifiable private information or identifiable biological specimens to another institution for research purposes.[34] In OHRP's new view, release alone is not equivalent to ''obtaining'' private identifiable information. At the same time, the draft guidance makes plain that ''obtain'' should be broadly understood as including use or analysis for research purposes of identifiable private information or specimens that the institution might already possess.[35] A transaction is not necessary for ''obtaining'' to take place. The draft guidance also warns that institutions releasing identifiable private information or specimens that initially were collected for another research study must ensure that release does not violate the earlier informed consent or, if consent was waived, is not inconsistent with the IRB's basis for granting a waiver.[36]

Another change in the proposed guidance is the expansion of scenarios in which providing clinical trial-related medical care would not constitute engagement in human subjects research. The draft guidance eliminates the requirement that an institution be a recognized ''Cooperative Protocol Research Program'' (CPRP), because OHRP now considers that to be an unnecessary condition.[37] However, providers of follow-up care or other clinical services to research participants must continue to meet a host of other conditions, including the now explicitly stated requirement that clinicians not administer the primary study interventions tested under the protocol.[38] The new proposed guidance further would classify as not engaged in research collaborating institutions that obtain coded private information, so long as the key to decipher the code is unavailable to that institution.

Another change not emphasized in the *Federal Register* notice, but that emerges from the comparison document that OHRP produced, merits attention. The 1999 guidance mentions an example in which consultants happen to access identifiable private information while onsite at the research institution and notes that these consultants are not engaged in research. The recent draft guidance revises that example to cut out the conditional phrasing, so that consultants may now deliberately plan to access individually identifiable information while at a research institution, so long as the consultants are overseen by an IRB and do not remove the private information.[39]

In the preamble and the draft guidance, OHRP also points out that, by entering into collaborations or joint review arrangements, institutions can minimize the burden of complying with requirements imposed as a consequence of engaging in research. OHRP allows institutional and independent investigators to operate under a collaborating institution's FWA by signing an Individual Investigator Agreement.[40] Similarly, the draft guidance permits an institution to depend upon the review of another qualified IRB, subject to certain exceptions described in the guidance.[41]

One final element of the draft guidance worth observing is OHRP's comment that the examples given are illustrative, not exhaustive.[42] Although fairly broad in its

[33] 45 C.F.R. §§ 46.103(a), (b), and (f).
[34] 71 Fed. Reg. 71170.
[35] OHRP Draft Guidance, p. 5.
[36] OHRP Draft Guidance, Engagement Comparison Table, B(1).
[37] 71 Fed. Reg. 71171.
[38] OHRP Draft Guidance, Engagement Comparison Table, III.B(7).
[39] OHRP Draft Guidance, Engagement Comparison Table, III.B(3).
[40] 71 Fed. Reg. 71171.
[41] OHRP Draft Guidance, Engagement Comparison Table, III.A.
[42] OHRP Draft Guidance, p. 5.

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hypotheses of activities, it should not be assumed that all activities not fitting into the examples cited as engaging in research are automatically not engaging in research. Careful analysis and analogy to the representative examples should be exercised. Moreover, the experience of the authors in raising ''engaged in research questions'' with OHRP's Division of Policy and Assurances is that OHRP recommends IRB review when an institution or entity is unsure if it is engaged in research under the existing (and presumably the proposed) guidelines; OHRP generally will respect an IRB's reasoned determination of non-engagement unless that determination clearly contravenes the guidelines.

If adopted in 2007, the new draft guidance on engagement in human subjects research likely would relieve physicians and other private practitioners from the necessity of complying with federal requirements governing researchers solely because they treat patients who concurrently are participants in research trials. It also might offer peace of mind to a number of institutions that allow external research use of their tissue banks and databases.

5. International Research: Federal Grant Compliance and Non-U.S. Research Regulations

More NIH, CDC, and other HHS funds (as well as funds from other agencies, such as the U.S. Agency for International Development and the State Department) are being devoted to internationally sponsored projects (including research studies) than ever before. Pharmaceutical, device, and biotechnology companies are conducting an increasing percentage of their clinical trials—particularly early-phase trials—outside the United States. In many cases, such studies are being done abroad because they involve infectious diseases or other conditions with higher prevalence rates in the target non-U.S. population. Yet the benefits of conducting clinical trials in foreign countries do not come without risks. U.S. governmental bodies, media, and the public are paying greater attention to the quality of research practices and treatment of study subjects in developing countries. And an increasing number of developing countries—including Nigeria in 2006[43]—have overhauled their national research regulations, requiring sponsors and investigators to pay more careful attention to local law compliance than ever before. This compliance may include consideration of whether U.S.-based physician investigators are required to register with local health professions boards—as, for example, in Zimbabwe[44]—even though they are not engaging in any clinical care of patients/subjects.

Many had expected that in 2006, FDA would finalize its revisions to requirements for studies conducted outside the United States, but that has not yet occurred. Under current FDA regulations, while international studies conducted under an approved IND or Investigational Device Exemption (IDE) must meet the same requirements that pertain to studies conducted in the United States, different standards have been applied to foreign studies not conducted under an IND or IDE. FDA mandates that non-IND and non-IDE studies that seek FDA acceptance conform to the principles contained in the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever is more stringent. In 2004, FDA proposed a final rule to change the standards for the acceptance of international clinical research by replacing the requirement to conduct international research in accordance with the Declaration of Helsinki with a requirement to conduct the research in accordance with more developed and detailed good clinical practice (GCP) standards.[45] The adoption of the internationally recognized GCP standards should create greater uniformity among clinical studies, regardless of where they are conducted, and increase protections to individual subjects in many cases. Although expected in 2006, we are now looking toward the possible adoption of the new standard in 2007.

In academic institutions and academic medical centers that are conducting unprecedented amounts of sponsored research outside the United States, the challenge is not only local research regulation compliance but also compliance with NIH, CDC, Health Resources and Services Administration, and other grant requirements. When such institutions have subcontractors outside of the United States, the Office of Management and Budget (OMB) circular requirements remain applicable to those subcontractors. Thus, for example, fixed equipment inventories, bidding and tender rules, time and effort reporting, and salaries based upon an established institutional base salary all remain applicable to non-U.S. subcontractors under these sponsored research grants and contracts. In 2006, across the country, as internationally funded projects expanded, medical schools, public health schools, schools of agriculture, and medical centers began to focus sustained attention on these international grant compliance issues. In many U.S. institutions during 2006, we saw positions created and filled solely for international program administration and compliance, and this trend no doubt will accelerate in 2007. We also saw, as noted above, stepped-up enforcement of grants-accounting standards in general, including the significant multi-agency investigation at Yale. In short, it has begun to dawn on U.S. academic and medical institutions that these international projects represent substantial monies and substantial risks and that the old model of allowing principal investigators to administer and fully control these programs is no longer sustainable. The compliance burdens, and the risks of noncompliance, are simply too great. For some institutions, in terms of their day-to-day research administration, measures taken to assure international program compliance may rival only research billing as *the* ''hot'' issue of 2007.

6. *Washington University v. Catalona*: Secondary Uses of Identified Data and Tissue

In 2006, *Washington University v. Catalona*—widely viewed as a bellwether case—was decided in federal District Court, and now is on appeal in the Eight Circuit Court of Appeals. The Catalona case has focused attention on the increasingly valuable research uses of data or tissue samples obtained in the course of a ''primary''

[43] Nigeria National Code of Health Research Ethics, 2006, *available at* http://www.nhrec.net/nhrec/code.html.

[44] Zimbabwe Medical, Dental and Allied Professions Act, Section 121 (even use of an M.D. title by an investigator necessitates professional registration).

[45] FDA, Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 70 Fed. Reg. 64554 (Oct. 31, 2005) (to be codified at 21 C.F.R. § 312.120).

clinical trial and on the legal and ethical concerns surrounding such research.

Companies, and in some cases researchers at hospitals or other institutions, are frequently using stored biologic materials, which allow them to conduct often quite meaningful research, such as pharmacogenomic or exploratory bench research. As a result, companies and some research institutions are attempting to secure access to these data and tissue samples through their clinical trial agreements and informed consent forms, and some research institutions are making corresponding efforts to limit this access. At the same time, these parties are becoming increasingly aware of and concerned about the possible legal implications of conducting this ''secondary'' research, including implications under the Health Insurance Portability and Accountability Act of 1996 Privacy Rule, the Common Rule, FDA research regulations, common law, and state law. Both industry and academia are developing policies and procedures to address some of the concerns raised by this secondary research, and while this issue has been the subject of industry-wide discussions and working groups for over a year, little consensus has been reached.

One central issue is whether the secondary research use of data and tissue collected in the course of a primary study violates rules dealing with informed consent, when the subjects in the primary study did not expressly consent to the secondary research. The Common Rule requires that patients have adequate information to make an informed decision about whether to participate in a research study and that a subject's eventual decision to participate be documented, absent an IRB waiver of these requirements. An informed consent that does not include ''a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental'' is legally insufficient.[46] This required specificity can pose problems for researchers seeking to conduct research, the details of which are largely unknown at the time of the informed consent. The regulations do not, however, explicitly prohibit a researcher from seeking or a patient from giving informed consent for future research in a general manner (although such a permission would be insufficient under the Privacy Rule), and researchers across the country are now conducting research studies on data and tissue that are not specified in the consent form pursuant to which the data or tissue samples were collected.

Emblematic of the controversy over secondary use of data and tissue has been the case of a prominent urologist, Dr. William Catalona, who sought to take research subjects' biological materials with him when he left his post at Washington University for a similar position at Northwestern University. In April 2006, a federal District Court in St. Louis ruled that he could not.[47] The court found that Washington University owned the materials stored in its biorepository (which had been assembled there while Catalona was a paid faculty member of the University), and that the research participants did not have the right to direct Washington University to transfer their specimens to Northwestern. Oral arguments in Catalona's appeal were heard by the Eighth Circuit on December 13, 2006. Research participants who joined the suit argued that their intent was to donate their biological materials to Dr. Catalona for his research.[48] These intervenors asserted that their right to withdraw from a study, enshrined in the Common Rule and in the consent forms they signed, entails a right to direct a transfer of the materials. That the lower court disagreed with them has somewhat clarified—at least for now—the law governing ownership and control of biological materials: according to the *Catalona* court, absent language in the informed consent specifying that the research participant can direct future use, the research institution to which the tissue was donated controls the tissue. The 2006 District Court ruling reinforced the two most important cases on ownership and secondary use of biological materials, *Moore v. Regents of the University of California* and *Greenberg v. Miami Children's Hospital Research Institute, Inc.* Under both opinions patients are held to have lost any ownership rights to the materials upon consenting to and effectuating their donation.

In reaching its conclusion, the court looked to Missouri's laws of ownership and donation. It held that the details of the informed consents created an inference under state law that the research participants intended to donate the materials, giving Washington University control over their use. The particulars the court pointed to included that the informed consent forms were on Washington University letterhead, stated that the materials were to be used for research and not for patient care, used the words ''donate'' and ''gift,'' and often stated that subjects could not claim ownership to property that could result from research performed with the materials.[49] The forms certainly nowhere indicated that the research participants would retain any ownership of the materials. Whether or not the ruling continues to stand, *Catalona* signals that the specific content of informed consent forms is crucial when determining ownership rights to biological materials.

The *Catalona* research participants argued that some of the informed consents included waivers prohibited by the Common Rule, and that the informed consents therefore were invalid.[50] The relevant provision in the forms stated: ''[by] agreeing to participate in this study, you agree to waive any claim you may have to the body tissues you donate.''[51] The Common Rule indeed prohibits the waiver of ''any of the subject's legal rights''[52] and a guidance document by OHRP's predecessor agency included as an example of impermissible exculpatory language a provision similar to that used by Washington University: ''By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course

[46] 45 C.F.R. § 46.116(a)(1); 21 C.F.R. § 50.25(a)(1).

[47] *Washington University v. Catalona*, 437 F. Supp. 2d 985 (E.D. Mo. March 31, 2006), *argued*, Nos. 06-2286 & 06-2301 (8th Cir. Dec. 13, 2006).

[48] *Id.* at 994.

[49] *Catalona*, 437 F. Supp. 2d at 990, 997.

[50] Brief of Appellant-Defendants at 36, *Washington University v. Catalona*, Nos. 06-2286 & 06-2301 (8th Cir. July 12, 2006).

[51] *Id.*

[52] 45 C.F.R. § 46.116.

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of the research.''[53] The *Catalona* court held, however, that the guidance document was not legally binding and interpreted the Common Rule ban as intended to prevent releases from malpractice or other negligence.[54] The court did not squarely address (and given the stance of the case, did not really need to address) whether the Common Rule's ban on exculpatory language applies to waivers of property interests in biological materials. So the important issue remains unclear.

In December 2006, the Catalona decision began to attract mainstream media attention: a *Wall Street Journal* commentary by popular author Michael Crichton excoriating the District Court highlights how unintuitive the *Catalona* decision can seem.[55] More than three years since the completion of the Human Genome Project, the public undoubtedly is absorbing the importance of DNA. Its descriptive and predictive power, its threat to insurance coverage, and its promise of financial gain all are becoming clear. There are vaguer notions, too, that genetic materials of the sort stored in the Washington University biorepository have some important connection to identity, such that anonymizing samples might not cure a withdrawing research participant's concerns. Indeed, commercial sponsors of research, research institutions, and investigators themselves must be cognizant of the concerns that donors increasingly will have as these notions percolate through the popular culture.

As the research community awaits the appellate decision in *Catalona*, some of the most emergent issues surrounding consent to ''future uses'' stem from the increasing demands from private research sponsors, including pharmaceutical companies, that informed consent forms and Privacy Rule authorizations permit a range of secondary uses that are broad and imprecise. Companies sometimes ask institutions to agree to protocols and clinical trial agreements that require the institutions to send data and tissue that have been gathered during a primary study and that often still are identified. These situations can put IRBs in a difficult position, given that, unlike the research activities of the medical staff over which the IRB and its institution have control, the conduct of private research sponsors largely falls outside continuing IRB oversight, and outside the restrictions imposed by Common Rule principles. The tension between sponsors seeking to expand the scope of their research and IRBs fearful of essentially unrestricted use of research data and materials after the conclusion of the primary study is likely to engender increasing debate within the human subject research community during 2007.

7. Gene Therapy: New Final FDA Guidance Will Influence 2007 Informed Consent Practice

In November 2006, FDA released the final version of a gene therapy guidance, ''Gene Therapy Clinical Trials—Observing Subjects for Delayed Adverse Events.''[56] Its implementation in the study context now looms before gene therapy researchers and their institutions.

Much of the potential benefit of gene therapy lies in the persistent activity of the genetic materials introduced into the body. By the same token, this persistence can lead to the development of adverse events months or years after the introduction of the genetic material. Prior FDA recommendations generally had called for observation for potential adverse events for 15 years, with a minimum of five years of annual examinations and 10 years of annual queries.[57] The new guidance, which replaces a draft guidance from August 2005, makes more specific recommendations for collecting data on delayed adverse events, while recognizing that long-term follow-up need not be of the same duration and type for vastly different therapies and study populations.[58] This guidance should be welcome to researchers as evidence that regulators do not perceive gene therapy monolithically seven years after Jesse Gelsinger's death attached tragic associations to the nascent technique.

The 2006 final guidance lays out recommended criteria for assessing delayed risks in gene therapy clinical trials. Researchers should use preclinical and clinical evidence, including information about similar products. When the risk is low, FDA ''generally will not require long-term follow-up observations following exposure to gene transfer technology.''[59] The guidance emphasizes that the assessment should be a continuous process, in which new information can signal a need for long-term follow-up or the lack of such need.[60] The guidance's Figure 1 provides a clear framework for assessing the level of risk by laying out an algorithm centered around four questions:

(1) Is your gene therapy product used only for ex vivo modification of cells?

(2) Do preclinical study results show persistence of vector sequences?

(3) Are vector sequences integrated?

(4) Does the vector have potential for latency and reactivation?[61]

The guidance recognizes, however, that certain populations are not suitable for long-term follow-up, even if the risk of delayed adverse events is high.[62] Examples include populations with short life expectancy, multiple morbidities, or exposure to another agent, such as radiation, that has its own potential for delayed adverse events.[63] The IND must include all of the primary data used to assess delayed risks, and if the population is determined to have limited suitability for follow-up observations the justification for that decision also should be included.[64]

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[53] OHRP Policy Guidance, Office for Prevention of Research Risks (OPRR, now OHRP), Cooperative Oncology Group Chairpersons Meeting, Nov. 15, 1996: ''Exculpatory Language'' in Informed Consent, *available at* http://www.hhs.gov/ohrp/humansubjects/guidance/exculp.htm.

[54] *Catalona*, 437 F. Supp. 2d at 998.

[55] M. Crichton, ''Body Snatchers,'' *Wall Street Journal*, Dec. 15, 2006.

[56] FDA Guidance for Industry, November 2006: Gene Therapy Clinical Trials—Observing Subjects for Delayed Adverse Events, *available at* http://www.fda.gov/cber/gdlns/gtclin.pdf.

[57] *Id.* at 3.

[58] *Id.* at 4.

[59] *Id.* at 6.

[60] *Id.*

[61] *Id.* at 9.

[62] *Id.* at 15.

[63] *Id.* at 15.

[64] *Id.* at 6, 15.

In cases in which long-term follow-up is appropriate, the new guidance provides recommendations for the design and conduct of the observations. While the 15-year observation benchmark remains, researchers may provide evidence to support shorter follow-up periods.[65] In addition to maintaining detailed case histories, the guidance encourages investigators to develop templates for subjects' health care providers to use in reporting observations.[66] Recommendations for the first five years after a gene therapy trial include scheduled visits to health care providers, establishment of a method for recording the emergence of new clinical conditions, and design of a plan to involve both study subjects and their health care providers in reporting adverse events.[67] For the subsequent 10 years, investigators should contact subjects at least once a year and tailor follow-up methods to previous test results.[68] The guidance provides new, specific recommendations for carrying out the long-term follow-up; gene therapy study designers should look closely at these recommendations on pages 17-18. They include increasing the frequency of follow-up visits in the case of a potentially reversible adverse event and testing annually for persistent vector sequences until they become undetectable.[69]

The guidance also discusses informed consent in trials involving long-term follow-up observations. Because the informed consent document must describe the purpose of the research, the expected duration of participation and the procedures to be followed,[70] it therefore must explain the purpose and duration of long-term follow-up, as well as the intervals, locations, and details of follow-up visits.[71] More specific guidance on informed consent is provided for trials involving retroviral vectors. After two children who participated in a French gene therapy trial for X-linked severe combined immunodeficiency disease (X-SCID, commonly known as bubble-baby syndrome) developed leukemia, FDA temporarily halted gene therapy trials using retroviral vectors. The informed consent forms for these trials should include a complete disclosure, in layman's terms, of the development of leukemia in the children with X-SCID.[72] Drafters of informed consent forms also are faced with the challenge of describing, in language understandable to subjects: a description of the study agent, the mechanism of action for retroviral vectors, the effect of DNA integration, and the risk of malignancy for the study.

8. Alternative Models of IRB Review: Centralized versus Local, For-Profit versus Not-for-Profit IRBs

After 2005 closed with *Bloomberg Markets Magazine*'s harsh condemnation of drug companies and the commercial IRBs that oversee an increasing number of privately sponsored clinical trials, 2006 saw thoughtful discussion of alternative models of IRB review. The historic model—local IRBs charged with approving all research conducted at their facilities—is seen by some as inefficient and even ineffective in protecting research subjects. The debate about alternatives is occurring along a number of dimensions: centralized versus local, single versus multiple, commercial versus nonprofit. While the advantages of local IRBs make unlikely a scheme composed solely of commercial, centralized IRBs, the research community finds itself having to adapt rapidly to a hybridizing system.

Any analysis of alternative models should carefully consider IRB members' conflicts of interest, which are prohibited by the Common Rule[73] and antithetical to the ethical mandate for unbiased review. A study published in the Nov. 30, 2006, issue of the *New England Journal of Medicine* found relationships between IRB members and industry to be common.[74] These included members with financial relationships with the companies whose protocols they review. The study authors argue that while such relationships do not always threaten subjects' safety,

> The goal from a public policy perspective is to encourage disclosure of these relationships and to identify conflicts of interests by means of clearly identified standards. When problematic relationships are discovered, IRBs must identify the steps that should be taken to eliminate or ameliorate the conflict. Failure to do so could call into question the ability of the IRB system to discharge its duty as the overseer of the safety and protection of human subjects in a fair and unbiased manner.[75]

If it is true that potentially conflict-ridden relationships are prevalent, it is uncertain which IRB model would best protect subjects. One might assume that central, for-profit IRBs (which are routinely used in industry-sponsored clinical trials) are more conflicted; the business success of these IRBs, the argument goes, hinges on satisfying sponsors. The chair of the Department of Clinical Bioethics at NIH argued against such a default position in a July 2006 article, emphasizing the lack of data comparing reviewer independence at for-profit and nonprofit IRBs.[76] Proponents of local IRBs argue that centralized IRBs do not have ties to the community where the research takes place, and so do not have a sufficiently deep sense of responsibility for the research subjects. On the other hand, members of local IRBs are more likely to have personal and even financial ties to the investigators whose research they are reviewing. Nonprofit central IRBs, such as the National Cancer Institute (NCI) Central IRB initiative[77] and IRBs formed by academic consortia, may not experience these conflicts, but without a significant source of funding, such IRBs are unlikely to be the panacea for this problem, as many have hoped.

Efficiency matters all the more as clinical trials multiply. When a single study is conducted and reviewed at

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[65] *Id.* at 15.
[66] *Id.* at 16.
[67] *Id.* at 17.
[68] *Id.*
[69] *Id.* at 18.
[70] 21 C.F.R. § 50.25(a)(1).
[71] FDA Guidance for Industry, Gene Therapy Clinical Trials, at 19.
[72] *Id.* at 21.
[73] ''No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.'' 45 C.F.R. § 46.116(e).
[74] Eric G. Campbell et al., ''Financial Relationships between Institutional Review Boards Members and Industry,'' 355 *New Eng. J. Med.* 2321 (2006).
[75] *Id.* at 2328.
[76] Ezekiel J. Emanuel, et al., ''Should Society Allow Research Ethics Boards to be Run as For-Profit Enterprises?'' 3 *PLoS Medicine* 941 (2006).
[77] *See* http://www.cancer.gov/clinicaltrials/conducting/new-national-system/page6.

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dozens of institutions, local approval can turn into a massive example of duplicative work by IRBs that do not have the time and staff to waste. Citing such efficiency concerns, the federal government thus far has expressed a predilection to shift away from the local IRB model. A March 2006 FDA guidance makes recommendations explicitly aimed at facilitating centralized IRB review.[78] In addition to guiding institutions through some of the logistics inherent in implementing a centralized model—for example, what procedures to write—the guidance also provides three models for distributing review between local and central IRBs.[79] Recognizing, though, that centralized IRBs lack local knowledge, the FDA guidance suggests that local institutions: (1) provide local information in writing, (2) provide local consultants to participate in the central IRB's deliberations, or (3) employ limited local IRB review for issues of concern to the community.[80] These recommendations—which will look quite familiar to anyone with experience using the NCI Central IRB system—undoubtedly represent a well-meaning attempt to resolve a difficult problem but may be unable to provide a centralized IRB with the amorphous local ''understanding'' envisioned as crucial to ethical review in the early years of IRBs.

In contrast to FDA's three models of cooperative review, a workshop sponsored in part by OHRP identified *ten* models of IRB review.[81] The report, released in March 2006, identifies the potential of alternative models but also discusses five key challenges: assurance of review quality, sensitivity to local context, liability (institutional and individual), control/accountability, and loss of resources.[82]

The developments of 2006 signal that, despite the inherent difficulty in transition, the trend will be movement away from purely local IRB review. The challenge to investigators and institutions will be to employ alternative models that harness the best of what both local and centralized IRBs have to offer. Navigation of IRBs, investigators, and research sponsors through these issues in multi-site trials is bound to be of increasing importance in 2007.

* * *

There are other issues, of course, that during 2007 will be fought over, debated, and decided by all the parties involved in human subjects research. These no doubt will include conflicts of interest of investigators, institutions, and IRB members; the reporting of adverse events; and liability for adverse events in clinical trials. Yet the issues set forth above are the ones we see as emerging in late 2006 and as poised to be of great and immediate relevance in 2007.

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[78] FDA Guidance for Industry, March 2006: Using a Centralized IRB Review Process in Multicenter Clinical Trails, *available at* http://www.fda.gov/cder/guidance/OC2005201fnl.pdf.

[79] *Id.* at 6-7.

[80] *Id.* at 5.

[81] NIH, OHRP, Association of American Medical Colleges, and American Society of Clinical Oncology, Nov. 17-18, 2005: Alternative Models of IRB Review *available at* http://www.hhs.gov/ohrp/sachrp/documents/AltModIRB.pdf.

[82] *Id.* at 3.