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Troubled Allegheny Cuts Cancer Programs; Institution Holds Grants for NSABP, ECOG

Cancer research was an important component of the healthcare empire the Allegheny Health, Education and Research Foundation built in Pittsburgh and Philadelphia.

For years, money appeared to be a minor consideration to *Allegheny's CEO, Sherif Abdelhak*, who last year publicly pledged to devote at least $5 million a year for five years to each of the system's two cancer centers.

AHERF routinely issued long press releases filled with names of prominent cancer specialists moving across the country—or across

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In Brief:

Survey Finds Americans Misinformed About Leading Cause Of Cancer Death

NEW SURVEY of more than 1,000 Americans by four cancer patient support and advocacy organizations reveals that most, especially women, are "grossly undereducated about the biggest cancer threat we face," lung cancer, according to **Diane Blum**, executive director of Cancer Care Inc., one of the survey sponsors. The survey found that 68 percent believe breast cancer is the leading cause of cancer death among women, while only 11 percent correctly named lung cancer. There are 65,000 lung cancer deaths among women a year in the U.S., more than breast cancer (44,500) and ovarian cancer (14,500) combined. Other sponsors were the Alliance for Lung Cancer Advocacy, Support and Education; the National Coalition for Cancer Survivorship; and the Cancer Research Foundation of America. . . . **MICHAEL WAITZKIN**, special counsel to the President in the White House counsel's office, has joined Fox, Bennett & Turner, Washington law firm specializing in biomedical research law and policy. Waitzkin's primary responsibilities at the White House were in Vice President Al Gore's office. . . . **RENA PASICK** has been named director of prevention sciences at the Northern California Cancer Center. She has been associate director for nine years. Pasick succeeds Bob Hiatt, who is now deputy director of the NCI Division of Cancer Control and Population Sciences. . . . **GIRL POWER:** Kirsten and Paul Goldberg, editors of **The Cancer Letter**, and their daughter Katherine, 8, announce the birth of **Sarah Pavlovna Goldberg**, on July 2, at George Washington University Hospital in Washington, DC. Sarah weighed 8 lbs. 4 oz.

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town—to the hospital system campuses.

Abdelhak's conquests in cancer included attracting the operations office of the National Surgical Adjuvant Breast and Bowel Project as well as the chairman's office of the Eastern Cooperative Oncology Group.

These days, AHERF is in no position to reach for the stars. CEO Abdelhak was ousted by the board last month, and his successors are slashing salaries, eliminating jobs, negotiating payment terms with suppliers, and trying desperately to limit the losses that averaged $27 million a month last fiscal year.

Meanwhile, Moody's Investment Service has downgraded the foundation's bond rating and has placed it on a watch list for further downgrading. What's worse, earlier this week, the Pittsburgh Post-Gazette and the Philadelphia Inquirer reported that Allegheny's management is considering seeking Chapter 11 protection from creditors for some portion of its holdings in Philadelphia.

So far, the hospital chain's most urgent problems have been confined to Philadelphia, where Allegheny's holdings include nine hospitals and two medical schools. Yet, many observers said they question the durability of "firewalls" between the Philadelphia and Pittsburgh operations.

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Founded Dec. 21, 1973 by Jerry D. Boyd

The Pittsburgh hospital —Allegheny General— has been the source of much of the money lost in Philadelphia.

The problems of AHERF are of more than regional significance, especially in cancer. In recent days, top NCI officials have been following the news from Pittsburgh and Philadelphia in an effort to track the impact the financial turmoil could have on NSABP and ECOG.

Officials at cancer centers nationwide said they are tracking the news from Pennsylvania to see whether the time has come to make a play for either of the groups. While cooperative groups don't make money for institutions that house them, their presence conveys prestige, enhances visibility, helps with recruitment of faculty, and attracts patients.

AHERF officials said *NSABP and ECOG are* not in peril.

"Allegheny is a system that is absolutely committed to NSABP and ECOG functioning well," said Barbara Atkinson, dean of school of medicine and academic affairs of Allegheny University of the Health Sciences. "They are important national resources. They have functioned well in the past, and we are making every provision that they will function well in the future."

It is unclear whether an institution trying to stay afloat would be able to hang on to an asset as desirable as cooperative groups, several observers said.

Interviews with officials in Pittsburgh, Philadelphia, and Bethesda indicate that the groups can be moved either by NCI, if the Institute determines that the grantee institution imperils the functioning of a cooperative group, or by the group itself.

Here is how *the AHERF relationship with the* two groups is structured.

—Allegheny is the grantee institution for the NSABP operations and chairman's office grant. In the current year, NCI paid $11 million to support the group. Of these funds, $2.4 million covers indirect costs. The center, which is located in Pittsburgh, has 40 full time equivalent employees. Many physicians employed by the headquarters also draw salaries from Allegheny, where they practice.

NSABP's application for competitive renewal is due at NCI next February, and the final award would be made a year later. The next installment of the NCI payment to the institution under the current grant is scheduled for next February.

NSABP does not have to work through a grantee institution, sources said. The cooperative group recently formed a foundation that would be able to act as an NCI grantee. More important, NSABP is a highly visible component of the NCI clinical trials program.

The group's trials have redefined the treatment of breast cancer, and the recently concluded Breast Cancer Prevention Trial attracted worldwide attention. Now, NSABP is in the midst of launching a followup trial to BCPT, a comparison of tamoxifen and raloxifene.

Should NSABP decide to move to another institution, NCI will have to approve that decision, sources said. If the work of the group is adversely affected by the grantee institution, NCI has the authority to initiate the transfer, Institute officials said.

The NSABP biostatistical center, funded through a separate NCI grant, is located at the University of Pittsburgh.

—In the case of ECOG, Allegheny administers a $650,000 a year contract for running the group chairman's office. The institution acts as a subcontractor to Boston-based Frontier Science, Technology and Research Foundation, which administers a $5.5 million a year contract for the ECOG operations office.

The ECOG chairman's office, which is based in Philadelphia, has about six full-time equivalent employees who handle matters that involve strategy, communications, and public affairs. Every month, Allegheny submits a bill for the chairman's office to Frontier. Indirect costs charged by Allegheny amount to about 12 percent, sources said.

Like NSABP, ECOG has a foundation that is capable of acting as a grantee. NCI sources said the Institute may not be required to sign off on a potential move by ECOG chairman's office.

Two weeks ago, AHERF abandoned its plans to develop a cross-state cancer clinical trials program and a freestanding cancer center in Pittsburgh, sources said. Both programs were under the direction of ECOG Chairman Robert Comis.

"ECOG chairman's functions are stable, and we are concentrating all our efforts on the competitive renewal, which is being defended in October," Comis said to **The Cancer Letter.**

Scaling back of development plans leaves AHERF with one cancer center, the Allegheny University Cancer Center in Philadelphia. However, that center's budget has been scaled back from $5 million to about $1.5 million a year, sources said.

"The former AHERF administration was unrealistic in its plans to expand," said cancer center director Howard Ozer. "We continue to have a smaller, more focused budget and program that will be oriented toward building clinical care, clinical research and basic science in Philadelphia."

It is unclear where AHERF's rescue could come from.

Last March, Allegheny officials began negotiations with Vanguard Health Systems Inc., a Nashville-based for-profit chain, for the sale of six of its nine Philadelphia hospitals.

However, formal negotiations ended June 22, shortly before a public hearing scheduled by the Pennsylvania Attorney General's office. Such hearings are required when not-for-profit hospitals are sold to for-profit chains.

Vanguard spokesman Beth Haglen said to **The Cancer Letter** that the deal proved to be more complicated than the company initially believed.

For one thing, billing and other administrative services for the six hospitals were being performed by the hospitals that were not for sale, which meant that at least initially Vanguard would have had to contract with Allegheny for billing, Haglen said. Another complication was the fact that a unit of Allegheny had purchased the practices of most physicians who worked at the six hospitals.

"We are pursuing a different structure that would be more agreeable to both parties," Haglen said.

Clinical Trials:

NSABP Invites Institutions To Apply For Raloxifene Trial

The National Surgical Adjuvant Breast and Bowl Project plans to begin a study this fall comparing tamoxifen with raloxifene for the prevention of breast cancer.

The trial is the logical followup to NSABP's Breast Cancer Prevention Trial of tamoxifen, the results of which were announced earlier this year (**The Cancer Letter**, April 10).

NSABP said it was inviting institutions to apply for participation in the trial, "Study of Tamoxifen and Raloxifene (STAR)," and expects as many as 200 clinical centers in North American to sign up. The new trial will be even larger than the first, with

an enrollment of 22,000 postmenopausal women over age 35 in the double blind, randomized clinical trial. The tamoxifen study involved 13,300 women.

Institutions applying for participation will be expected to provide the following information:

—A detailed description of the recruitment strategies to be used.

—Evidence of access to and commitment from agencies, organizations, or individuals involved in the recruitment process.

—A description of the applicant's organizational structure showing how it ensures adequate accrual, treatment, followup, and data submission.

—A contingency plan for staff turnover and organizational changes.

—Sources and plans for enrolling women from diverse ethnic and racial populations.

—Verification of available staff with experience in recruitment and clinical trial care.

—Plans for maintaining high rates of both investigator and participant compliance to the protocol.

—Demonstration of the ability to maintain acceptable data submission rates in previous or ongoing clinical trials.

—Evidence of adequate resources for training, education, and internal quality control.

—Verification of appropriate medical staff, support staff, and facility availability required for enrolling and monitoring study participants.

Applications and additional information may be obtained by mailing a letter of interest to Gladys Hurst, Assistant Director, Membership Affairs Section, NSABP Operations Center, East Commons Professional Building, four Allegheny Center, 5th Floor, Pittsburgh, PA 15212-5234, or faxing to her attention, 412/330-4662. Applications must be returned to NSABP by Aug. 15, 1998.

NCI Programs:

Advisors Approve Programs For Imaging Research Grants

The NCI Board of Scientific Advisors approved in concept the Institute's plans for two new grant programs in imaging research.

Excerpts from the concept statements follow:

Small Animal Imaging Resource Programs. Concept for a new RFA, total cost $22 million over five years, four to six awards, first year set-aside $4.5 million.

Small animal models, particularly genetically engineered mice, are increasingly recognized as powerful discovery tools in cancer research. NCI is committing considerable resources to exploit the potential of small animal models. For example, a proposal for a Mouse Animal Models Consortium was approved at the March 1998 meeting of the BSA.

The potential that could be realized by the use of animal models has not yet been fully captured. One of the limitations is the need to sacrifice the animals to perform tissue or molecular analysis. This prevents researchers from observing in vivo the natural or perturbed evolution of the processes under study. Functional, quantitative imaging techniques are an important tool for providing data about biochemical, genetic or pharmacological processes in vivo, and repetitively in the same animal.

To study tumors one must make spatially distributed measurements. Imaging is a means of making and displaying spatially coherent measurements and is therefore a key resource for studying the development, growth and therapeutic response of neoplasms. One of the important research directions for imaging research is to provide quantitative images and data in the setting of cancer diagnosis and therapy. Quantitation of image data for small animals will lead the way to quantitative methods for application in human beings.

A major limitation to studying tumors with current imaging techniques is the limited availability of small animal imaging systems. Most biomedical imaging devices have been optimized for human studies and have suboptimal spatial resolution for small animals and their tumors. However, imaging techniques can be scaled down to yield very high spatial resolution and signal sensitivity for in viva images of mouse-sized organs. Furthermore, there are some applications of imaging techniques which could provide valuable information in small animal models, but are not feasible for human subjects. Therefore, in order to take full advantage of the small animal tumor models being developed, it has been recommended that dedicated small animal imaging laboratories be developed. The In Vivo Molecular/Functional Imaging Subgroup of the Imaging Sciences Working Group recommended that NCI support small animal imaging facilities focused on the study of genetically engineered tumor models.

Small Animal Imaging Resource Programs (SAIRP) should be established to promote the development and dissemination to the cancer research community of new imaging technologies and associated resources.

Small Animal Imaging Resource Programs should address 2 related needs: (a) providing "turnkey" imaging services to oncology investigators, and (b) pursuing research on existing and new imaging technology to expand the possibilities for non-invasive, quantitative, in vivo imaging. Although some small animal imaging facilities exist, most oncology investigators do not have

access to such services. Some researchers ship their mice across the country to have them imaged, and some sacrifice and preserve their mice for subsequent imaging at distant sites. More than one type of imaging modality needs to be available to meet different needs. Research and development of imaging technologies should occur at the same facilities where imaging services are being provided as a resource. As imaging researchers come to better understand the needs of the oncology researchers, they can more optimally develop existing technologies or novel approaches to provide the information desired.

Small Animal Imaging Resource Programs (SAIRP) would provide:

—*Multiple* imaging technologies for small animals, emphasizing those technologies which can provide biochemical, genetic or pharmacological information in vivo.

—Technology research and development on *innovative new imaging technologies* appropriate for small animals, as well as refinement and development of technologies for which proof of principle has already been demonstrated.

—Facilities and personnel to assist in the development of necessary probes for the imaging technologies provided. Facilities and personnel to aid in small animal anesthesia, management, and care, as well as to consult on the optimal use of animals in connection with the imaging experiments.

The structure of the SAIRP must reflect the need to ensure that the small animal imaging technologies available for access or under development through this mechanism are pushing the state of the art. In addition, the SAIRP should explore the broadest range of cancer research possible.

The SAIRP should use approximately one-half to two-thirds of its resources and time to provide imaging services and to collaborate with cancer-related research projects. As part of the initial application, there must be commitments from at least 3 cancer-related research projects that will use the small animal imaging resource *beginning in year 2. After implementation*, the applicants would be expected to form similar collaborations with at least three additional cancer-related research projects by the mid-point of the project. Thus, the SAIRP would provide imaging services to a minimum of 6 cancer-related research projects.

Applicants would be expected to demonstrate that at the time of application they have available at least one state-of-the-art imaging technology optimized for small animals. In addition, they must show evidence of experience with in vivo imaging of small animals using the available technology.

Applicants must provide plans for providing at least one additional imaging technology for small animals within the first year of the project. This could be acquired commercially or developed in-house.

The SAIRP should use approximately one-third to one-half of its resources and time for research and development of small animal imaging technology. This could be further development and optimization of existing technologies or exploration of novel technologies. Methods to produce valid quantitative results would be particularly encouraged.

Applicants would be expected to describe their plan for governance, and methods to be used to evaluate and select protocols to support with the SAIRP. It is suggested that a scientific advisory board of collaborators and other cancer investigators be established for this purpose.

At the midpoint of the 5-year award there would be a review to confirm that:

—2 or more small animal imaging technologies have been implemented and are operational;

—collaboration with a minimum of 6 cancer-related research projects requiring imaging data from small animals is in progress;

—developmental research on small animal imaging systems is in progress.

If these components do not exist or are insufficient, the award will be phased out.

Plans for partial or complete cost recovery for the service and collaborative efforts could be discussed in the application. It is recognized that in general investigators value more highly what they must pay for, but that there might not be budgeted funds to start the collaborations. A system of cost recovery is not considered essential for NIH-funded collaborators.

SAIRP will offer a unique opportunity for multidisciplinary teams within the cancer research community to address critical cancer research questions. Scientific personnel in the SAIRP would be expected to represent a variety of fields such as radiology, oncology, physics, chemistry/radiochemistry, biochemistry, cell and molecular biology, computer science, pharmacology, veterinary anesthesiology, and pathology.

The amount of funds requested is based on the following assumptions. Currently available technologies, such as small animal MR imaging systems and small animal PET units, have an average cost of $750,000. Operating costs will include personnel such as the principal investigator to direct the operation of the instrument development and service, another Ph.D. to provide additional knowledge and skills, a post-doctoral fellow to work with instrument and technique development, technologists to operate the unit and process the data, technologists to create the imaging probes, and veterinary anesthesiologists and technologists. These could be expected to add approximately $200,000 to the budget per year. In the first year, remodeling costs of $100,000 might be expected to accommodate the Program. Service costs in the industry are an average of 10% of the purchase price of the major components per year, or a budget item of $75,000 per year. The funding of

non-personnel costs for developmental imaging research might add another $200,000 per year. Thus the first year budget might be on the order of $1.25M in direct costs or $1.5M in total costs due to start-up equipment costs. Investigators might be able to obtain some equipment funds from other sources, and this would be encouraged. In succeeding years, costs shift to personnel, service, infrastructure modifications or upgrades. A sample budget used to calculate these estimates is attached. Each site might average $4.3M total for 5 years or $22M for 4 sites for 5 years. The funding level required will be influenced by what imaging technology is currently available at the applicant site, and what needs to be purchased or developed in the first year. Funding 4 to 6 such centers with various capabilities would allow for disseminated access of a number of technologies to a wide variety of cancer researchers.

Development and Application of Imaging in *Therapeutic Studies.* Concept for a new RFA, total amount $11.2 million over four years, six to eight awards, first year set-aside $2.8 million.

The purpose of this RFA concept is to encourage investigators to apply imaging technologies in the assessment of investigational cancer therapeutic agents. In simplest terms, the intent here is to use imaging techniques to determine non-destructively where an administered therapeutic agent goes and what it does.

Following are two general categories of interest:

1. Development and application of labeled therapeutic agents as compounds for imaging studies. These imaging agents can be used as tracers to monitor the metabolism and distribution of therapeutic agents in both the tumor and normal tissue. These techniques can be applied to early clinical trials or pre-clinical studies in animal model systems. The evaluation of drug distribution and metabolism are part of the standard studies that accompany drug development in early clinical trials. However, data on intra-tumoral uptake, distribution and metabolism are usually lacking because obtaining such information usually requires sequential biopsies. *Non-invasive imaging* may prove useful for evaluating the distribution kinetics and PK-PD relationships of certain anti-tumor agents for which pharmacokinetics using standard pharmacological methods is particularly problematic (e.g., bryostatin).

Information on gene therapy delivery and distribution is of particular interest. Biological endpoints in cancer gene therapy trials, including the determination of gene transfer efficiency/expression and of tumor cell apoptosis, are important for the optimization of these therapies. It is often difficult to perform the invasive procedures that are necessary for tissue procurement, and the sites of gene transduction may be missed by the biopsy needle. Noninvasive imaging technologies could greatly facilitate the development of cancer gene therapies.

2. Development arid application of imaging agents as metabolic markers of response to newly-developed therapeutic agents. For example, imaging agents could be molecules that are substrates or analogues of substrates for the biochemical pathway of action of the drug. Since some antitumor agents target specific enzyme systems (e.g., dihydropyrimidine dehydrogenase, thymidylate synthase), the development of technologies that image those enzyme systems may prove valuable tools to evaluate pharmacokinetic-pharmacodynamic relationships. These markers of drug action could be used to monitor metabolic response to the drug both in vitro and in vivo.

Radiolabeled FDG is an example of a substrate analogue that is incorporated into the cell in proportion to its glucose utilization, but is not metabolized fiercer. Its accumulation thus serves as a marker of cellular metabolic activity. Although FDG studies may have some utility in measuring tumor response, *glucose utilization* is a non-specific indicator, is highly variable in tumors, and is a somewhat late marker relative to other cellular biochemical alterations.

Incorporation of non-degradable analogues of thymidine are being investigated as markers of DNA proliferation or thymidine kinase (TK) activity. Development and use of probes such as the thymidine analogues are examples of the kind of techniques that could be important adjuncts to early clinical trials.

An example of a molecular mechanism of interest is angiogenesis, although cell proliferation, necrosis, apoptosis, and other pathways would be equally suited as targets of study. Agents that inhibit tumor-associated angiogenesis differ from the usual cytotoxic chemotherapeutic drugs. They may only induce tumor stasis, are frequently non-toxic, and probably need to be administered continuously for prolonged periods of time. The usual paradigms of anti-tumor drug development involving establishing the maximally tolerated dose, administering the agent intermittently, and using frank tumor response to assess activity are not applicable. Thus, there is a great need for *in vivo assays, tests,* or mechanisms for assessing the biologic activity of these agents in early clinical trials. The development of non-invasive methodologies for assessing changes in tumor blood flow as well as tumor metabolism would significantly enhance the development of anti-angiogenic agents. Radiologic imaging techniques are currently being developed that can do just that. However, these techniques are still in their infancy with respect to their validation and use in drug development. Mechanisms that would speed and enhance the development of imaging studies assessing tumor blood flow, tumor metabolism, drug delivery within tumors, etc. would have a significant impact on the clinical development of agents that inhibit tumor associated angiogenesis.

Implementation of quantitative, functional imaging

studies as part of early clinical trials requires:

1. Identification of appropriate molecular targets;

2. Development of multi-disciplinary research teams including oncologists, imaging scientists, molecular biologists, chemists, pharmacologists and mathematical modelers;

3. Development of appropriate probes;

4. Development of quantitative imaging techniques.

With new drug-development methods producing ever increasing numbers of molecules for investigation, there is a important opportunity to integrate and exploit imaging techniques in the assessment of this process. The collaborations required for the implementation of these ambitious projects may be in place in a limited number of institutions. However, an important focus of this initiative is to encourage and facilitate the formation of new teams of investigators that have not been scientifically interactive.

The proposed projects will be required to integrate the development and utilization of a novel imaging agent into the investigation of a specific therapeutic agent (or the defined biochemical pathway in which it acts). Applications to study or develop new imaging agents that are not specifically involved in a pathway that is a direct target for current drug development will not be considered responsive to this initiative. An approximate average cost for each award would be $350,000 total costs.

HHS Inspector General:
Research Environment Leaves IRBs Vulnerable, Report Says

Institutional review boards, which are involved in the approval process of all clinical research carried out in the U.S. with the primary task of protecting human research subjects, have "vulnerabilities" that threaten their effectiveness, according to a report by the Department of Health and Human Services Inspector General.

The three volume report, which was released in June, noted that the review by the IG did not find widespread abuses of patients in clinical trials. "We offer a warning signal and a framework for a concerted response to it," the report said. The recommendations in the report "are especially important in view of current federal plans to increase significantly the numbers of human subjects participating in clinical trials, and proposals to give IRBs increased responsibility in the areas of genetics and confidentiality."

The IG did not carry out audits of IRBs or investigations of particular cases. The review included a look at federal records and pertinent literature, interviews and group discussions with federal officials and with representatives of about 75 IRBs, and visits with IRBs at six academic health centers where extensive clinical research is taking place. Reviewers attended IRB meetings and accompanied FDA inspectors on IRB site visits.

Among the report's findings:

—The effectiveness of IRBs is in jeopardy. They face major changes in the research environment. Current IRB practices evolved in the 1970s when research typically was carried out by a single investigator working under government funding with a small cohort of human subjects in a university teaching hospital.

"In recent years that environment has been changing dramatically as a result of the expansion of managed care, increased commercialization of research, proliferation of multisite trials, new types of research, the increased number of research proposals, and the rise of patient consumerism. Each of these developments has presented major disruptions and challenges for IRBs."

—IRBs review too much, too quickly, with too little expertise. "This is especially apparent in many of the larger institutions. Expanded workloads, resource constraints, and extensive federal mandates contribute to a rushed atmosphere where sufficient deliberation often is not possible. At the same time, the IRBs frequently are hardpressed to gain access to the scientific expertise they need to reach informed judgments about the research taking place under their jurisdiction."

—IRBs conduct minimal continuing review of approved research. With the pressures noted above, "continuing review often loses out. Even where there is the will, there often is not the time to go beyond the perfunctory obligations. A lack of feedback from other entities that oversee multisite trials contributes to the problem. The result is that IRBs have all too little information about how the informed consent process really works and about how well the interests of subjects are being protected during the course of research."

—IRBs face conflicts that threaten their independence. Because clinical research provides revenue and prestige to the institutions to which many IRBs belong, those institutions expect IRBs to support those interests as well as protect human subjects. "The resulting tension can lessen the IRBs' focus on their basic mission. The minimal outside representation that typically exists on IRBs deprives them of an important counterbalance to the

institutional interests. For independent IRBs, the dependence on revenue from industry sponsors exerts similar possibilities for conflict."

—IRBs do not provide sufficient training for investigators and board members. The IRB system depends on researchers' commitment to human subject protections. "But as that system now operates, it offers little educational outreach to investigators to help them become informed and sensitized about these protections."

—Neither IRBs nor HHS devote much attention to evaluating IRB effectiveness. "IRBs rarely conduct inquiries to determine how well they are accomplishing their mission; their judgments of effectiveness rely mainly on the number of protection lapses or complaints that are brought to their attention. HHS agencies conducting oversight seldom go any further. The NIH Office for Protection from Research Risks focuses almost entirely on upfront assurances. FDA relives on compliance focused inspections."

The report directed its recommendations at the two HHS agencies responsible for IRB oversight, the Office of Protection from Research Risks and FDA:

—Recast federal IRB requirements to grant IRBs greater flexibility and hold them more accountable for results. This could be done by eliminating or reducing some of the procedural requirements directed to IRBs. IRBs could be required to undergo regular performance focused evaluations.

—Strengthen continuing protections for human subjects participating in research. Require data safety monitoring boards for some multisite trials; provide IRBs with feedback on developments concerning multisite trials; routinely provide IRBs with feedback about FDA actions against investigators; require sponsors and investigators to notify IRBs of prior reviews of research plans; and call for increased IRB awareness of onsite research practices.

—Enact federal requirements that help ensure that investigators and IRB members are adequately educated about and sensitized to human subject protections. Require that research institutions have a program for educating investigators about human subject protections; require that investigators provide a written attestation of their familiarity with and commitment to human subject protection; require that IRBs have an educational program for board members.

—Help insulate IRBs from conflicts that can compromise their mission in protecting human subjects. Require more representation on IRBs of nonscientific and noninstitutional members; reinforce to IRB institutions the importance of IRBs having sufficient independence; prohibit IRB equity owners from participating in the IRB review process.

—Recognize the seriousness of the workload pressures that many IRBs face and take actions that aim to moderate them. Require that IRBs have access to adequate resources.

—Reengineer the federal oversight process. Revamp the NIH/OPRR assurance process; revamp the FDA onsite inspection process; require the registration of IRBs.

The report generated response from NIH, FDA, the American Association of Medical Colleges, the Applied Research Ethics National Association , the Consortium of Independent Review Boards, and Public Citizens' Health Research Group.

The NIH response, written by Anthony Itteilag, deputy director for management, agreed with most of the recommendations and suggested that even more attention be given to the "challenges posed by multisite clinical trials." Itteilag pointed out that NIH had already initiated some of the changes, particularly in improving informed consent.

Acting FDA Commissioner Michael Friedman noted that some of the recommendations for increasing protection of research subjects could increase the burdens and pressure on IRBs. Friedman defended the current FDA inspection program.

HHS Inspector General June Gibbs Brown, responding to Friedman, urged that FDA take "near term action in ensuring that IRB processes conform to the letter of the law."

Sidney Wolfe and Peter Lurie, responding for Public Citizens' Health Research Group, took issue with the IG's conclusion that there is "no widespread abuse" of human research subjects. "The increasingly large number of violations found by FDA investigators in IRB approved informed consent documents, the dangerous lack of onsite inspections for HHS funded research by NIH's OPRR, the rise of for profit IRBs.... and many other problems documented in these reports belie the conclusion of no widespread abuse."

The IG responded, "Public Citizen incorrectly states that we concluded that there are no widespread abuses of human subjects. Our concluding assessment on this point was that we do not claim there are widespread abuses of such subjects."